Cranial computer assisted tomography and electroencephalography in children with acute lymphocytic leukemia

A longitudinal study

(Computertomografie van de schedel en electroencephalografisch onderzoek bij kinderen met een acute lymfatische leukemie. Een longitudinale studie)

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. C.J. RIJNVOS
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN
DE OPENBARE VERDEDIGING ZAL PLAATS VINDEN OP
DONDERDAG 28 JUNI 1990 OM 13.30 UUR

DOOR

KAREL HÄHLEN

GEBOREN TE 'S-GRAVENHAGE

universiteits drukkerij

1990

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List of abbreviations

#	patient number
6-MP	6-mercaptopurine
ALL	acute lymphocytic leukemia
BBB	blood brain barrier
BM	bone marrow
CNS	central nervous system
CNSL	central nervous system leukemia
CR	complete remission
crXRT	craniocervical radiotherapy
crspXRT	craniospinal radiotherapy
CSF	cerebrospinal fluid
CT	computer assisted tomography scan of the brain
CVI	cerebroventricular index
CYT	cytoxan (= cyclophosphamide)
DCLSG	Dutch Childhood Leukemia Study Group (the Hague, the Netherlands)
DNR	daunorubicin
EEG	electroencephalogram
Gy	Gray (= 100 rad)
HD	hypodense area
HR(-ALL)	high-risk (acute lymphocytic leukemia)
HU	Hounsfield Units
Hz	Herz (cycles per second)
i.th.	intrathecal(ly)
ITP	idiopathic thrombocytopenic purpura
i.v.	intravenous(ly)
L-ASP	l-asparaginase
LP	lumbar puncture
MTX	methotrexate
n	number (amount)
NHR(-ALL)	non-high-risk (acute lymphocytic leukemia)
nr	number (= #)
p	probability
PCP	Pneumocystis carinii pneumonitis
PRED	prednisone
pt(s)	patient(s)
SA	spectral analysis of EEG recordings
SD	sulcal dilatation
(SD)	standard deviation
(SEM)	standard error of the mean
SJCRH	St Jude Children's Research Hospital (Memphis, Tennessee, USA)
TMP/SMX	trimethoprim/sulfamethoxazole (= cotrimoxazole)
VCR	vincristine
VD	ventricular dilatation
VP	vena puncture
WBC	white blood cell count
XRT	radiotherapy

C H A P T E R 1

Introduction

Before cure could be reached in children with acute lymphocytic leukemia (ALL), improvement of systemic treatment led to longer periods of remission duration. However, this prolonged duration of remission was accompanied by an increase in the rate of first relapse in the central nervous system (CNS). Reported rates of first relapse in the CNS amounted up to 50 -80% (Evans et al 1970, Price and Johnson 1973). Whenever a relapse in the CNS occurred, the ultimate outcome was death. Thus, treatment protocols with the aim to prevent the development of overt central nervous system leukemia (CNSL) were initiated. Such protocols incorporated early CNS treatment with irradiation or intrathecal injections of a.o. methotrexate or combinations of these. This proved to be successful and has led to an incidence of relapse in the CNS of only 5 - 15%, resulting in a cure rate of at least 50% in children with an ALL. However, once a relapse in the CNS occurred the prognosis was dismal even with very intensive treatment. In order to prevent the remaining CNS relapses methods had to be developed to predict a high chance for a CNS relapse. It is also crucial to be informed about the side effects of the methods of treatment in order to be able to weigh the benefits of intensification of therapy against toxicity.

One way to investigate the neurological status of patients is to obtain electroencephalographic (EEG) recordings. At the start of this study reports of EEG recordings in children with ALL were scarce. Most of the time these were related to the occurrence of neurological symptoms.

A specific problem consists of the interpretation of the EEG recordings, which to a certain extent depends on the individual skill and experience of the reviewing physician. By applying computerized readings it is possible to evaluate EEG recordings in an objective way. This is done by spectral analysis (SA) whereby the mean frequencies and the contributions of the different wave frequencies are calculated. At the time of the start of this study no serial evaluations by spectral analysis of EEG recordings in children with ALL had been reported.

With the introduction of computer assisted tomography of the brain (CT) in 1973, a noninvasive method to investigate structural abnormalities of the

brain became available. Several investigators reported about the occurrence of structural abnormalities, in particular cerebral calcifications, in children with neurological complications (Müller et al 1976, McIntosh et al 1977). Only one report concerned children without neurological signs, investigated at different times after cranial irradiation. Nevertheless, abnormalities had been found on CT scans in 33 - 50% of children. These consisted of ventricular dilatation, sulcal dilatation, hypodense areas and/or calcifications (Peylan-Ramu et al 1978).

A relation between these abnormalities and the treatments, either cranial irradiation and/or especially intrathecal methotrexate, was suggested by several authors (McIntosh et al 1977, Price and Birdwell 1978, Wendling et al 1978, Kolmannskog et al 1979). However, these early CT scan studies were performed at extremely variable time intervals after CNS-prophylaxis, either when neurological symptoms were present or absent. The conclusions about the possible side effects of the different treatment modalities could therefore be questioned. The same goes for the cumulative dosages of the used drugs on the occurrence of abnormalities. Moreover, no follow-up studies which had been designed to investigate the time of occurrence of structural abnormalities in relation to treatment had been reported.

Therefore, it seemed feasible to undertake a prospective study, in which children would be evaluated by means of CT scans, EEG's and SA's at diagnosis as well as at specific times during treatment and thereafter, in order to obtain information about the sequence of occurrence of these structural and functional abnormalities in relation to the treatment applied.

The purpose of this study comprises the evaluation of the following items in children with ALL:

1. the presence of abnormalities in CT scans and EEG recordings at diagnosis
2. the nature and the course of the changes in CT scans and EEG recordings during treatment and thereafter
3. the predictive value of CT and/or EEG investigations for the later occurrence of CNS leukemia.
4. the methods of evaluation of CT scans

C H A P T E R 2

The central nervous system in childhood leukemia
A review of the literature

Central nervous system leukemia

After the recognition of the high relapse rate in the CNS when no specific therapy was delivered, it was postulated, that already at diagnosis an inapparent leukemic infiltration of the CNS existed. Presumedly, these leukemic cells are protected by the blood brain barrier (BBB), and could thus escape the cytostatic effects of the drugs delivered systemicly. Consequently, the concept of delivering early treatment to the CNS with circumvention of the BBB was developed. Such effective treatment for the CNS consists either of irradiation (XRT) - craniospinal (crsp) or craniocervical (cr) - or of intrathecal (i.th.) injections of certain drugs like methotrexate (MTX) and prednisolone. Another possibility consists of the systemic delivery of normal, moderate or high doses of drugs with a tendency to penetrate in a measurable amount into the CNS. Combinations of these treatment modalities can be used also.

At St Jude Children's Research Hospital (SJCRH) in Memphis, Tennessee, Pinkel et al conducted a series of studies comparing different regimens of early CNS treatment. The most effective and least toxic treatment regimen was considered to be the one with crXRT with 2400 rads plus 5 i.th. injections of MTX. The incorporation of this "CNS-prophylaxis" in their treatment protocol resulted in a 50% disease free survival of children with ALL for more than 5 years, with a potential of cure (Auer et al 1971). This result proved to be sustained after a follow-up of more than 18 years (Pinkel 1987). After the first reports about these results, many study groups incorporated this kind of CNS-prophylaxis in their childhood ALL treatment protocols.

Although concern about possible adverse effects from this kind of prophylactic CNS treatment, especially in relation to the crXRT, was raised, early reports denied the occurrence of such events, more specifically with regard to malfunctioning of the hypophysis.

Some groups proceded to investigate the effectivity and toxicity of other methods of CNS-prophylaxis, either with the early delivery of i.th. MTX, which was maintained throughout treatment (Sullivan et al 1969), or with the use

of moderate high doses of i.v. MTX infusions combined with i.th. MTX (Freeman et al 1977, Moe and Seip 1978). The results of these treatments proved to be as good or nearly as good as those which incorporated central nervous system irradiation (Green et al 1980, Sullivan et al 1982, Freeman et al 1983).

Central nervous system leukemia is believed to develop via hematogenous spread of circulating leukemic blasts or by direct invasion from adjacent diseased cranial bone marrow. Of these two, hematogenous spread is the most important. As Price and coworkers elucidated in a series of studies (1973, 1975, 1978), CNS involvement occurs in a certain sequence:
Leukemic cells, which are present in the small vessels of the arachnoid trabeculae move through the walls of these vessels into the trabeculae. They then divide and eventually break through the lining of these trabeculae and seed into the cerebrospinal fluid (CSF). At this moment, few leukemic cells will circulate in the CSF and concentrate in the lumbar sac, giving for the first time the opportunity to diagnose a central nervous system leukemia. When left untreated, leukemic cells will subsequently infiltrate the entire arachnoid, which extends into the deepest portions of the brain, with obliteration of CSF channels and compression of small veins as a consequence. Such a leukemic infiltration interferes with the flow and absorption of CSF, resulting in an increase of intracranial pressure and widening of the ventricles. This will usually involve the whole ventricular system, indicating that the obstruction is most prominent at the base of the brain. This can also give rise to clinical symptoms like cranial nerve palsies. Even in this advanced stage, the infiltration of malignant cells still remains extracerebral and extraneuronal.
Finally, the expanding cell mass destroys the pia-glial membrane and infiltrates into the cerebral parenchyma. This represents quite a late occurrence, mostly found only after multiple relapses: such an degree of infiltration proved only to be present in less than 15% of children, autopsied after they died of relapse (Price and Johnson 1973).

The most common symptoms of meningeal leukemia are headache, nausea, vomiting, lethargy and irritability. Less common symptoms are anorexia, visual disturbances, vertigo, ataxia, convulsions and coma.
The most frequent clinical signs in children with meningeal leukemia are papilledema, nuchal rigidity, cranial nerve palsies, and weight gain. Body tem-

perature is almost always normal.

The diagnosis is made on the finding of unequivocal blasts in a cytocentrifuge preparation of the CSF, regardless of the total number of cells present. The CSF protein concentration is increased in only 20 - 50% of children with meningeal leukemia (Hyman et al 1965, Sullivan et al 1969), low sugar CSF concentrations are present in 55 - 70% of these patients. Neither the CSF sugar nor protein concentrations are helpful or necessary for diagnosing CNS leukemia.

Nowadays, pediatric patients are regularly checked by performing spinal taps during and after maintenance therapy after having received CNS prophylaxis early after diagnosis. As a consequence, a meningeal leukemia is usually diagnosed on cytospin preparations while the child has no symptoms whatsoever. However, as mentioned earlier, the degree of infiltration with leukemic cells in the CNS and damage inflicted is rather high at that moment.

Neurological toxicity of treatment

Adverse neurological reactions on the treatment can be the consequence of

1. the damage, inflicted by the infiltration of leukemic cells,
2. the removal of this infiltration by successful treatment and the consequent repair thereof in the tissues,
3. the effects of the different treatments instituted, i.e. individual cytostatic drugs , irradiation or any combination of these.

These adverse reactions can be divided in short- and long-term effects:

Short-term reactions comprise meningeal syndrome, partial or total paralysis, pseudotumor cerebri, vincristine induced neuropathy and postirradiation syndrome.

Long-term reactions are neuropsychological or neuroendocrine disturbances, cortical atrophy, mineralizing microangiopathy, necrotizing leukoencephalopathy, radionecrosis or necrotizing leukomyelopathy.

Neurotoxicity of cytostatic drugs

Vincristine

Vincristine (VCR) is the most neurotoxic of the vinca alkaloids. These drugs bind to mitotic spindle protein and thus arrest division of cells. They also prevent the formation of neurofilaments, disrupt those already formed, and impair axonoplasmic transport. Peripheral neuropathy is the result of these effects. The severity of the neuropathy is dose related in the case of VCR.

Symptoms begin with paresthesias in hands and feet. Next, disappearance of ankle reflexes, followed by the patellar reflexes is seen. Then, distal weakness starting in the lower limbs appears gradually. Especially in bedridden children, this weakness occurs rather early. Cranial nerve palsies can be observed also. Most commonly involved are the oculomotor nerves (resulting in ptosis), facial nerves and the recurrent laryngeal nerve. In essence, all these symptoms are symmetrical. VCR-induced neuropathy is slowly reversible after discontinuation of the drug.

VCR produces a dysfunction of the autonomous nervous system also. This results in constipation, ileus, and rarely urinary retention and hypotension.

VCR crosses the BBB in less than 1% of the plasma concentration. In accordance, Johnson et al (1973) reported an incidence of seizures which could not be attributed to causes like meningeal leukemia, intracranial bleeding or electrolyte disturbances, of only 1% in 350 children. Dieterich et al (1978) stated to have seen no seizures in 188 children during VCR treatment nor EEG changes attributable to VCR in 67 children.

However, inappropriate secretion of antidiuretic hormone resulting in hyponatremia and seizures have been reported by others. Mental changes, confusion, speech difficulties, delirium, slow mentation, hallucinations, and coma have also been described (reviewed by Hildebrand 1978).

Daunorubicin

Daunorubicin (DNR) is a glycosidic anthracyclene antibiotic which intercalates between adjacent base pairs on a DNA strand.

Daunorubicin, which is administered intravenously, does not cross the BBB. Toxicity consists primarily of bone marrow depression and gastrointestinal disturbances; with higher cumulative doses, cardiac toxicity becomes evident. No specific neurological toxic effects have been reported.

Prednisone

Prednisone (PRED) and prednisolone are glucocorticoids, which have numerous and diversified effects in vivo. In this context, some of these have to be mentioned.

Glucocorticoids cause a rapid lysis of lymphatic tissue, especially striking in cells of the thymus: within 1 - 3 hours after administration of glucocorticoids to rats or mice, dissolution of lymphocytes in lymphoid tissue becomes apparent. This effect is mediated by glucocortoid receptors on the membrane of lymphocytes or lymphoblasts. In man, this effect is less pronounced, although in Cushing's syndrome lymphocytopenia and reduced lymphoid tissue mass are seen indeed. Especially leukemic lymphatic cells suffer from this lympholytic mechanism (Thompson et al 1983).

Administration of glucocorticoids leads to an increase in the number of granulocytes in blood, probably as a result of an increased rate of entrance of granulocytes into the blood from the bone marrow.

Administration of corticosteroids influences the electrolyte and water balance: an enhanced reabsorption of sodium from the renal tubular fluid into the plasma occurs, with a consequent expansion of the extracellular fluid volume. Such changes may indirectly affect the CNS.

It has been shown that steroids (prednisone and hydrocortisone) inhibit cellular uptake of MTX (Bender et al 1975).

After withdrawal of corticosteroids, a characteristic, socalled "withdrawal syndrome" consisting of fever, myalgia, arthralgia and malaise may occur. Sometimes symptoms of pseudotumor cerebri with papilledema are seen.

Prednisone crosses the BBB (Balis et al 1987); in a dosage of 40 mg/m2 it can reduce cerebral edema associated with surgical and other brain trauma or malignancies. It has also effects on mood, behaviour and brain excitability. In patients with Cushing's syndrome, slowing of background rhythm in the EEG is seen, which pattern is reversible.

Thus, neurological adverse effects are behavioural disturbances like nervousness, restlessness, aggressivenes, insomnia, euphoria, other changes in mood

and even psychopathies of the manic-depressive or schizophrenic type. Also signs of water and salt retention, hypertension, hypertensive encephalopathy and signs of pseudotumor cerebri are mentioned as probably indirect neurological toxicity.

L-asparaginase

L-asparaginase (L-ASP) is an enzyme derived from Escherichia Coli or Erwinia Carnotovera. Its combination with VCR and PRED has significantly improved the rate of remission of induction treatment in childhood acute lymphocytic leukemia (Ortega et al 1977). The enzyme hydrolyses L-asparagine, thereby depleting the supply of this amino acid to leukemic cells, which are unable to synthesize this amino acid. L-glutamine is depleted also. The use of this enzyme takes advantage of metabolic differences between malignant leukemic cells and normal host cells. Normal cells, however, suffer also from the action of L-ASP resulting in a disturbed protein synthesis, although in a lesser degree. This results in a wide variety of adverse reactions due to L-ASP, apart from the frequent hypersensitivity reactions. L-ASP does not cross the BBB, but the depletion of L-asparagine and L-glutamine in the serum leads to a secondary depletion of these amino acids in the CSF.

The reported frequency of CNS toxicity varies from 25% to 50%. Symptoms consist mostly of lethargy, somnolence or confusion and the incidence of these side effects were related to the dosage of L-ASP (Oettgen et al 1970). Other less frequently reported side effects include personality changes, in particular depression, and also acute brain syndrome, seizures and coma (Ohnuma et al 1970, Land et al 1972, Pochedly 1972, Weiss et al 1974).

In 75 - 85% of patients studied with an EEG, a reduced frequency of the basal rhythm and the presence of diffuse slow waves was seen (Moure et al 1970, Land et al 1972). This has been related to metabolic alterations in the CSF caused by the depletion of L-asparagine and L-glutamine (Pochedly 1972, Weiss et al 1974).

Methotrexate

Methotrexate (MTX) represents the most commonly used cytostatic in the treatment of acute leukemia. It inhibits dihydrofolate-reductase (DHFR) by

binding to it, thus inhibiting the formation of tetrahydrofolate. This coenzyme acts as a carrier of one-carbon units in the formation of purines and thymidylate. Depletion of the tetrahydrofolate pool results in inhibition of DNA synthesis. Citrovorum factor (folinic acid, 5-formyltetrahydrofolate) bypasses the metabolic block of MTX and can be used to rescue cells from the effects of MTX, provided it is given within about 48 hours after the administration of MTX. This rescue is considered to act selectively on normal cells.

MTX is poorly transported across the blood-cerebrospinal fluid barrier. However, when given in moderate or high dosage by i.v. infusion, MTX enters into the CNS and is equally distributed in the CSF. Under these circumstances, the concentration of MTX in the CSF is between 1 and 3% of that in plasma (Shapiro et al 1975, Freeman et al 1977, Bleyer and Poplack 1978).

When administered intrathecally, distribution in the CSF and especially in the ventricular CSF is variable and unpredictable: ventricular concentration of MTX is less than 10% compared with that in the lumbar sac (Shapiro et al 1975, Bleyer and Poplack 1978). It is assumed, that concentrations of MTX in the CSF up to the level of the cisterna magna are comparable with those at the lumbar level, when MTX is given intrathecally (Shapiro et al 1975). This can explain the effectiveness of the substitution of spinal irradiation by 5 intrathecal MTX injections as a prophylaxis for CNS leukemia.

When given by intraventricular injection however, MTX is fairly evenly distributed over the intraventricular and lumbar CSF (Shapiro et al 1975, Bleyer and Poplack 1978).

The neurotoxicity depends on the route of administration. When given intrathecally, a meningeal syndrome, sometimes associated with paresis or paralysis may develop. It also may lead to encephalophatic syndromes. After intraventricular administration, convulsions or encephalopathic symptoms may occur, especially during treatment for CNSL. When given in high dosages by intravenous infusion, convulsions with a transient hemiparesis or a transient encephalopathy may be seen (Allen and Rosen 1978). The degree and signs of neurotoxicity of MTX depend also on the previous or concomitant use of other routes of administration or the application of radiotherapy (vide infra).

6-Mercaptopurine

6-Mercaptopurine (6-MP) is a hypoxanthine analoque, which after several

metabolic conversions is incorporated in DNA as a false nucleotide, resulting in cell death.

After oral administration, low plasma levels are obtained. It has been shown, that CSF levels of 6-MP are about 45% of those of plasma during maintenance treatment with 50 mg/m2 oral 6-MP (Schouten et al 1984).

Toxicity concerns primarily bone marrow depression, which develops gradually. Anorexia, nausea and vomiting are common manifestations, presumedly of gastrointestinal toxicity. No specific neurotoxic effects have been reported.

Cytosine-arabinoside

Cytosine-arabinoside (cytarabine)(ARA-C) is a pyrimidine analoque, which selectively inhibits DNA-synthesis by the incorporation of the active metabolite ARA-C-triphosphate into DNA.

When injected intravenously, it is rapidly inactivated by deamination to arabinoside-uracil. Given by continuous intravenous infusion, levels reached in the CSF are about 40% of those in plasma. After intrathecal administration, relatively little deamination occurs, resulting in a half-time of 2 hours (Ho and Frei 1971).

Reported toxicity is primarily myelosuppressive and gastrointestinal. Nausea and vomiting are frequently seen after i.v. and i.th. administration; these may be direct neurological effects of this drug. Drugfever of short duration may occur especially after i.th. administration and after i.v. delivery of high doses of ARA-C. Ataxia and other cerebellar symptoms have been described after high i.v. dosages (Lazarus et al 1981, Salinsky et al 1983).

Cyclophosphamide

Cyclophosphamide (CYT) belongs to the group of nitrogen mustards; this alkylating agent can be administered orally and has to be metabolized to become biologically active.

Only minute amounts of CYT penetrate into the CSF.

Toxicity is primarily myelosuppressive and immunosuppressive. Alopecia occurs frequently. A specific toxic effect on the urinary bladder may become evident as a hemorrhagic cystitis.

Nausea and vomiting are common and may be the result of a direct effect on

the CNS. With high dosages (> 40 - 50 mg/kg) the syndrome of inappropriate antidiuretic hormone secretion has been observed. No other specific neurotoxic effects have been reported for CYT, in contrast to the other nitrogen mustards.

Summarizing, most drugs used in the treatment of ALL have some neurotoxic side effects of their own. These may depend on the route of administration, the dosage and the cumulative dosage. However, as leukemia treatment consists of a combination of drugs, it is not always easy to attribute a certain side effect to a specific drug.

Neurotoxicity of radiotherapy

Acute effects of radiotherapy on the central nervous system are uncommon. Radiation-induced cerebral edema may occur during the first week of treatment, in particular when larger than conventional fractions (> 200 rads) are used. If necessary, steroids can be given to counteract the symptoms.
Transient symptoms, attributed to temporary demyelination occur 3 - 9 weeks after completion of radiotherapy to the brain. This "somnolence syndrome" or "postirradiation syndrome" has been reported to occur in up to 79% of children treated with cranial irradiation for ALL. It usually disappears spontaneously within a few weeks. A similar subacute reaction following spinal cord irradiation is described as Lhermitte's syndrome, consisting of shock-like paresthesias of the extremities during neck flexion. This usually appears about 8 weeks after completion of radiotherapy and may persist for up to 3 months.
Late effects are more severe and usually irreversible. The damage to the CNS is likely due to a combination of direct injury of glial cells, especially oligodendroglia, and damage to the vasculature. Cell injury predominates in the first months and years after treatment, whereas vascular damage becomes apparent later, after several months to years. Histologically, constriction due to medial fibroblastic thickening and focal degeneration of the elastic membrane is seen. This may render the vessels better permeable for cytostatics, contributing to the toxic effects of systemic treatment. Partial or

total thrombosis may occur (Wright and Bresnan 1976 , Hildebrand 1978) with patchy necrosis in the brain tissue as a consequence.
In leukemic children, the combination of cranial irradiation with intrathecal therapy, and the maintenance treatment with systemic MTX after irradiation is thought to be the cause of abnormalities on CT scan and other late effects, like impaired psychomotor and intellectual function and neuroendocrine abnormalities (Eiser 1978, Bode et al 1985, Jannoun and Chessels 1987). Although reduction in growth hormone is reported, linear growth is stated to be relatively unaffected (Shalet et al 1975, 1979, Swift et al 1978). In our experience however, growth during puberty is much less accelerated in children after cranial irradiation, resulting in a deficit of 10 - 14 cm in final height.

Neurological syndromes

Meningeal syndrome

The meningeal syndrome is caused by a chemical arachnoiditis, induced by an intrathecal injection of MTX or less often of ARA-C. It is seen especially after the administration of intrathecal drug injections given repeatedly with short intervals.
Symptoms usually occur within 2 - 4 hours after i.th. injection of MTX, but may appear up to 72 hours thereafter. They consist of headache, vomiting, nuchal rigidity, Kernig's sign, photophobia, delirium and obtundation. Sometimes, partial or total paralysis may occur. The frequency of this syndrome varies according to different reports from 10% to 90%. This syndrome occurred especially in patients with meningeal leukemia (reviewed by Hildebrand 1978).
CSF changes consist of an increase of mainly mononuclear cells, and an increase in protein. Differentiation from an infectious cause may be difficult. The neurotoxicity of i.th. MTX in this respect was shown to be more frequent and more severe in cases whith high MTX concentrations in the CSF (Bleyer et al 1973).

Postirradiation syndrome

Druckmann (1929) presented the first description of the postirradiation syndrome (PRS) in 30 of 110 children who had been irradiated on the head for a Trychophyton infection. Six to eight weeks after the treatment apathy, slow speech, sleepiness and anorexia were present in these children. In most of them, slight fever up to 38.5 °C was noticed. A few had headaches. These symptoms had been present for 4 to 14 days, depending on the severity of the syndrome and subsequently vanished completely.

With the incorporation of prophylactic central nervous system irradiation in the treatment of children with acute lymphocytic leukemia, this syndrome was also recognized in these patients, at first by Freeman et al in 1973.

The reported incidence of this syndrome varies widely. Von Lieven et al (1976) saw this in 3%, Hustu et al (1973) in 10%, Terheggen and Rado (1978) in 69% and Freeman et al (1973) in 79% of children. However, no mention of this syndrome was made by Sackmann-Muriel et al (1974). Willoughby (1976) especially stated that no encephalopatic syndrome was found in 29 children, irradiated for central nervous system leukemia. This variance in the reported incidence of PRS could be due to the difference in awareness of this syndrome and the precision of recording of possible related symptoms by the investigators. Freeman et al already pointed out in 1973 that the true occurrence of PRS could only be elucidated by specific questioning of the parents. This was later once more underlined by Terheggen and Rado (1978).

The first clinical signs of PRS were seen between 24 days and 8 weeks after the end of the prophylactic cranial irradiation (Druckmann 1929, Freeman et al 1973, von Lieven et al 1976, Terheggen and Rado 1978). The duration of symptoms varied between 3 and 49 days (Terheggen and Rado 1978).

Symptoms consist of tiredness, sleepiness, apathy and lethargy; less frequently, headaches, vomiting, ataxia, slurred speech, slight fever, enhanced reflexes and wordfinding disturbances are seen.

Slight pleiocytosis in the CSF as well as increased protein content may occur (Freeman et al 1973, Hustu et al 1973). EEG's were obtained in some patients; a moderate to severe generalized slowing of the background rhythm was found in most of the investigated children (Aronson et al 1974, Terheggen and Rado 1978).

The PRS has been observed in children, prophylactically treated with craniospinal irradiation as well as in those treated with cranial irradiation com-

bined with intrathecal MTX and also in patients, treated with cranial irradiation only (Druckmann 1929, Freeman et al 1973, Hustu et al 1973, Aronson et al 1974, von Lieven et al 1976, Terheggen and Rado 1978). Therefore, it is generally accepted, that this syndrome is evoked by irradiation. Freeman et al (1973) reminded that irradiation temporarily disturbed myelinisation, as was shown in animal studies (Reynolds 1946, Arnold et al 1954, Innes and Carsten 1961).

Subacute necrotizing encephalopathy

Subacute necrotizing encephalopathy is a relatively uncommon form of delayed neurotoxicity. It occurs especially in patients who have received cranial irradiation together with intrathecal and/or systemic methotrexate treatment (Price and Jamieson 1975, Rubinstein et al 1975, Bleyer and Griffin 1980). It has also been reported to occur rarely in children who had received only intrathecal or intravenous MTX or only cranial irradiation in relatively high doses. Most frequently, it occurs in children who had received all three modalities of CNS treatment in combination (Price 1983). It is stated, that the risk of developing a leucoencephalopathy is related to the total radiation dose and to the cumulative dose of systemically administered MTX (Bleyer and Griffin 1980). These authors calculated that the risk for the development of a leukoencephalopathy ranged from less than 1% to 45% depending on the treatment given (table 1).

Table 1. Risk of leukoencephalopathy.
(Bleyer and Griffin 1980)

Cranial irradiation	(> 2000 rad)	< 1 %
MTX i.th.	(> 50 mg cumulative)	< 1 %
MTX i.v.	(> 40 - 80 mg/m2/week)	< 2 %
MTX i.v. + MTX i.th.		2 %
Cranial irradiation + MTX i.th.		5 %
Cranial irradiation + MTX i.v.		15 %
Cranial irradiation + MTX i.th. + MTX i.v.		45 %

Histopathologically, demyelination is found. First, axonal swelling and fragmentation occur, followed by the development of focal areas of white matter necrosis and reactive astroglyosis. The focal areas become confluent, leading to extensive white matter degeneration and cavitation. Varying amounts of mineralized cellular debris can be found. The gray matter remains unaffected. On CT scans, these changes become visible as hypodense areas and as a sharper distinction in density between white and gray matter. Focal hypodensities may occur also. Atrophy of the white matter and extensive subcortical calcifications can be seen later.

Leukoencephalopathy may become evident after a variable period of time after irradiation. Most frequently, symptoms develop 4 - 12 months after completing radiotherapy (Price and Jamieson 1975, Bleyer and Griffin 1980).

Symptoms may at first be fairly discrete and varied, consisting of poor school performances, personality changes and slight gait disturbances. These may progress to mild confusion, lethargy, dysarthria, dysphasia, aphasia, ataxia, spasticity, progressive dementia, seizures, decerebration, coma and death. Most often however, it presents as a acute, severe neurological disturbance, which unpredictably may follow a more or less rapid downhill course. It may also become stationnary or even show improvement, although these patients are nearly always left with neurological abnormalities.

Mineralizing microangiopathy

Price and Birdwell (1978) described mineralizing microangiopathy, as a form of delayed neurotoxicity in children treated with crXRT and i.th. or i.v. MTX. This disease affects predominantly the gray matter, mainly the putamen, cerebral cortical sulci, and, less frequently, cerebellar gray matter. Histologically, deposits of calcium are found in small vessels. The lumens of smaller vessels can be totally occluded by mineralized debris. Primarily affected are the smaller arteries, precapillary arterioles, capillaries and venules. Varying amounts of mineralized necrotic brain tissue are present around the diseased vessels. There are no signs of inflammation.

The clinical consequenses of these destructive changes in specific areas of the brain are not clear. In the autopsy series, described by Price, it was not the cause of death. In his series of 28 children with mineralizing microangiopathy, only 4 had shown signs of abnormal CNS functions. These consisted of headaches, focal seizures, extremity discoordination, gait abnormalities

and transient abnormal EEG's. In one child, somnolence occurred 1.5 years after cranial irradiation (Price and Birdwell 1978). On the other hand, McIntosh et al (1977) reported neurological problems, consisting of ataxia, perceptual-motor disabilities and seizures in 8 out of 10 children with calcifications on CT scan. These calcifications had been found in 10 of 29 children, surviving in first complete remission for more than 9 months after CNS irradiation.

When mineralizing microangiopathy and leukoencephalopathy coexist, the clinical symptoms of leukoencephalopathy will predominate.

Radionecrosis

Radionecrosis is an infrequent late complication of radiotherapy. Most cases have been reported in adults, but it may also be seen in children (Wright and Bresnan 1976, Sheline 1980). It occurs in 0.1 to 1% of patients treated with irradiation of 5000 - 6000 rads to the brain at a dose fraction of 150-200 rads (Sheline 1980). Such dosages are given to patients with cerebral tumors. Radionecrosis has not been reported after prophylactic cranial irradiation with less than 2500 rads.

Histopathology is marked by hyalinization, thickening and necrosis of blood vessels, often associated with tissue necrosis. Coagulation necrosis, involving both gray and white matter, is seen. Marked astrogliosis, often with bizarre multinucleated cells, is usually found.

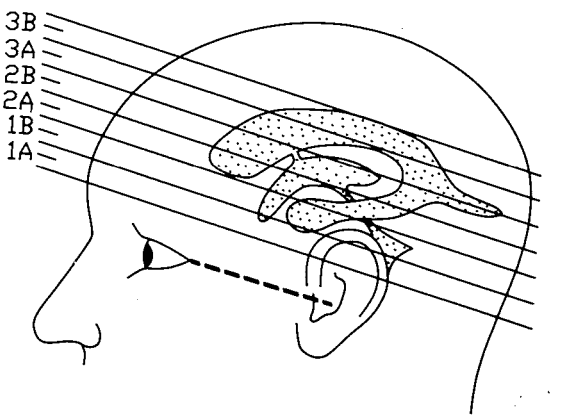
On CT scan, a mass lesion with surrounding edema is usually present. The differentiation between radionecrosis and tumor is often difficult. Angiography may be necessary: radionecrotic areas are avascular in contrast to abnormal neovascularity seen in tumors (Deck 1980).

Children with radionecrosis usually develop symptoms between 6 months and 3 years (range 1 month to 12 years) after irradiation. The clinical presentation is dependent on the location of the lesion in the CNS. Most patients have signs of increased intracranial pressure in addition to more focal neurological defects. Especially headaches, personality changes , seizures, ataxia, hemiparesis and obtundation are observed.

Cranial computer assisted tomography

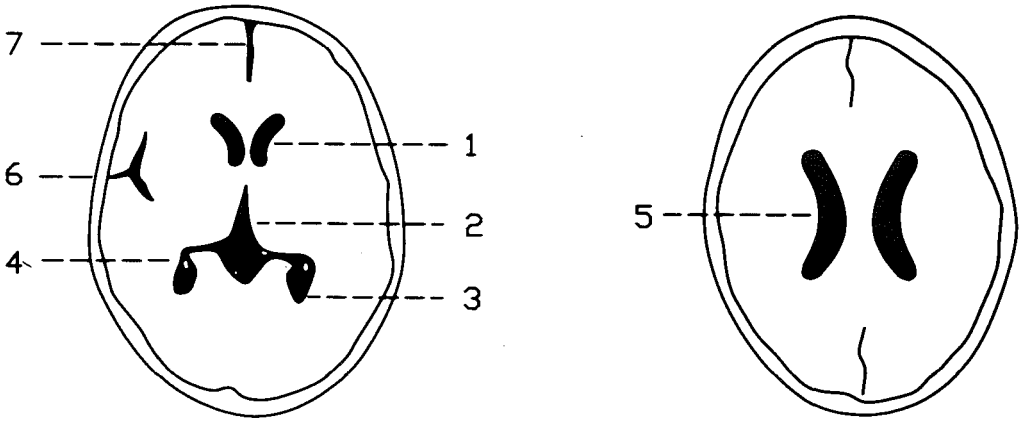
Computertomography was discovered by Hounsfield and was presented for the first time in the literature in 1973. The principle of this technique consists of the passing of a fine beam of X-rays through a transverse body slice and the registration of an intensityprofile on a detector behind the film. By rotating around the body slice, a multitude of intensityprofiles is obtained. A computer then calculates all data and forms a spatial image of the slice under investigation. An image of the upper and lower side of this slice is obtained with a high contrast since there is no overprojection of the different intensities as is the case in convential X-ray imaging.
Cerebral CT scans are made along slices parallel to the orbitomeatal line. With an EMI 1010 scanner, slices of 13 mm thickness are obtained; each pixel has a volume of 1.5 x 1.5 x 13 mm3. Usually, 6 to 8 images are made, which are designated 1A, 1B, 2A, 2B etc. (figure 1).

Figure 1. Localization of CT scan slices



Thus, standard images of the cerebrum are obtained. Structures within the skull, in particular ventricles and sulci are visualized (figure 2). With this technique, it became possible to study the anatomy of the brain without invasive procedures.

Figure 2. Common ventricular images on CT scan.



1. Frontal horn
2. Third ventricle
3. Posterior horn
4. Plexus chorioideus
5. Cella media
6. Fissura Sylvii
7. Fissura interhemispherica

The preciseness of the CT image depends on the number of units (pixels) which compose the picture in horizontal and vertical directions (matrix) and also depends on the differences in contrast. The first generation of CT scanners had a matrix (collimator) of 80 x 80, the second generation such as the EMI 1010 scanner had a collimator of 160 x 160. Later generations were equipped with 256 x 256 or higher collimators. With later generations of CT scanners, the resolution of the images have become better. Thus, structures, not visible on pictures made with early CT scanners, are visible when later generation scanners are used. Therefore, the CT scanner used has to be mentioned for a correct interpretation of the images obtained.

The imaged density, i.e. absorption of X-rays by a structure, is given in arbitrarily units, socalled Hounsfield Units (HU). At first, these ranged from -500 for air to +500 for bone, while water had a density of 0. Later on, the lower and upper limits were set to -1000 and +1000 resp.. Each absorption coëfficient, i.e. HU, is made up of the mean of absorptions of all different structures in a given pixel. Thus, all structures, which are partly within that pixel, influence the intensity of contrast: a small piece of structure

with a high density, like a calcification, can heighten the mean considerably, while a structure with a small difference in density in relation to cerebral tissue, like CSF, has little impact on the mean value. This may limit the detection of small abnormalities and may also explain why ventricles and sulci seem to be a little bit smaller on CT scan than in reality (partial volume phenomenon).

Each picture is made up of 10 steps in shades of "grays" from black at low HU-levels to white at high HU-levels. These may be positioned at will along the HU-scale. The "window level (WL)" offers the position of the middle of the scale of grays. The "window width (WW)" determines the range of the scale of grays. With the EMI 1010 and with the range of HU from -500 to +500, the usual settings of these windows are +18 for "window level" and 40 (range -2 to +38) for "window width"; with a HU range of -1000 to +1000, WL is set at +36 and the WW-range from -4 to +76.

Within the HU range from -500 to +500, the HU for fatty tissue is in the range from -50 to -10, for water at 0, CSF at +2, edema at about +2 to +10, white matter at about +10 to +18, gray matter at about +18 to +26, hemorrhages at about +26 to +38, and bone in the range of +200 to +500.

Intracerebral hemorrhages show a high density of roughly about +30 - +40 HU; hemorrhages are resorbed in 2 - 4 weeks. Infarctions on the other hand show a low density of about 0 - +10 HU and, most of the times, become visible after 3 - 4 days. Leukemic mass infiltrations ("chloromas") or lymphomatous masses show a density in the same range as hemorrhages, with sometimes an enhancement by contrast medium.

Normal values for cerebral CT scans in children

Normal values for cerebral CT scans are usually derived from scans obtained from patients with minor or vague complaints in whom no neurological abnormalities are found during follow-up. These values may also be obtained from scans of patients in whom no abnormalities or predictable anatomic defects are expected. There are only a few reports with "normal" values for CT scans in children as is also the case for adults.

Huckman et al (1975) examined cerebral atrophy in patients over the age of 60 years with the aid of a CT scan. One group consisted of 35 patients with senile dementia, the other group concerned 20 patients with mainly headache

or dizziness but with no major neurological abnormalities. Although no particulars were given, the scanner must have been one of the early generations. Measurements were made on the films with a translucent millimeter ruler. The following dimensions were measured:

I. The frontal horn span (A)
II. The bicaudate width (B)
III. The total width of the 4 largest cortical sulci seen in the highest three tomographic cuts.

The sum of the frontal horn span and the bicaudate width (A + B) was taken as the measurement of the ventricular size. The third measurement represented the degree of sulci enlargement. On the basis of these measurements each of the cases was put into one of five categories as judged by CT examination (table 2). Thus, normal ventricular size, defined as " frontal horn span + bicaudate width ", should be 15 mm or less, while questionable ventricular enlargement should be between 16 and 20 mm. To attain the actual dimensions these values had to be multiplied by a factor 3.63. These are then 54.45 mm and 58.08 - 72.6 mm respectively. Based on these definitions, the upper limit of normal for ventricular size according to this socalled Huckmannumber (A + B) is 57 mm in patients aged 60 years or over.

Table 2. Categories of CT scans for adults aged over 60 years Measures on röntgenfilms (Huckman et al 1975)

Interpretation	Ventricle size mm	4-Sulci size mm
1. Normal	=< 15	=< 5
2. Questionable atrophy	16 - 20	=< 5
	=< 15	6 - 9
3. Mild atrophy	16 - 20	6 - 9
4. Moderate to severe atrophy	16 - 20	> 9
	> 20	6 - 9
	> 20	> 9
5. Ventricle enlargement only	> 20	=< 5

Hahn and Rim (1976) studied more than 1500 CT scans retrospectively. The CT scans of 180 patients who were ultimately considered neurologically normal were evaluated to define normal values. CT scans were also obtained from 20 healthy volunteers. These 200 "normal" individuals included 97 males and 103

females aged 10 to 81 years. Only 5 children between the age of 10 and 15 years were involved. The type of scanner was not mentioned, but must have been one of the first or second generation. All Polaroid images were transposed on 35 mm film and projected with the proper magnification on the screen of a Vanguard Motion Analyzer. The dimensions measured concerned:

I. The maximum bifrontal diameter
II. The first transverse dimension of the brain, measured on the same level as I
III. The maximum bicaudate diameter
IV. The second transverse dimension of the brain, measured on the same level as III

The ratios between I/II and III/IV were calculated. These were named as the first and second cerebroventricular index (CVI) respectively. Each ratio was multiplied by 100 in order to obtain percentages. These percentages were plotted according to age. A line, representing the least square fit to all the points, was drawn through each graph. The first CVI varied from 19% to 39% with a mean value for all ages of 31% and a standard deviation (SD) of 4%. The second CVI varied from 8% to 23% with a mean for all ages of 15% and a SD of 3%. For the purpose of this study we reviewed the plots in their article. Although the number of children aged less than 15 years was small, an increase of these percentages related to age was evident: the first CVI was approximately 28% at the age of 15 years and increased to 31% at the age of 70 years. Accordingly, the second CVI increased from approximately 13% to 17%.

Disregarding this age relationship, Hahn and Rim suggested that a first CVI (I/II * 100) of less than 18% or more than 40% and that a second CVI (III/IV * 100) of less than 8% or more than 22% could be considered abnormal.

Enzman and Lane (1977) studied patients with anorexia nervosa. In addition, 46 "normal" CT scans of children aged 1 - 15 years were evaluated. These children were scanned because of headache or seizures but showed no evidence of CNS lesions on follow-up. The scanner used was an EMI 1010.

Normal values for the anterior horn span ("A") of < 36 mm, for the maximum width of the frontal horn ("A1") of < 7 mm and for the intercaudate distance ("B") of < 15 mm were established. The ventricular system was considered to be abnormal when 2 out of these 3 measurements were abnormal. Sulci were considered to be dilated when they could be seen on the polaroid pictures. With the minification factor taken into account, this means that only

sulci greater than 3.6 mm could be visualized and thus be considered abnormal.

Because these measurements can be obtained quite easily, these values have often been used as a reference.

Pedersen et al (1979) evaluated the ventricular system and subarachnoid space on CT scans judged to be normal among a total of about 1400 CT scans. This "normal" material consisted of 155 CT scans of 155 children, aged 0.2-14.7 years, with diagnoses of epilepsy (n = 66), psychiatric disorders (n = 15), and others (n = 74) including patients with idiopathic encephalopathy, headache and focal EEG abnormalities. The scanners used were an EMI Mark I and an EMI CT 1010. Linear measurements were taken from the photographs with a transparent ruler and multiplied by a minification factor (3.3 and 3.7 resp.) in order to obtain actual dimensions. Measurements taken concerned:

1. Distance between right and left anterior horns (A)
2. Right and left septum - caudate distance (B)
3. Maximum width of third ventricle (C)
4. Minimum width of cella media (E)
5. Maximum width of interhemispheric fissure
6. Maximum width of the Sylvian fissure
7. Maximum width of hemispheric sulci
8. Maximum internal width of the skull (G)
9. Maximum external width of the skull (H)

Two indices were calculated:

Evans ratio : measurement 1 divided by measurement 8

Cella media index : measurement 9 divided by measurement 4

Since the maturation of the brain takes place in the first 2 - 3 years of life, the material was divided in a group of 46 children under 3 years of age and a group of 109 older children. The median values and the 5th and 95th percentiles were calculated (Table 3).

Table 3. Normal values for the ventricular system and subarachnoid space mm, except for the indices (Pedersen et al 1979)

Distance	< 3 years Percentile			>= 3 years Percentile		
	5	50	95	5	50	95
1 = A	12.7	33.0	38.3	26.2	33.0	39.6
2 = B	7.0	12.2	17.6	6.6	11.2	16.6
3 = C	1.9	3.7	6.6	1.7	3.3	5.0
4 = E	19.8	26.4	33.3	19.8	26.4	33.3
5	3.3	3.7	6.6	< 1.7	1.9	3.7
6	3.3	5.0	7.4	< 1.7	3.3	5.0
7	1.7	1.9	3.7	< 1.7	1.9	3.7
8 = G	85.8	109.7	127.6	108.9	123.8	138.6
9 = H	99.0	121.1	140.5	122.1	137.8	151.8
Evans	0.22	0.28	0.35	0.21	0.26	0.31
CM Index	3.7	4.4	6.1	4.2	5.2	7.4

Meese et al (1980) obtained 150 normal CT scans from healthy volunteers aged 2 - 70 years. They scanned 20 volunteers for each decade. Additionally, scans from 10 patients, aged 0.5 - 2 years, with a single (probably febrile) seizure and normal neurological and EEG findings were evaluated. Scans from 20 normal children in the age-group 3 - 10 years and 20 normal children in the age-group 11 - 20 years, were also obtained.

It proved that the normal values in the first two decades of life were differing significantly from those in all other age-groups. A separate set of normal values was even required for children under 2 years of age. In children over 2 years of age, normal values for the intercaudate distance were <= 20 mm, for the width of the third ventricle <= 7 mm and for the cella media index >= 4.0 (Table 4).

Table 4. Normal values for CT scans in children according to Meese et al

	< 2 years	>= 2 years
I. Huckmannumber (A + B)	<= 35 mm	<= 45 mm
II. Frontal horn index (F/A)	>= 3.5	>= 3.7
III. Cella media index (H/E)	>= 3.8	>= 4.0
IV. Width 3d ventricle (C)	<= 5 mm	<= 7 mm

CT scan abnormalities in childhood leukemia

At the start of this prospective study, only a few reports on CT scan abnormalities were present (Müller et al 1976, McIntosh et al 1977, Peylan-Ramu et al 1977). In 1978 some other reports concerning CT scan investigations were published (Peylan-Ramu et al 1978, Enzmann and Lane 1978, Casteels-van Daele et al 1978, Mott and Bullimore 1978, Day et al 1978, Wendling et al 1978). All these studies were retrospective and concerned single CT scans. Most authors had used the criteria of Enzmann and Lane (1977) as a reference.

The earliest publications concerned case reports about specific observations on CT scans, mainly as a result of clinical complications.

Müller et al (1976) described 3 children with meningeal leukemia and with paraventricular calcifications after i.th. MTX. Their first diagnostic X-ray or CT scan investigations had been performed at 26, 19 and 31 months resp. after meningeal leukemia had been diagnosed. One child had also shown ventricular and sulcal dilatation.

Peylan-Ramu et al (1977) investigated 5 children with ALL and with symptoms of leukoencephalopathy, 8 - 72 months after CNS prophylactic or therapeutic irradiation. Three of them suffered from CNS leukemia. All 5 showed CT scan abnormalities, consisting of ventricular and/or sulcal dilatation, hypodensities or calcifications.

Wendling at al (1978) reported on a child with transient periventricular hypodensities after CNS prophylaxis with cranial irradiation and intrathecal methotrexate.

Later publications concerned cross-sectional studies of larger groups of children. CT scans had been performed at variable intervals either after CNS prophylaxis or after treatment for CNS relapse.

McIntosh et al (1977) reported on intracranial calcifications on CT scans in children in first complete remission. CNS prophylaxis consisted of 2400 rads cranial irradiation combined with 5 i.th. injections of MTX. Maintenance therapy consisted a.o. of MTX 80 mg/m2 i.v. biweekly or MTX 20 mg/m2 orally weekly. In 9 children scans were obtained within 7 weeks after diagnosis du-

ring chemotherapy but prior to CNS-prophylaxis. No calcifications were seen. In 39 children scans were obtained between 5 months and 6 years after CNS-prophylaxis. In 10 (25%) of these children, calcifications were found. Eight of these 10 children had shown clinical signs of chronic CNS toxicity. The authors suggested that a cumulative dose of 4.5 gram MTX/m2, most of which had been given intravenously, predisposed for the occurrence of calcifications. Twenty five children had been fully evaluated. Among 11 children who had received less than 4.5 gram MTX/m2 only 1 (9%) showed calcifications. This was in contrast to the presence of calcifications in 9 of 14 (64%) patients who had received a higher cumulative dose. Moreover, all 10 children with calcifications had also received ARA-C i.v. (table 5), probably indicating a synergistic effect for the induction of calcifications.

Table 5. Calcifications in childhood leukemia
(McIntosh et al 1977)

total pts n	abnormal n	%	ARA-C i.v.	Cumulative dose gram MTX/m2 i.v. or p.o. =< 4.5	> 4.5
11	1	9		+	
14	9	64			+
6	0	0	-	+	
5	1	20	+	+	
3	0	0	-		+
11	9	82	+		+

Peylan-Ramu et al (1978) examined 43 children in first remission from ALL with an EMI Mark I or an EMI 1010 scanner. The criteria of Enzmann and Lane were applied. They established an overall incidence of abnormal CT scans of 42%.

Eleven children in whom no CNS prophylaxis with either irradiation or intrathecal therapy had been given were scanned 16 - 149 months after the end of treatment. In only one of them (9%) ventricular dilatation was found.

Thirty two children were scanned 19 - 67 months after prophylactic CNS-irradiation; 17 (53%) showed abnormalities. In 14 of these children, intrathecal MTX had been administered during the period of irradiation and once

monthly thereafter; hypodensities were found in 4 and calcifications in 1 of them. In the other 18 children, intrathecal ARA-C had been given instead; no hypodensities or calcifications were present in these children. Ventricular or sulcal dilatation was found in 7 children of the former and in 10 children of the latter group.

Casteels-van Daele et al (1978) reported an incidence of 50% of abnormal CT scans in 20 children without CNS leukemia, who had been scanned more than 36 months after CNS prophylaxis. Neither the scanner nor the reference values were mentioned.

Mott and Bullimore (1978) however, found only 2 abnormal scans among 28 children (7%), scanned 20 - 84 months after CNS prophylaxis with cranial irradiation and i.th. MTX. Again, no mention about the scanner or normal values was made.

Day et al (1978) performed CT scans in 27 children 4 months to 4 years after CNS prophylaxis with 2500 rads cranial irradiation and i.th. MTX. All children were asymptomatic and had not suffered from meningeal involvement. The type of scanner was not stated. As normal values, those according to Enzmann and Lane and those according to Hahn and Rim were used. In four children, sulci were stated to be more obvious than in the others, but were considered to be within normal limits. In only one child (4%), enlarged ventricles according to the criteria of Enzmann and Lane were found. The authors considered the possibility of an intracranial hemorrhage at diagnosis as a cause of this enlargement. According to the criteria of Hahn and Rim all scans were considered normal.

Kolmannskog et al (1979) performed CT scans with an Delta Scanner 50 FS or an EMI 5005 scanner. Normal values were according to Enzmann and Lane. Nineteen children with ALL in first complete remission were investigated. The age of the children ranged from 3 to 14 years. Scans were obtained 2 to 64 months after the CNS prophylaxis was finished. CNS prophylaxis consisted of i.th. MTX and moderate dose i.v. MTX infusions. Only one child showed a small lesion in the region of the insula. This abnormality could hardly be seen one year later. The authors investigated also 3 children 5 to 60 months after CNSL had developed. These children had received monthly MTX intrathecally as maintenance. None showed enlarged ventricles, one had slightly dilated sulci.

Ochs et al (1980) obtained CT scans with an Ohio Nuclear Delta Scanner, Model 50 with a 8-mm collimator. Some children were reexamined with an EMI

1010 scanner in high-resolution mode. The results did not differ from those obtained with the Ohio scanner. Normal values were those according to Enzmann and Lane. They studied 43 asymptomatic children with ALL in continuous complete remission. The ages at the time of diagnosis ranged from 22 months to 17 years. The CNS prophylaxis consisted of i.th. MTX in 10 patients and i.th. MTX combined with intermediate dose i.v. MTX in 33 patients. The time interval from completion of CNS prophylaxis to CT scanning ranged from 10 - 59 months. Eight CT scans (19%) were abnormal. Only one of these was clearly abnormal showing mildly dilated ventricles and sulci. Three children had borderline dilatation of the lateral ventricles as well as visualization of the cortical sulci. Four patients had visualization of cortical sulci. In none of the children hypodense areas or calcifications were found. None of the children showed clinical signs of leukoencephalopathy.
In addition, 13 children were scanned within 24 hours of diagnosis of ALL, and prior to institution of chemotherapy. Two CT scans (15%) were considered abnormal: one showed minimal ventricular dilatation and visualization of the sulci, and one showed visualization of the sulci only. A third group consisted of 50 noncancer pediatric patients in whom neurological examination was normal, who were scanned because of recurrent headaches. In two children (4%) minimal ventricular dilatation combined with visualization of the sulci was found.

Esseltine et al (1981) studied 26 long term surviving children with ALL. All children were in first CR and without CNSL. The median time from diagnosis till scanning was almost 7 years (range 4 - 12 years). Seventeen children were off therapy. Fourteen children had received cranial irradiation with 2400 rads plus intrathecal MTX and 12 had received i.th. MTX alone. A Delta 50 FS scanner was used. Six abnormal CT scans were seen among the irradiated patients (43%) and three in the children treated with i.th. MTX alone (25%). This difference was not statistically significant. The abnormalities consisted of ventricular dilatation and cortical atrophy in three (2 and 1 per group respectively), lateral ventricular asymmetry in three (1 resp. 2), atrophy alone in one and calcifications in two. The latter two abnormalities were only found in the irradiation group. Both children with calcifications were on anticonvulsive medication; the onset of seizures occurred 4.5 years after CNS prophylaxis.
Two patients were on steroids at the time of CT scanning, one had a normal scan and the other lateral ventricular asymmetry. These authors noted, that

neither the time of onset of CT brain scan abnormalities, nor their potential reversibility had been defined. They therefore stressed the need for a prospective study.

Allen et al (1981) investigated 42 children with various systemic malignancies in complete remission. CT scans were made with a Delta Scan 50 CT scanner. Normal values were those according to Hahn en Rim. Seventeen children with ALL were included. Ten of them had received CNS prophylaxis with i.th. MTX, seven had received 2400 rads crXRT and i.th MTX. Hypodensities were seen in 2 children of the first group and enlarged sulci in 2 children of the latter group. In the 25 children with other malignancies, two showed abnormal hypodense areas and 2 showed enlarged sulci. Additionally, 9 children with ALL and multiple systemic and meningeal relapses were investigated. One of them had hypodense areas on the CT scan and 6 had enlarged sulci. All showed enlarged ventricles. In four of these 9 children, follow-up scans had been obtained. These showed the same abnormalities as before.
Also, 7 children with sarcomatous meningitis were scanned. In all patients enlarged ventricles were found and one of them had also enlarged sulci. In four children, scans were repeated. The original abormalities were still present. One patient had developed hypodensities and calcifications after 6 months of intraventricular MTX and ARA-C.

Metz et al (1983) examined 42 children with ALL or non-Hodgkin lymphoma (NHL) with a Siemens Somatom 2 scanner. Eighteen children had received i.th. injections with 198 radiogold colloid as CNS prophylactic treatment. The normal values were not stated. In 17 children CT scans were performed 3 - 7 years after the start of treatment. All were in continuous first complete remission and off therapy. Slight abnormalities, which were considered to be physiological deviations were seen in 3 children.
Eight children were examined before CNS prophylaxis. Two children showed minimal cortical atrophy and one had minimal enlargement of the Fossa Sylvii. The scans of these three children were not classified as pathological however.
Six children were examined 10 months to 8 years after crXRT with 1800 - 2250 rads and i.th. MTX. Ventricular dilatation was seen in one patient, and in combination with sulcal dilatation in one other. Sulcal dilatation only was found in one child. Calcifications were present in one other patient.
Ten children were investigated either during florid central nervous system leukemia or while in remission of a CNSL. All these children had received

crXRT as CNS treatment. Those, who had earlier CNS prophylaxis with radiogold showed no abnormalities on CT scan. Among the other six, who had received earlier CNS prophylaxis with cranial irradiation, 4 showed ventricular and sulcal dilatation, one of whom also had calcifications, and one showed only sulcal dilatation.

Habermalz et al (1983) investigated 64 children with ALL or NHL with the aid of an EMI 1010 scanner. All were in continuous complete remission and 2 months to 7 years after the end of treatment. CNS prophylaxis consisted of cranial irradiation with 850 - 2400 rads and i.th. MTX. Normal values were those of Enzmann and Lane. Minimal widening of the sulci was seen in 20 children (31%) and obvious widening in 17 (26%).
In the group children treated with 850 rad 2 out of 6 had abnormal CT scans, in the group treated with 1800 rad 32 out of 48 and in the group treated with 2400 rad 3 out of 10. Ventricular enlargement, calcifications or hypodense areas were not seen.

Brecher et al (1985) reported on CT scan findings in children with ALL in initial CR and 1 - 9 years from the end of CNS prophylaxis. All children had been randomly assigned to one of three different methods of CNS prophylaxis. Those children who were still on chemotherapy when tested were at least 6 weeks from their last steroid pulse. All children had received CNS prophylaxis with i.th. MTX. Twenty nine received 6 i.th. MTX injections only (group I), 30 received crXRT as well (group II) and 34 received i.th. MTX combined with intermediate high dose MTX infusions. No intrathecal maintenance chemotherapy had been given. The scanner nor the reference values were stated.
The overall incidence of abnormal scans was 35% (33/93): 30% in group I, 40% in group II and 35% in group III. These differences were not statistically significant. Most of the abnormal scans were felt to represent minimal abnormalities. Three scans, rated as moderately or markedly abnormal were found in children who had been irradiated.
In group I, 6 children showed minimal dilatation of the ventricles and 4 showed dilated cortical sulci. In group II, 8 had minimal dilated, 2 moderately dilated and 1 markedly dilated ventricles. Dilated sulci were seen in 6 children. Only in this group, calcifications were seen in two patients, hypodense areas in one and questionable hypodense areas in two others. In group III, 11 children had minimal dilatation of the ventricles and 3 had dilated sulci.

Carli et al (1985) studied 72 children with ALL in first complete remission who were 3 months - 6 years off therapy and 3 - 9 years after the end of CNS prophylaxis, which had consisted of 2400 rads crXRT and i.th. MTX. CT scans were performed with an Ohio Nuclear Delta 25 scanner. Normal values were those according to Enzmann and Lane. Thirty-five (49%) of the children showed abnormal CT scans. Widening of the ventricles was found in 3 children, widening of the sulci in 8 and a combination of these in 9. Ventricular dilatation associated with periventricular hypodensity was seen in 2 children and parenchymal hypodensities in one. Calcifications were seen in 12 patients.
A higher proportion of abnormal CT scans was seen in children aged less than 5 years at diagnosis.

In some studies, a number of patients were examined more than once.

Gastaut et al (1978) reported on 12 children with ALL, aged 3 to 16 years, among 88 patients of all ages with hematological disorders. Eight children had shown abnormalities on CT scan examination; all CT scans in these children were made because of clinical symptoms. One child in CR presented with a frontal lobe syndrome. The CT scan showed a hypodense zone in the right frontal lobe, which was not found after the symptoms had disappeared. One child in CR had presented with epileptic seizures. The CT scan showed an abnormal image in the left thalamic region, which was felt to represent lymphoblastic infiltration. Six children had a history of one or more CNSL relapses. In two of these children calcifications were found. In one other child, an unusual finding of infiltrations of the cerebral convolutions, enhanced by contrast material, was established and was presumed to correspond with leptomeningeal involvement. In the three remaining children hyperdense zones were present, which were diagnosed as lymphoblastic infiltrations. This was histologically proven in one case only. Five of the seven last mentioned children showed ventricular dilatation with or without sulcal dilatation.
Without offering further details, the authors mentioned that CT scans were performed in 16 patients before and/or after crXRT with 2400 rads plus i.th. MTX, alone or in combination with ARA-C; in all cases, images were normal after therapy. They explained this finding by stating that the doses of radiotherapy, responsible for inducing cerebral atrophy, had to be in excess of 2400 rads.

Enzmann and Lane (1978) analyzed in a retrospective study CT scans perform-

ed with an EMI Mark 1 with a 160 x 160 matrix. They included 76 patients with non-central nervous system malignancies and 25 patients with leukemia. The age of the patients varied between 1 and 30 years.

Fourteen of the 76 patients with non CNS malignancies had abnormal CT scans (18%). Among these, 6 had ventricular enlargement only, 3 had enlargement of cortical sulci only, and 5 had both abnormalities. Radiation therapy had been rarely applied in this group.

Ten of the 25 leukemic patients had abnormal CT scans (40%). Eight of these 10 patients had both ventricular and sulcal enlargement. Eight of the 16 patients with documented CNS leukemia had abnormal CT scans in contrast to 2 of 9 patients without known CNSL.

Fourty-one patients were scanned more than once within a period of 1 to 20 months of follow-up. Six patients (4 with leukemia) had progression of enlargement of ventricles and/or sulci; three progressed from initially normal scans. Four of these six patients showed regression of the changes over a period of several months. The findings in three of these four became normal.

Neuropathologic findings were available in 10 cases. In the four patients with non CNS malignancy, two of whom had mildly abnormal CT scans, examinations were normal. In the six patients with leukemia, four had abnormal CT scans and the findings in three of these were confirmed neuropathologically as ventricular enlargement and cortical atrophy. Mild to moderate neuronal loss, gliosis and mild demyelinization were found. In one patient, the white matter disease suspected on the CT scan was confirmed neuropathologically. Meningeal involvement was found in three patients and was associated with mild gliosis and mild demyelinization. One of these three patients had a normal scan.

Serious cerebral dysfunction appeared to be correlated with greater CT scan abnormalities. Patients who had reversal of the CT scan abnormalities never had any clinically obvious neurologic deficits. Cranial irradiation alone, given in a prophylactic dose of less than 2500 rads to their leukemic patients, did not correlate with abnormal CT scans. They also stated, that steroid therapy could not be implicated in patients with reversible changes. Sex nor the duration of survival correlated with abnormal scans. Younger children (1 - 7 years) appeared to be more susceptible to cerebral changes as seen on the CT scan. They concluded, that the end point of ventricular and cortical sulcal enlargement probably represented a spectrum of abnormalities ranging from reversible structural changes to irreversible cerebral atrophy and leukoencephalopathy.

Gutjahr and Kretzschmar (1979) investigated 35 children with ALL (n = 28) or NHL (n = 7) with an EMI Mark I or an EMI 1010 2 months to 7 years after diagnosis. CNS prophylaxis had consisted of 1500 - 2400 rad crXRT combined with 4 - 5 i.th. injections MTX. The children were clinically normal. In 8 children ventricular and sulcal dilatations were found. Four of these children had also been examined during induction treatment before CNS prophylaxis had been given. They had shown the same abnormalities already at that time.

Kretzschmar et al (1980) performed CT scans with an EMI Mark I or an EMI 1010 on 72 children with ALL or NHL. CNS prophylaxis consisted of a.o. 1500-2400 rads crXRT. In 32 children CT scans were made within 14 days after the start of treatment (group 1). Twenty-one children were scanned one year after completion of CNS prophylaxis, 16 of whom were also part of group 1 (group 2). Thirty-nine children were investigated 2 - 8 years after CNS treatment, five of whom had follow-up studies since the beginning of therapy (group 3).

Ten children (31%) in group 1 had an abnormal CT scan with ventricular and sulcal dilatation. In group 2, 8 children (38%) had dilated ventricles and sulci. Six of these had been examined before CNS prophylaxis and had shown the same abnormalities. One child was found to be normal although dilated CSF spaces had been demonstrated before CNS prophylaxis. One other child had a normal scan, as had been the case before CNS prophylaxis. He however had also been scanned shortly after radiotherapy demonstrating dilated CSF spaces at that time. In group 3, 7 children (18%) showed abnormal CT scans. Three of the 5 children examined before radiotherapy showed dilatation of the ventricles and sulci as before. Two of the children, scanned for the first time in this group, showed calcifications.

During the observation period 12 children with ALL had relapsed in the CNS. Four of them had shown widening of the CSF spaces at that time.

Some studies have been reported about CT scan findings at initial diagnosis or before CNS prophylaxis only.

Gutjahr et al (1980) reported on CT scan examinations in 30 children with ALL (n = 27) or NHL (n = 3). Scans were performed with an EMI 1010 within the first 10 days of treatment. The children had received 1 or 2 injections of vincristine and daunorubicin, 1 - 10 doses of L-asparaginase and 1 - 10 days of prednisone. Ten children showed ventricular and sulcal dilatations.

Although the difference was not statistically significant, the mean white blood cell count at diagnosis was higher in the children with abnormal scan findings than in those with normal scans (54.2 and 12.3 * 10^9/L resp).

Jankovic et al (1989) examined 40 children with a newly diagnosed ALL on admission and prior to any treatment. CT scans were performed with a Philips Tomoscan 310 and evaluated according to Enzmann and Lane. Scans were scored as "borderline" when "slight or moderate dilatation of the ventricular system and/or basal cisterns and/or convolutional sulci" was found and as "pathologic" in the presence of severe cerebral atrophy an/or calcifications and/or hypodensity of the white matter. Fourteen (35%) of the children demonstrated borderline CT scans and 2 (5%) pathologic scans.

Only a few reports concerned prospective follow-up studies in all patients.

Pedersen and Clausen (1981) investigated 23 children with ALL at least twice with an EMI 1010 scanner. Normal values were those according to Pedersen et al (1979). Eleven children were examined at initial diagnosis and reexamined at least 14 months later. Seven of these had received CNS prophylaxis with 2400 rads crXRT combined with i.th. MTX, the other four had received i.th. MTX and intermediate doses of i.v. MTX. Two of the 11 children had slight enlargement of the ventricles and sulci at diagnosis. This proved to be unchanged at repeat examination 15 and 19 months later. One child had received crXRT, the other intermediate dose MTX. No abnormalities on the CT scans, obtained during treatment 14 - 29 months later had developed in these 11 patients.

Twelve children with a CNS leukemia relapse, diagnosed 10 - 105 months after initial presentation with ALL, were also studied. Only children with normal CT scans before or at the time of CNS involvement had been included. All children had been treated with craniospinal irradiation and intensive i.th. or intraventricular MTX for their CNSL. On examination at least 11 months later, all were in remission of their CNSL. In seven children abnormalities had developed. In five, slight enlargement of ventricles and sulci became manifest. Hypodense areas became visible in 3 children, one of whom also showed increasing subcortical calcifications. Later on, CT scans revealed unchanged or progressive abnormalities in all children in this group. Essentially the same results were reported by Clausen and Pedersen in 1982.

Ochs et al (1983) described serial CT scans in children, treated with two different forms of CNS prophylaxis according to the Total Therapy Study X.

One group of patients (RT) had received 1800 rads crXRT combined with i.th. MTX, followed by i.th. MTX every 3 months. The other group (IVIT) had received CNS prophylaxis consisting of 3 infusions with intermediate dosages of i.v. MTX combined with i.th. MTX. These infusions were repeated every 6 weeks for the first 1.5 years of therapy. CT scans were performed with a GE 8800 CT-T scanner with a 10 mm. collimator. Standards for ventricular and sulcal size were based on the findings of Bentson et al (1978).

Approximately 30% of patients in both treatment groups had mild ventricular dilatation and/or prominent cortical sulci which reverted to normal within 6 weeks after the completion of the early CNS prophylaxis. These findings were attributed to steroid therapy and not included in the further analysis.

Five (9%) of 55 patients in the RT group had presented at least one abnormal scan. Four had hypodensities on the CT scans, first detected at either six weeks (2) or six months (2) after completion of cranial irradiation. The scans reverted to normal in the three children who had examinations repeated. The fifth child had cerebral calcifications first seen after one year of therapy with progression in the size of calcifications on repeat scan.

Ten (19%) of the 53 patients in the IVIT group had shown abnormal scans. In each instance areas of decreased attenuation around the frontal horns were detected. The first abnormal scan findings were already seen at six weeks (6) after the completion of the three courses of weekly MTX infusions. The scans of 8 patients reverted to normal. However, hypodensities reappeared in 2 children.

Riccardi et al (1985) reexamined 24 of the original 32 children, reported on by Peylan-Ramu et al (1978). CT scans were performed with an EMI 1010 in 1977 - 1979 or an GE 8800 CT in 1981 - 1982. Normal values were according to Enzmann and Lane. All children had been in continuous complete remission for at least 7 years and off therapy for at least 3 years.

Twelve children had a normal scan when investigated for the first time. Three of them proved to have calcifications on follow-up.

Four children (17%) had ventricular dilatation on the first scan. This remained so during follow-up. In one of them, calcifications were present at the last examination.

Five children (21%) had dilated sulci initially. In one of them calcifications became apparent. One other had become normal at the last investigation.

One child (4%) showed ventricular and sulcal dilatation initially, and only ventricular dilatation on repeat scans.

In one child (4%) with sulcal dilatation and hypodense areas, only sulcal dilatation was present on follow-up.
Finally, one child (4%) with hypodensities was normal on repeat examination and remained so.
Thus, calcifications developed in 5 children between 5 and 7 years after CNS prophylaxis. Three had received i.th. ARA-C and two i.th. MTX. All these children were less than 8 years of age at the time ALL was diagnosed. Hypodensities were transient and were only found on the first CT scans in two children. Ventricular and sulcal dilatations were quite stable over the time of follow-up.

O'Hare et al (1988) scanned 29 children with ALL with an EMI 1010. CT scans were performed as soon as possible after diagnosis and before the onset of CNS prophylaxis, which consisted of 1800 - 2400 rad crXRT combined with i.th. MTX. Sixteen children had been scanned after 2 years of treatment and at 2 years after therapy had been completed.
Six of the 29 (20%) initial scans were abnormal. One child had dilated ventricles initially, which werestill present 2 years later. Three children showed sulcal dilatation which was attributed to steroid treatment. Two of them were scanned 2 years later and had become normal. One child with asymmetrical enlargement of the lateral ventricles developed a CNS relapse. One child who developed encephalopathy 9 days after the start of treatment had a scan which showed choroid plexuses with hypertrophy and plethora. A scan made one month later showed improvement.
Twenty five percent of the scans performed 2 years after diagnosis were abnormal. One child had developed calcifications. One child, under 2 years of age when irradiated, showed hypodensities. Two children had slight enlargement of the fourth ventricle, which resolved after chemotherapy had been discontinued.
Of the 16 children scanned 2 - 3 years after treatment had been stopped, only 1 (7%) was abnormal showing minor asymmetry of the lateral ventricles.
No relation between CT scan abnormalities and WBC's at diagnosis or the amount of radiation to the cranium was found.

Jankovic et al (1988) reported on a multicentre study in which serial CT scans were made in 145 children. CT scans were performed with an EMI 1010, Siemens Somatom DR3 or a GE 8800 in the participating hospitals. All scans were evaluated in one institution according to the criteria of Enzmann and Lane. CT scans were made within 15 days from the start of therapy, 2 - 3

months after crXRT with 1800 rads in combination with 6 i.th. injections of MTX and at the end of treatment. None of the children had shown CNS symptoms. Ninety (62%) of the 145 children examined at diagnosis had abnormal CT scans. Onehundred-thirty children were reexamined after CNS prophylaxis. Of the original 45 normal CT scans, 9 had become borderline and 3 pathological. Three of the original 64 borderline scans had become normal and 17 pathological. Of the original 21 pathological scans 7 had become borderline.
Seventy-seven children had been scanned both at diagnosis and at the end of treatment. Of the original 33 normal scans, 10 had become borderline. Of the 36 borderline scans at diagnosis, 11 had become normal and 6 pathological. Of the 8 pathological scans, 1 had become normal and 4 borderline.
All 12 children with a CNS relapse were among the 66 children with an abnormal CT at initial diagnosis: four had a borderline scan and 8 a pathological one. The authors suggested that the observed alterations might be secondary to the leukemic process itself.

Finally, some studies tried to correlate CT scan findings with clinical observations.

Oliff et al (1979) evaluated hypothalamic-pituitary function and CT scans in 23 patients with ALL. Eighteen patients, aged 6 - 20 years, had recieved CNS prophylaxis with 2400 rads crXRT and intrathecal injections monthly for 30 months with MTX (9) or ARA-C (9). Maintenance therapy was completed in all but two patients 3 - 45 months prior to testing. Cranial irradiation was completed 42 - 84 months before testing. Eleven of these 18 patients had CT scan abnormalities. Eight patients had ventricular dilatation, seven had sulcal enlargement, three had intracerebral calcifications and two had hypodense areas. Nine patients had abnormally low growth hormone responses to insulin-induced hypoglycemia. Seven of these also manifested ventricular dilatation on CT scans. Such a CT scan finding was found in only one of the patients with normal growth hormone responses (p 0.015). Five patients, aged 17 - 32 years, with ALL and in complete remission were also tested. One patient had received i.th. MTX as prophylaxis. The other four had received no CNS prophylaxis at all. All were off therapy for at least 48 months. All patients had normal growth hormone responses and normal CT scans.

Brouwers et al (1985) studied 23 long-term survivors with ALL with neuropsychological tests and tried to correlate the outcome with CT scan findings. All children had been scanned in late 1976 as part of the CT scan study of

Peylan-Ramu et al (1978). They were reexamined in 1981 and 1982 with a GE 8800 Scanner. Again the criteria of Enzmann and Lane were applied. All children were in continuous complete remission for 7 - 11 years and had received no chemotherapy for at least 3 years. All were asymptomatic. Eight children showed dilatations of ventricles and sulci and five showed calcifications. No differences in CT scan abnormalities were found for groups having received either MTX or ARA-C intrathecally. On the basis of the neuropsychologic measures, the authors were able to predict with 100% accuracy which of the children had intracerebral calcifications. In addition, there was a 83% correct discrimination between the patients with normal CT scans and those with ventricle and sulci dilatation. The children with calcifications demonstrated more severe neuropsychologic abnormalities, in particular for long-term verbal memory and for memory loss between immediate and delayed recall.

Mulhern et al (1987) reported a retrospective analysis of the intellectual and academic performances of 40 children who had survived 2 years or more after an isolated CNS relapse. These children had been treated with i.th. MTX and 1800 -2400 rad crspXRT at St. Judes Children's Research Hospital. A total of 29 children were irradiated twice, prophylacticly and/or therapeuticly with a maximum cumulative dose to the cranium of 4800 rad. Psychological studies were conducted 1.8 to 13.1 years after the first CNS relapse. Sixteen patients had been referred for clinical reasons. All children were in complete remission and neurologically intact. The mean scores for full-scale IQ (87.5), verbal IQ (90.3) as well as academic achievement in reading, spelling and mathematics were significantly below normal expectations for age.
In 27 patients, CT scans were obtained before psychologic testing. Thirteen (48%) showed calcifications. The authors showed, that cerebral calcifications predicted for deficient intellectual and academic performance, and that they were strongly associated with seizure disorders.

Summarizing, a varying proportion of 0% - 53% of abnormal CT scans is reported in cross-sectional studies. This difference is partly due to the different times at which the CT scans are performed after diagnosis or CNS prophylaxis. This also depends on the criteria used to determine ventricular and sulcal dilatation.
Furthermore, the kind of CNS prophylaxis seemed to be of importance for the occurrence of abnormalities (tables 6 to 8).

Table 6. Summary of CT scan findings at diagnosis or before CNS prophylaxis in children with acute lymphocytic leukemia.

CNS prophylaxis crXRT	MTX i.th	ARA-C i.th	MDMTX i.v.	moment CT made	n pts	total abnl. %	VD %	SD %	VD+ SD %	HYPO %	CALC %	Reference
-	-	-	-	at Dx	13	15		8	8			Ochs 1980
-	-	-	-	at Dx	11	18			18			Pedersen 1981
-	-	-	-	at Dx	40	40						Jankovic 1989
-	-	-	-	before	9	0					0	McIntosh 1977
-	-	-	-	before	32	31						Kretzschmar 1980
-	-	-	-	before	8	0						Metz 1983
-	-	-	-	before	55	30		30				Ochs 1983
-	-	-	-	before	53	30		30				Ochs 1983
-	-	-	-	before	29	20	6	10				O'Hare 1988
-	-	-	-	before	145	62						Jankovic 1988

Table 7. Summary of CT scan findings in children with CNS leukemia or in children with non-CNS malignancies or in "control" children.

CNS prophylaxis crXRT	MTX i.th	ARA-C i.th	MDMTX i.v.	Dx - CT interval months	n pts	total abnl. %	VD %	SD %	VD+ SD %	HYPO %	CALC %	Reference
-	+		?	at Dx	12	0						Pedersen 1981
+				on Rx	16	50						Enzmann 1978
	+			5 - 60	3	33	33					Kolmannskog 1979
+	+			> 11m Rx	12	58			42	25	8	Pedersen 1981
+(2)	+	+		on Rx	9	100	33		67	13		Allen 1981
+	+			on Rx	6	83		17	67		17	Metz 1983
+	+			on Rx	7	100			71		29	Gastaut 1978
-	-	-	-	malign.	76	19	8	4	7			Enzmann 1978
-	-	-	-	controls	18	6				6		Allen 1981
-	-	-	-	noncancer	50	4			4			Ochs 1980

Table 8. Summary of CT scan findings during or after treatment in children with acute lymphocytic leukemia in first remission.

CNS prophylaxis				Proph-CT								
crXRT	MTX i.th	ARA-C i.th	MDMTX i.v.	interval months	n pts	total abnl. %	VD %	SD %	VD+ SD %	HYPO %	CALC %	Reference
+	+			5m - 6yr	39	25					25	McIntosh 1977
–	–	–	–	16 -149	11	9	9					Peylan-Ramu 1978
+	+			23 - 67	14	57	29	21		29	7	Peylan-Ramu 1978
+		+		19 - 63	18	56	22	33				Peylan-Ramu 1978
+	+			> 36	20	50						Casteels 1978
+	+			20 - 84	28	7?						Mott 1978
+	+			4m - 4yr	27	4	4					Day 1978
				?	9	22						Enzmann 1978
	+		+	2 - 64	19	5				5		Kolmannskog 1979
+	+			2 - 84	35	23			23			Gutjahr 1979
+		+	or +	42 - 84	18	62	44	39		11	17	Oliff 1979
–	–	–	–	> 72	4	0						Oliff 1979
	+		+(33)	10 - 59	43	19		9	9			Ochs 1980
+	+			4 - 12yr	14	43	7	7	14		14	Esseltine 1981
	+			4 - 12yr	12	25	17		8			Esseltine 1981
	+3yr			> 9	10	20				20		Allen 1981
+	+			> 45	7	29		29				Allen 1981
+(7)	+		+(4)	14 - 29	11	18			18			Pedersen 1981
+	+			1	55	5				5		Ochs 1983
+	+			6	55	4				4		Ochs 1983
+	+			> 12	53	2					2	Ochs 1983
	+		+	1	53	11				11		Ochs 1983
	+		+	6	53	4				4		Ochs 1983
	+		+	> 12	53	15				15		Ochs 1983
+	+			10 -100	6	67	17	17	17		17	Metz 1983
+	+			2 - 84	64	58		58				Habermalz 1983
	+			mean 6.3yr	29	31	17	10	3			Brecher 1985
+	+			mean 4.7yr	30	40	20	3	17	10	7	Brecher 1985
	+		+	mean 3.2yr	34	35	26	3	6			Brecher 1985
+	+			3 - 9yr	72	49	7	11	13	4	17	Carli 1985
+	+	or +		19 - 67	24	50	17	25	4	8		Riccardi 1985
+	+	or +		> 5yr	24	58	21	25			17	Riccardi 1985
+	+	or +		> 7yr	24	54	21	21			21	Riccardi 1985
+	+	(+)		24	16	25	13			6	6	O'Hare 1988
+	+	(+)		48	16	6	6					O'Hare 1988
+	+			2 - 3	130	72						Jankovic 1988
+	+			24	77	55						Jankovic 1988

EEG studies in children with acute lymphocytic leukemia.

Although abnormal EEG's have been found at diagnosis of CNS leukemia, no consistent abnormalities are evident (Shaw et al 1960, Hyman et al 1965). Diffuse dysrhythmias are usually seen and occasionally focal abnormalities. Nonspecific theta and delta waves occur diffusely (Shaw et al 1960). Focal abnormalities include sporadic increased voltages, slowing of cycles, and disorganization in the bifrontal areas (Hyman et al 1965).

In later studies, normal EEG's at diagnosis were found in 15 - 80% of children with ALL (Hässler et al 1976, Korinthenberg et al 1979, Ch'ien et al 1979, 1980, Mahoney et al 1981).

Prolonged administration of prednisone has been associated with a gradual increase in 4 to 7 cycle/sec activity, more obvious over the posterior than the anterior halves of the hemispheres (Butcher et al 1970). In patients with Cushing's syndrome, slowing of background rhythm in the EEG is seen also, which pattern is reversible.

Vincristine treatment did not give rise to EEG abnormalities among 67 children of all ages with leukemias or extracranial tumours, investigated 5 weeks to 2 years after the last vincristine injection. However, in 3 of the investigated children a diffuse slowing of background activity was seen, coinciding with a relapse of the leukemia (Dieterich et al 1978).

With L-asparaginase treatment, a reduced frequency of the basal rhythm and the presence of diffuse slow waves was seen in 75 - 85% of patients studied (Moure et al 1970, Land et al 1972). This has been related to metabolic alterations of the CSF caused by the depletion of L-asparagine and L-glutamine (Pochedly 1972, Weiss et al 1974).

A few weeks after cranial irradiation, i.e. during the PRS, a moderate to severe generalized slowing of the background rhythm was found in most of the investigated children (Aronson et al 1974, Terheggen and Rado 1978, Ch'ien et al 1980).

Meadows and Evans (1976) studied 23 children with leukemia or lymphoma, who had survived at least 5 years from the time of diagnosis and whose treatment had included MTX for at least 2 years. Four children with abnormal neurological signs and symptoms and five children without any neurological impairment were reported to have abnormal EEG's with slow and irregularly spiking waves.

Stephani et al (1983) recorded EEG's in 46 of 64 children before therapy

was started. Twenty-one (47%) were considered abnormal because of slowing of the background frequency without hypersynchronous activity. In 24 children EEG's were obtained after the first four weeks of treatment, prior to cranial irradiation. Seventeen (63%) proved to be abnormal with slowing of background activity.

Carli et al (1985) performed EEG's in 65 children, who had been off therapy between 3 months and 6 years. In 17 children (26%) minor abnormalities consisting of sharp waves and/or intermittent polymorphic slowing were revealed. In these children a CT scan was also obtained. Seven abnormal EEG's were found among 33 children with a normal CT scan and 10 abnormal EEG's among 32 children with an abnormal CT scan.

Ch'ien et al (1980) studied 49 children with ALL in first complete remission with serial EEG's for more than 4 years. EEG's had been obtained at diagnosis, shortly after remission was achieved, at the end of the irradiation, and seven weeks later. Additional recordings were made three months, six months and one year after diagnosis and each subsequent year.
The mean EEG background frequency was determined by visually counting the number of waves per second in three or four 10-second periods in each EEG obtained during wakefulness, and was expressed as standard deviations from the expected normal means. They presented an equation for the calculation of the mean background frequency, expected for children of any age (in years):

$$\text{mean frequency} = 5.375 + 0.606\ (\text{age}) - 0.019\ (\text{age})^2$$

With this formula, the mean frequency is 5.962 Hz at one year of age, 7.022 at 3 years, 8.327 at 6 years, 9.290 at 9 years and 10.190 Hz at 15 years.
At diagnosis, they found an abnormal EEG with slowing of the background rhythm in 85% of children. The EEG background frequencies became gradually faster during induction treatment and CNS prophylaxis with crXRT and i.th. MTX. The frequencies then decreased precipitously in 29 children who had clinical signs of the somnolence syndrome (PRS). This occurred 6 - 8 weeks after the completion of CNS irradiation. Symptoms lasted from 4 days till over 2 weeks. The frequencies proved to be risen again at the next investigation. In the children without clinical signs of the PRS no such differences were observed. The children who later developed somnolence had initially slower background frequencies (- 2.22 SDS) than those without this syndrome (- 1.57 SDS).
All children showed a slowing of background frequencies at diagnosis and during the four years of evaluation. The mean frequencies were at least 1.5 standard deviations below the normal mean for age at each occasion.

C H A P T E R 3

Study design, patients and methods

Study design

For the purpose of this study cerebral CT scans and EEG recordings with normal visual interpretation and spectral analysis were added to the diagnostic workup, the investigations at the end of induction treatment and to some of the regular checkup routines.

These checkup routines were done after every two maintenance treatment courses, at the end of therapy and every 13 to 14 weeks thereafter. These consisted of interim history, physical examination, examination of a cytospin preparation of the cerebrospinal fluid (CSF), bone marrow (BM) examination and renal- and liver-function tests.

Initially, patients were also examined by a pediatric neurologist at the same time as the EEG's and CT scans were performed. Since it turned out that these examinations did not yield additional information than already obtained by pediatric oncologists, they were discarded after two years.

The CT and EEG investigations were done prospectively at fixed moments: at diagnosis before any treatment was delivered, at the end of induction therapy but prior to CNS-prophylaxis, immediately after CNS-prophylaxis, during maintenance treatment and after completion of antileukemic treatment (table 1). The timings for these investigations were chosen in order to be able to record possible effects of the different treatment modalities and to follow the course of these effects during treatment and for one year thereafter.

CT and EEG investigations were performed on the same day. At week 9 however, only an EEG was recorded, because it was assumed that it would take some time before the effects of cranial XRT would become visuable. Such in contrast to the possible changes in the EEG due to the direct impact of cranial XRT.

All CT and EEG investigations during and after maintenance treatment were performed prior to the lumbar puncture (LP) as part of the checkup. Thus, volume effects due to the removal of CSF would not have to be considered in the evaluation of the CT scan findings in particular. The CT scan pictures could therefore be considered as representative for the actual steady state situation.

Table 1. Timing of CT and EEG investigations.

wk 0 :	at diagnosis, before any treatment
wk 6 :	at the end of induction treatment, prior to CNS prophylaxis
wk 9 :	after the end of CNS prophylaxis (EEG only)
wk 18 :	after the postirradiation syndrome period
wk 32 :	half a year after diagnosis
wk 60 :	one year after diagnosis
wk 116 :	two years after diagnosis; for children with NHR-ALL at the end of treatment
wk 144 :	only in children with NHR-ALL: half a year after stopping treatment
wk 172 :	in children with NHR-ALL : one year after completion of treatment in children with HR-ALL : at the end of treatment
wk 200 :	only in children with HR-ALL : half a year after stopping treatment
wk 228 :	only in children with HR-ALL : one year after the end of treatment

Criteria for eligibility

All children admitted to the Sophia Children's Hospital with a newly diagnosed ALL were eligible. Induction treatment could have been started elsewhere, but should not have been given for more than 2 weeks.

Patients were assigned to one of the ALL categories according to current standard definitions in the Netherlands as laid down by the Dutch Childhood Leukemia Study Group (DCLSG):

A. Non-high-risk ALL (NHR-ALL)
   Initial white blood cell count (WBC) < 50.0 * 10^9/L
   No mediastinal enlargement
   No central nervous system involvement at diagnosis

B. High-risk ALL (HR-ALL)
   Initial WBC >= 50 * 10^9/L and/or
   mediastinal enlargement

C. Initial central nervous system leukemia (iCNSL)
   Presence of leukemic lymphoblasts in the cerebrospinal fluid (CSF) at diagnosis or immediately after induction treatment prior to CNS irradiation, irrespective of the number of blasts.

Children with iCNSL were not eligible. If this diagnosis was made at the end of the induction treatment, investigations which had been already performed

were not considered for evaluation.
Children were taken off study in case of:

A. failure to achieve hematological remission after induction treatment (primary refractory leukemia),
B. relapse, regardless of its location,
C. other causes, i.e. death due to nonleukemic incidents, moving house etc.
D. completion of all investigations as described in this studyprotocol, i.e. at one year after completion of treatment.

Investigations not performed according to schedule for whatever reason were not considered for the purpose of this study and designated as "missing". This however was no reason to take the patient off study.
Meticulous efforts were taken to perform the CT and EEG investigations at the proper times. Schedules were made every six months in advance to fix the dates for the future investigations. These appointments were handed to the patients or their parents at least two months in advance in order to make minor adjustments possible. Investigations performed at other times were not accepted for evaluation in this study. Investigations during maintenance treatment had to be done **before** the start of intermittent consolidation courses with prednisone and vincristine.

Patients and diagnoses

From february 1978 till february 1984 eighty-three children with ALL were consecutively admitted to the Sophia Children's Hospital. At diagnosis, a consecutive number (#) was assigned to each child.
Ten children were not eligible for this study :

- one child suffered from a lymphoblastic blast crisis of chronic myeloid leukemia and received a different treatment,
- four children with a WBC > 50 * 10^9/L at diagnosis had lymphoblasts in their cerebrospinal fluid obtained either before therapy (n=1) or after systemic induction treatment (n=3). These children received an Ommaya reservoir for further CNS treatment.
- five children were treated according to a newly introduced protocol VI of the DCLSG with a different type of central nervous system prophylaxis.

The remaining 73 children were assigned to the categories HR-ALL or NHR-ALL according to the criteria of eligibility.

Twenty-six children suffered from HR-ALL and were treated uniformly according to a local HR-ALL protocol. Fourty-seven had a NHR-ALL and were treated according to different protocols after randomisation by the DCLSG:

2 children were allocated to protocol IIIA,
3 to protocol IIIB,
19 to protocol VA,
23 to protocol VB.

There were 41 boys and 32 girls with ages at diagnosis varying from 0.8 to 14.8 years. Their distribution over age categories in HR-ALL and NHR-ALL is presented in table 2.

Table 2. Age groups and sex of children in ALL categories

age group years	total n	NHR-ALL n	boys n	girls n	HR-ALL n	boys n	girls n
0 - 2	7	4	4	0	3	2	1
2 - 4	25	19	10	9	6	3	3
4 - 6	13	7	5	2	6	5	1
6 - 10	14	8	4	4	6	1	5
> 10	14	9	4	5	5	3	2
total	73	47	27	20	26	14	12

The characteristics of the children and their disease at diagnosis are presented in table III.1 - III.3. The course of their illness is summarized in table III.4.

Eleven children were taken off study because of failure to achieve remission or because of events during first remission:

- Three children (#31, #55, #57) proved refractory to initial treatment and were taken off study after the second CT and EEG investigations at week 6.
- One girl (#84) experienced a cerebrovascular accident during induction and received CNS prophylaxis with i.th. MTX and MTX infusions. She got a CNS relapse shortly after.
- Six children in first complete remission died of infections: three of sep-

ticemia (#8, #15 and #58), one of Pneumocystis Carinii pneumonitis (#23) and two of varicella (#17 and #26).

- One child (#42) developed a second malignancy after having been 22 months in first remission. This malignant fibrous histiocytoma at the ear tragus could completely be resected and did not need further treatment. Follow-up for this study was stopped at that moment; 1.5 years later, he experienced an ALL BM relapse.

Twenty-three children were taken off study because of a relapse as a first event:

- Eleven relapses occurred in the BM, 7 in children with HR-ALL (#9, #16, #38, #40, #41, #72, #79) and 4 in children with NHR-ALL (#19, #27, #36, #51),
- nine in the CNS, 3 in HR-ALL (#20, #33, #48) and 6 in NHR-ALL (#22, #30, #49, #50, #54, #60),
- two in the testicles (HR-ALL #34, #80), and
- one combined relapse in the BM and testicle (NHR-ALL #74).

Two children had relapses after completion of this study:

- one child (#7) had a relapse in his BM just after completion of this study, another (#4) had a very late combined relapse in the BM, CNS and ovaries.

In one child (#10) a mediastinal Hodgkin lymphoma was diagnosed more than 6 years after the first diagnosis of ALL.

Treatment protocols

Three treatment protocols were in use during the 6 years of patient intake:

A. Children with NHR-ALL were treated according to protocol III or V of the DCLSG.

B. Children with HR-ALL were treated according to the local protocol HR77.

In protocol III, in use from june 1975 untill november 1978, remission induction treatment consisted of 6 weekly doses of vincristine (VCR) (2 mg/m² i.v.), together with 4 weeks of daily prednisone (PRED) (40 mg/m² orally in 3 doses) tapering to 0 in the next 10 days.

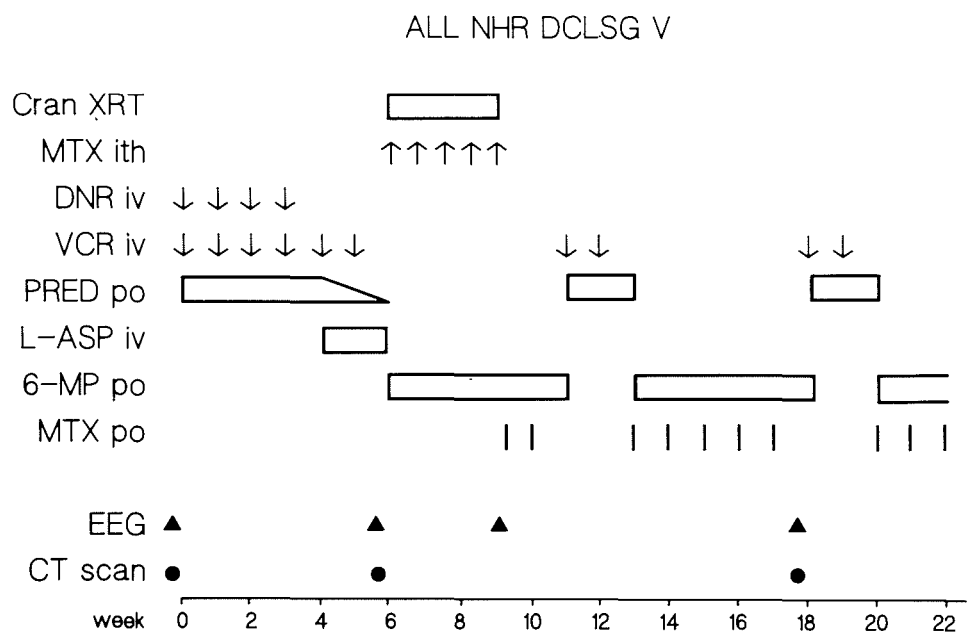
After achievement of complete remission patients were randomised by the DCLSG to arm A or B of maintenance treatment.

In arm A, maintenance treatment consisted of 2 weeks of prednisone (40 mg/m²

orally in 2 doses) together with 2 i.v. injections of vincristine (2 mg/m² i.v.) on the first and eighth day of every course, alternating with 5 weeks of daily 6-mercaptopurine (50 mg/m² orally) together with 5 weekly dosages of methotrexate (30 mg/m² orally).
In arm B, maintenance treatment consisted of daily 6-MP together with weekly MTX orally in the same dosages. No consolidation courses with VCR and PRED were given.

In protocol V (figure 1), in use from november 1978 till july 1983, children were randomised by the DCLSG to arm A or B of induction treatment.
In arm A induction treatment consisted of VCR and PRED with the addition of L-asparaginase (200 IU/kg bodyweight in daily one-hour i.v. infusions) in the last two weeks.
In arm B a fourth drug, daunorubicin (25 mg/m² i.v. once weekly), given together with the first 4 i.v. injections of VCR was added to the treatment.
Maintenance treatment in protocol V was for all patients identical to the treatment given in protocol IIIA.
In both protocols III and V maintenance treatment was prescribed for 2 years and completed at week 116 after diagnosis.

Figure 1. Outline of treatment protocol V



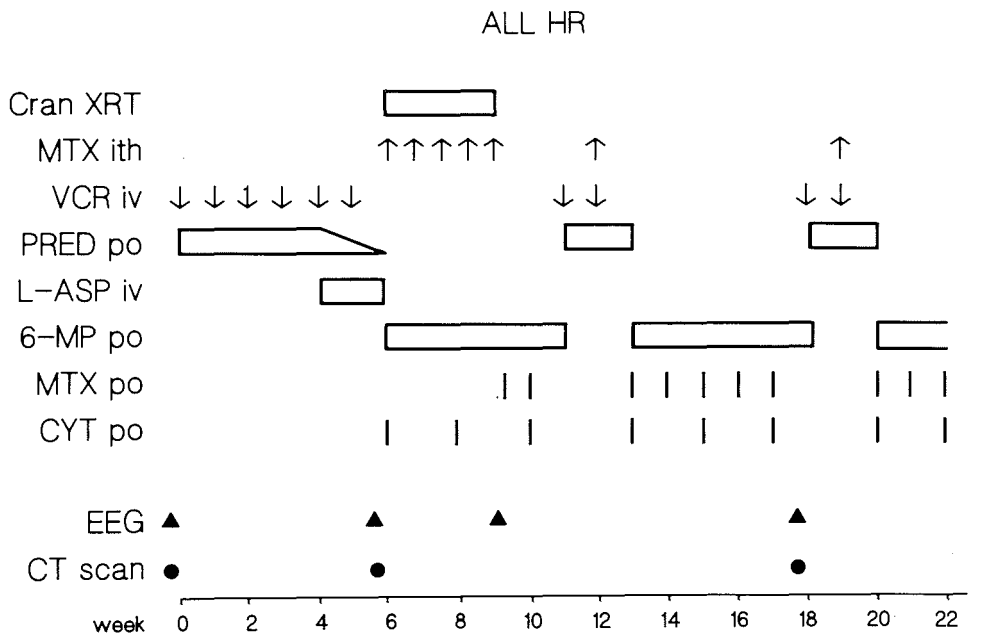
In protocol HR77 (figure 2), which was initiated in july 1977 and was in use during the period of this study, induction treatment was identical to the one used in protocol VA.

Maintenance treatment was almost the same as used in protocols IIIA and V. Cyclophosphamide was added in a dosage of 200 mg/m² orally once every 2 weeks during the 5-week courses of 6-MP and MTX (i.e. 3 times per course) for the first year of maintenance. Additionnally, 6 intrathecal injections of MTX and prednisolone (both 12.5 mg/m², with a maximum of 15 mg), coinciding with every second VCR injection of the consolidation courses, were given during the first year of maintenance treatment (i.e. at week 12, 19, 26, 33, 40 and 47 after diagnosis).

Thereafter, maintenance treatment, identical to the one described for the protocols IIIA an V, was given for another 2 years.

Thus, maintenance treatment for children with HR-ALL lasted for 3 years and was completed at week 172.

Figure 2. Outline of treatment protocol HR77



Primary CNS-prophylaxis was identical in all treatment protocols and consisted of craniocervical radiotherapy together with five i.th. injections of MTX and prednisolone, both in a dosage of 12.5 mg/m² (maximum dose 15 mg) pro time. The first and last of these i.th. injections were scheduled at the first and last day of the XRT, the other three were given at about even intervals in between.

Craniocervical XRT was delivered by two planparallel fields to the cranial vault and the two uppermost cervical vertebrae. Dosages were calculated in the midplane areas. The total dose was given in 12 or 13 fractions over a period of 2.5 to 3 weeks (4 or 5 irradiations per week).

In children, aged 2 years or over, a total dose of 25 Gray (Gy) was given in one fraction of 1 Gy and 12 fractions of 2 Gy. The total dose was reduced to 20 Gy for children aged 1 year and to 15 Gy for children under 1 year of age.

Children with HR-ALL received daily cotrimoxazole (TMP/SMX) as a prophylaxis for Pneumocystis Carinii pneumonitis (PCP), starting after induction treatment and continued untill 6 months after stopping cyclophosphamide, i.e. at week 84 after diagnosis.

All children with a history of recurrent respiratory infections were also given TMP/SMX prophylaxis. In these children, either with HR-ALL or NHR-ALL, TMP/SMX was started after completion of induction treatment and continued untill six months after stopping antileukemic treatment. Finally, children who recovered from biopsy-proven PCP or from non-biopsy-proven interstitial pneumonitis with treatment of high dose TMP/SMX received also prophylactic TMP/SMX.

Table 3. Summary of treatment protocols

	induction				/CNS proph/			maintenance				
	VCR iv	PRED po	L-ASP iv	DNR iv	XRT	MTX ith	6-MP po	MTX po	CYT po	VCR iv	PRED po	MTX ith
HR77	+	+	+		+	+	+	+	+	+	+	+
IIIA	+	+			+	+	+	+		+	+	
IIIB	+	+			+	+	+	+				
VA	+	+	+		+	+	+	+		+	+	
VB	+	+	+	+	+	+	+	+		+	+	

Methods

Measurement of cerebral CT scans in children with ALL.

CT scans were made on a EMI 1010 scanner with a collimator of 160 x 160. Scans were photographed on X-ray film. Measurements were made on these films with a plastic ruler, which was photographically reduced in such a way, that one could read the real dimensions directly.

Later on a Philips scanner 300 or 310 was used. These scanners had a higher resolution factor. On the scans, a horizontal line, corresponding with a real distance of 50 mm was generated. In general, this corresponded with 55 mm on the ruler; slight differences were however found. Thus, the measurements, obtained with the ruler, had to be multiplied generally by a factor 0.909090 in order to get the real dimensions. Whenever the indicator line on the Philips scans proved to be different from the aforementioned length, the real multiplication factor was calculated and used to obtain the real measurements. All measurements were rounded off in the usual way to the nearest whole mm.

None of the scans were routinely saved on floppy-disks. Thus, it was not possible to measure distances with a light pen directly on the computer images or to determine Hounsfield Units in areas with hypo- or hyperdensities. However, the opportunity arose to compare methods of measurements temporarily. Ten scans were saved on purpose on floppy-disks for measurement with a light pen on restored images. The same scans were measured separately with the aforementioned method by hand.

The data obtained with the computer were compared with the data as calculated from the measurements with the ruler, which were multiplied with the differencefactor between ruler and indicator line. The differences between the computer data and the data obtained by hand proved to be small: plus or minus 1 mm on distances less than 20 mm and plus or minus a maximum of 2 mm on larger distances. It was concluded, that measurements obtained by hand were reliable for the purpose of this study.

Each measurement obtained by hand was performed at least three times on different occasions. For the sake of uniformity in assessment and in order to secure good reproducibility, measurements were performed during extended periods of time, i.e. weeks. The first scans, which had been measured at the start of such a period, were reevaluated later on during the same period. Only the data obtained by reevaluation were used. The means of the three ob-

tained values were used for further evaluations.

The measurements made are shown in figure 3; in the legend the full designations and their abbreviations are named.

Normal values as defined by Enzmann and Lane (1977) have been widely used to establish normal and abnormal dimensions in CT scans of children, in particular in the American literature. Their childhood population comprised only children with headaches or seizures without evidence of CNS lesions. The children examined by Meese and coworkers (1980) may be considered even more suitable to determine reference values. Children younger than 2 years of age had only suffered from single (probably febrile) seizures and the older ones had been healthy "volunteers". Therefore, normal values as defined in the last mentioned study are considered to be representative for childhood CT scans by our neuroradiology department.

The measurements of the ventricles and sulci on the photographs were multiplied by the minification factors to obtain actual dimensions. These were evaluated in three ways (table 4):

1. According to Enzman and Lane (1977)
2. According to the Huckmannumber as defined by Meese et al (1980)
3. According to Meese et al (1980)

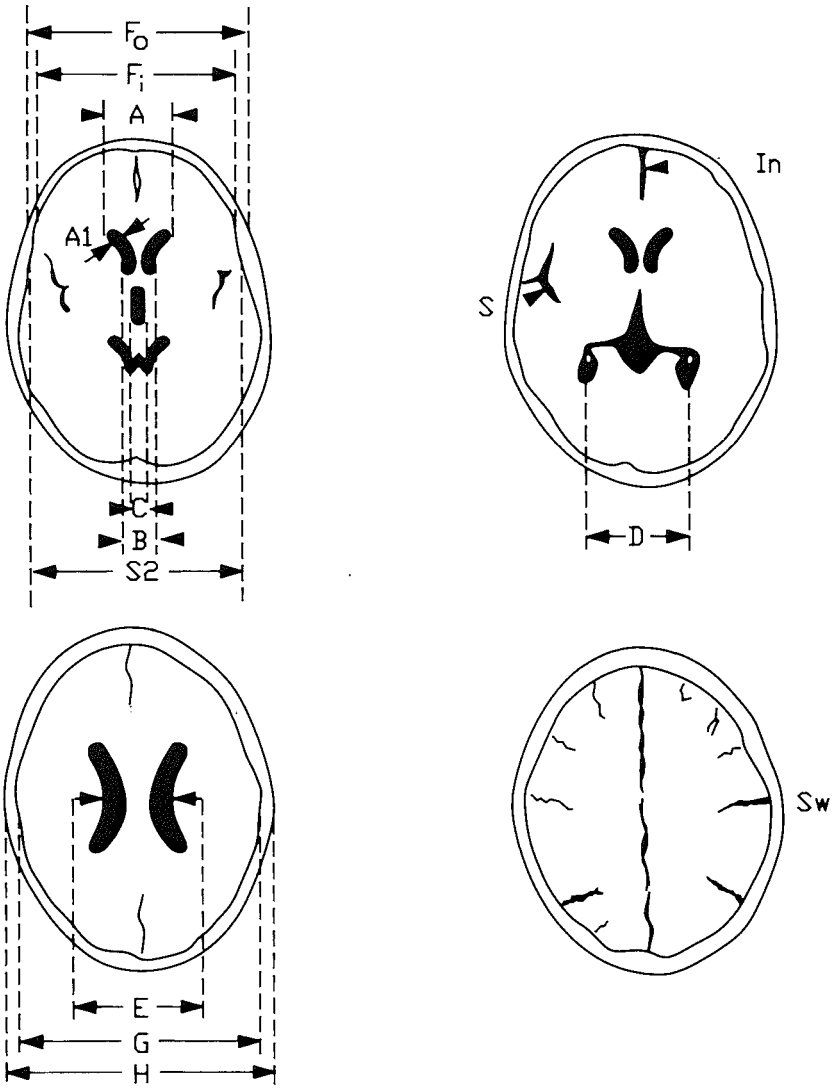
Table 4. Normal values for CT scans in children used in this study

1.	I. Anterior horn span (A)	<= 35 mm	
	II. Width frontal horn (A1)	<= 6 mm	
	III. Intercaudate distance (B)	<= 14 mm	
	Abnormal when 2 out of 3 are abnormal		
		< 2 years	>= 2 years
2.	Huckmannumber acc. Meese (A+B)	<= 35 mm	<= 45 mm
3.	I. Frontal horn index (Fi/A)	>= 3.5	>= 3.7
	II. Cella media index (H/E)	>= 3.8	>= 4.0
	III. Width 3d ventricle (C)	<= 5 mm	<= 7 mm
	Abnormal when 2 out of 3 are abnormal		

The limits of normal values are considered to represent borderline values. For interpretation as borderline acc. to Meese or acc. to Enzmann at least two borderline codes or one borderline and one abnormal code are needed.

Sulci are considered abnormal if visible on an EMI CT scan.
On a Philips scan, sulci were coded as abnormal if more than two sulci are > 2 mm or at least one is > 2.5 mm.

Figure 3. Measurements on CT scan



A : Frontal horn distance
A1 : Maximal diameter of frontal horn
B : Bicaudate maximum distance
C : Width of 3d ventricle
D : Plexus chorioideus distance
E : Width of cella media
Fi : Inner tabula distance at the level of A
Fo : Outer tabula distance at the level of A
S2 : Inner tabula distance at the level of B
G : Maximal inner tabula distance
H : Maximal outer tabula distance
In : Interhemispheric fissure width
S : Fissura Silvii width
Sw : Sulci width

EEG's and visual interpretation

EEG's were obtained with a 16 - channel Elema-SchÖnander apparatus. The electrodes were placed according to the international 10 - 20 system. Standard recordings were obtained. At the same time, the curves were preserved by a 7 - channel Philips recorder on magnetic tapes for computerized spectral analysis.

Visual interpretation of EEG

The EEG's were interpreted by inspection of the recordings. All EEG's were reviewed and described by an experienced neurologist (Prof. M. de Vlieger). The age of the patient and the eventual former recordings were taken into account. From the description and the conclusion about the EEG recordings the further work-up was done. The interpretations were then coded for a general impression of background rhythms and for focal abnormalities.
The codes expressing the general impression of background rhythms of the EEG's are:

1 normal
2 borderline normal/abnormal
3 slightly abnormal
4 moderately abnormal
5 severely abnormal

The codes attributed to the presence or absence of focal abnormalities in the EEG's are:

0 no focal abnormalities
1 one area (one or double-sided) with focal abnormalities
2 two or more areas with focal abnormalities

By visual interpretation, no exact figure for the frequency of the background rhythm can be given. In the total analysis of the EEG's, recurring wavepatterns as well as types of waves can be recognized and taken into account.

Spectral analysis of EEG

Parallel with the normal EEG recordings signals were registered on magnetic tape for later analysis. This was done with a PDP 11/34 computersystem (Digital Equipment Corporation). Three artifact-free epochs of 100 seconds in the leads T3-O1 (left side) and T4-O2 (right side) were analyzed. The mean frequencies and the proportions of delta, theta, alpha and rest waves were calculated.

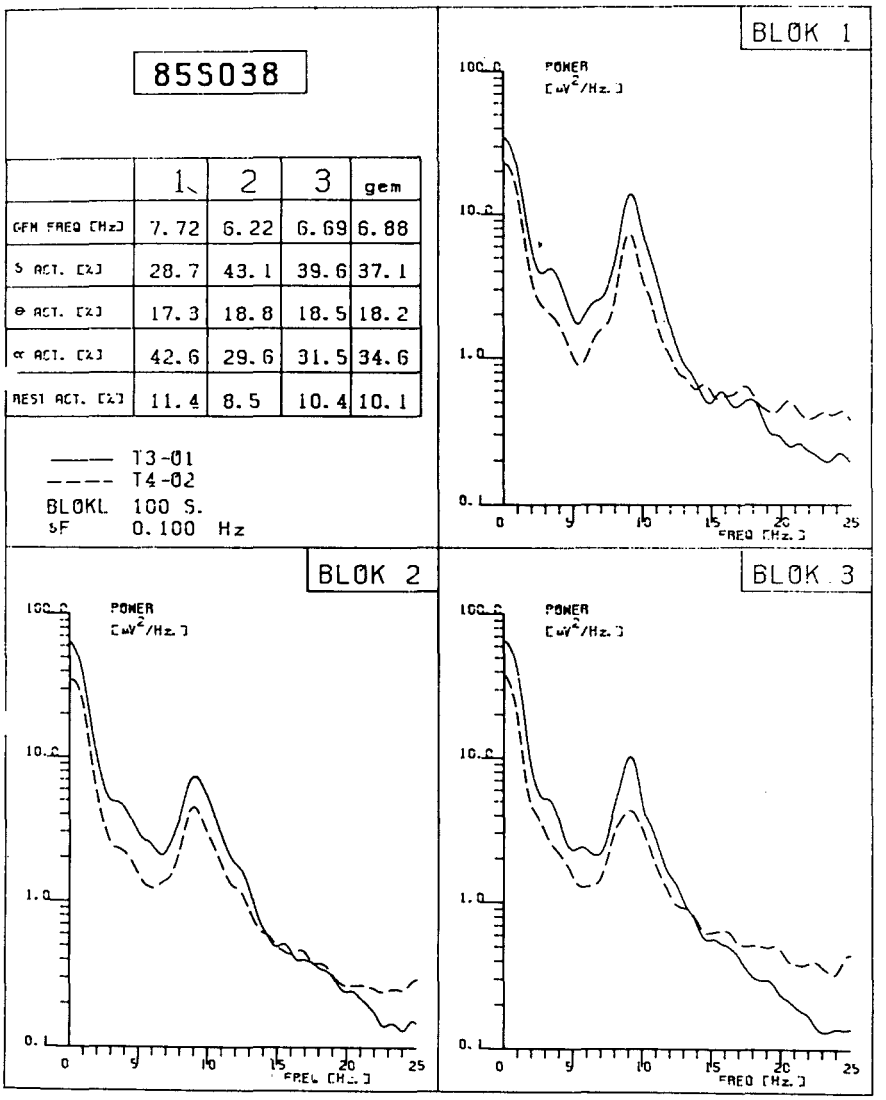
The mean frequency was calculated from the frequencies between 1.0 and 25.0 Hz, recorded in steps of 0.1 Hz. Each of these was multiplied by his respective power. The outcomes were added together and then divided by the sum of all power components. Thus, a weighted mean frequency was derived.

The delta band ranged from 0.5 to 3.5 Hz, the theta band from 3.5 to 8.0 Hz, the alpha band from 8.0 to 13.0 Hz and the rest waves comprised the frequencies from 13.0 to 25.0 Hz. The relative contributions of each band were calculated by dividing the sum of all powers accompanying the frequencies in that particular band by the sum of all powers of the frequencies between 1.0 and 25.0 Hz (Fast Fourier Transformation). Results were presented graphically together with the calculated values (figure 4).

Statistical methods

The paired Wilcoxon test (2 - tailed) with a H0 hypothesis that there was no difference was applied for the comparison of the results of the evaluations at the different times.

Figure 4. Spectral analysis of a 13-year old girl (#53 week 172)



C H A P T E R 4

Results of CT evaluation

Comments on measuring CT scans

Although meticulous care was taken in order to obtain all CT scans in a standardized manner, it proved that differences in imaging could not be avoided completely, which subsequently resulted in difficulties in measuring and comparing the width of the ventricles.

Firstly, slices were not obtained at exactly the same level parallel to the meato-orbital line each time. The ventricles (and other structures) were then imaged at a higher or lower level than on former scans with consequently greater or smaller dimensions. Sometimes certain landmarks and structures were even not visualized and the relevant measurements could not be obtained. This concerned especially the plexus chorioideus, the cella media and the width of the lateral ventricles at that level.

Secondly, a slight tilt of the head resulted in images of slices, not parallel to the meato-orbital line. The sectional plane went then through a lower or higher level in the frontal or occipital region with consequently different images. In these cases certain measurements could be done while others could not.

Thirdly, sometimes the head of the child could not be maintained in a straight and upright position, resulting in a tilt of the head to the right or left. Consequently, the measurements had to be taken in an oblique fashion. In such cases, the borders of the ventricles tended to be less precisely delineated due to a greater partial volume effect. Also, the vertical dimensions on the films were slightly elongated as compared with the horizontal ones, giving rise to a small overestimate of the oblique measurements.

Lastly, in a few cases restlessness of the child gave distorted images on which measurements could not be made.

Thus, certain measurements could not be obtained because structures were not adequately visualized on the scan. It was nevertheless possible to assign a code (especially "normal") to such scans on visual interpretation in some cases. For instance, when the frontal horns were small and the bicaudate diameter was small also, a code of "normal" according to Enzmann could safely be assigned. The same could be done when two of three parameters, used for as-

sessment according to Meese, were normal. This explains, why in some cases the number of patients with exact measurements was less than the number of coded patients.

Measurements in the different CT scans were made at slices which were best comparable with the ideal image as depicted in figure 3 in chapter 3. For the measurements of the frontal horns, bicaudate distance and third ventricle, an image like "a" in that figure was considered ideal. As next best an image as depicted in "b" was acccepted for evaluation. The best comparable CT scan images in one series of a certain patient were always used for evaluation. Whenever an obtained image deviated to much from each of the reference pictures, no measurements were performed.

Another problem concerned the change in CT scan equipment over the 10 years of the study. The later scans, made with Philips scanners, had a higher resolution than those with the EMI 1010 scanner. Consequently, the delineation of the ventricles was sharper and measurements were more precise. For most of the distances this was not felt to be a problem, while it concerned a difference of only 1 or 2 mm in real dimensions. The sulci however were also more precisely depicted. The original definition for normal sulci, defined by Enzmann and Lane as "not visible", was derived from the EMI 1010 scan. This definition could not be applied as such to the Philips scans. In effect, when sulci were visible on the polaroids of our EMI 1010 scan, they proved to be 2 mm or more when measured with the ruler, which was specially made in order to obtain the real dimensions directly from an EMI polaroid. With the latest Philips 310 scanner, the foveal distance could be changed with consequently different magnifications. In order to be able to calculate the real dimensions, a horizontal reference line of 50 mm was always depicted on the scan. On later scans, a vertical reference line of 50 mm was also given, while this line proved to be a little bit longer than the horizontal line.
With a higher magnification, smaller sulci became visible on the polaroids. But even with the standard magnification, sulci of 1 mm measured with the ruler, (after correction comparable with 0.9 mm in reality) can be seen.
On Philips scans, sulci were coded as borderline when one or two sulci were calculated to be at least 2 mm (without rounding off) in real dimension and as abnormal when more than 2 sulci were 2 mm or at least one sulcus was 2.5 mm or larger.

Results of measurements

The measurements of the different distances in each child are presented in the tables IV.1 to IV.11, and the Huckmannumber per child in table IV.12.
The means of the measurements A to E and of the Huckmannumber (the sum of A + B) are presented in the tables 1 to 3 for all children and for the children with HR-ALL or NHR-ALL separately. All values increased after induction treatment and remained the same or became slightly smaller at the end of the postirradiation period. Thereafter, the means remained about the same in the HR-ALL group, but became smaller in the NHR-ALL group.
The means of the measurements S2 to H in all children are given in table 4-6. These remained about the same at all times. There were no differences between the means of children with HR-ALL or NHR-ALL.
Two children (#1, #10) were scanned for the first time at day 16 and day 26 resp. after the start of induction treatment and are not presented in the tables. Both showed a definite ventricular and sulcal enlargement already at that time.

Table 1. Means of measurements (mm) on CT scan
All children

wknr	n	A	A1	B	A+B	C	D	E
0	68	31.4	3.6	8.2	39.5	3.2	44.9	26.8
6	67	34.0	6.0	11.7	45.7	5.2	47.8	30.7
18	64	33.0	5.8	11.5	44.4	5.5	48.3	30.7
32	63	32.8	5.1	10.3	43.1	4.8	48.3	30.0
60	55	33.1	4.9	10.0	43.0	4.5	48.4	29.1
116	44	32.6	5.0	9.7	42.3	4.3	47.8	30.2
144	30	31.6	3.7	8.2	39.8	3.3	47.2	29.2
172	37	32.1	4.3	8.5	40.6	3.8	46.8	28.0
200	8	34.0	6.1	11.6	45.6	4.9	48.6	32.9
228	7	34.3	5.4	11.3	45.6	4.1	47.1	32.7

Table 2. Means of measurements (mm) on CT scan
Children with HR-ALL

wknr	n	A	A1	B	A+B	C	D	E
0	24	30.6	3.3	8.4	38.6	3.2	44.3	26.4
6	22	34.8	6.3	12.7	47.5	5.4	47.0	30.6
18	20	32.7	5.8	12.6	45.2	5.5	46.6	29.6
32	19	33.6	5.5	11.7	45.3	5.2	48.7	31.6
60	16	34.3	5.5	12.4	46.4	5.3	47.7	28.4
116	12	33.1	6.1	12.1	45.2	5.2	48.2	31.8
144								
172	10	34.6	5.6	11.1	45.7	5.5	47.9	30.5
200	8	34.0	6.1	11.6	45.6	4.9	48.6	32.9
228	7	34.3	5.4	11.3	45.6	4.1	47.1	32.7

Table 3. Means of measurements (mm) on CT scan
Children with NHR-ALL

wknr	n	A	A1	B	A+B	C	D	E
0	44	31.9	3.8	8.1	40.0	3.2	45.2	27.0
6	45	33.6	5.9	11.2	44.8	5.1	48.3	30.7
18	44	33.1	5.8	11.0	44.1	5.5	49.0	31.2
32	44	32.5	5.0	9.7	42.1	4.6	48.1	29.4
60	39	32.6	4.7	9.0	41.6	4.2	48.7	29.5
116	32	32.5	4.6	8.8	41.3	3.9	47.7	29.6
144	30	31.6	3.7	8.2	39.8	3.3	47.2	29.2
172	27	31.2	3.8	7.6	38.7	3.2	46.4	27.0

Table 4. Mean values of measurements (mm) on CT scans
All children

week	n	S2	Fi	Fo	G	H
0	69	107.8	102.3	115.8	121.9	133.8
6	68	108.4	102.9	119.1	122.1	133.7
18	64	107.8	102.1	115.8	122.7	134.4
32	63	107.4	102.1	115.7	122.7	134.7
60	55	107.8	102.6	115.7	123.1	135.1
116	44	107.9	103.0	116.1	123.2	135.1
144	31	108.0	103.1	116.4	123.3	135.2
172	37	108.0	103.0	116.1	123.2	135.2
200	8	110.1	105.5	120.3	126.3	138.9
228	7	111.0	106.6	119.7	126.6	138.7

Table 5. Mean values of measurements (mm) on CT scans
Children with HR-ALL

week	n	S2	Fi	Fo	G	H
0	24	107.2	101.5	115.9	121.4	133.6
6	22	108.2	102.2	115.5	121.6	133.2
18	20	107.3	102.5	116.4	122.4	134.4
32	19	107.7	103.0	116.7	123.4	135.5
60	16	108.0	103.4	117.4	123.9	136.2
116	12	106.9	102.6	115.8	122.5	134.5
144						
172	10	107.0	101.6	115.6	123.6	135.2
200	8	110.1	105.5	120.3	126.3	138.9
228	7	111.0	106.6	119.7	126.6	138.7

Table 6. Mean values of measurements (mm) on CT scans
Children with NHR-ALL

week	n	S2	Fi	Fo	G	H
0	45	108.2	102.7	115.6	122.1	133.8
6	45	108.5	103.3	116.4	122.4	134.0
18	44	108.0	102.0	115.5	122.8	134.4
32	44	107.3	101.7	115.3	122.5	134.3
60	39	107.6	102.2	115.1	122.8	134.7
116	32	108.3	103.2	116.2	123.4	135.3
144	31	108.0	103.1	116.4	123.3	135.2
172	27	108.4	103.6	116.3	123.0	135.2

Huckmannumber according to Meese

The Huckmannumber is composed by the sum of the measurements A and B (frontal horn span and intercaudate distance).

In the 67 children, in whom this value could be calculated at diagnosis, the mean Huckmannumber was 39.5 mm (SEM 0.7). In 61 of these children plus 6 others, measured after induction treatment, the mean was found to be 45.7 mm (SEM 0.8)(paired Wilcoxon $p < 0.001$). At week 18, after the irradiation, the mean in 64 evaluable children was 44.4 mm (SEM 0.8)(not significant). This mean value gradually decreased untill week 144 and increased thereafter. In the group of children with HR-ALL as well as in the group of children with

NHR-ALL, the mean values were significantly higher ($p < 0.001$) after induction treatment. In the HR-ALL group, the mean values after irradiation (at week 18) declined slightly and remained about the same thereafter. In the NHR-ALL group there was a steady decline in the mean values, with significant differences between week 18 and week 32 ($p=0.003$), week 116 and week 144 ($p=0.016$) and week 144 and week 172 ($p=0.013$) (tables 1-3 and figure 1). Because the upper limit of normal values of the Huckmannumber acc. to Meese differ between children less than 2 years of age and those aged 2 years and older, the groups were divided accordingly.

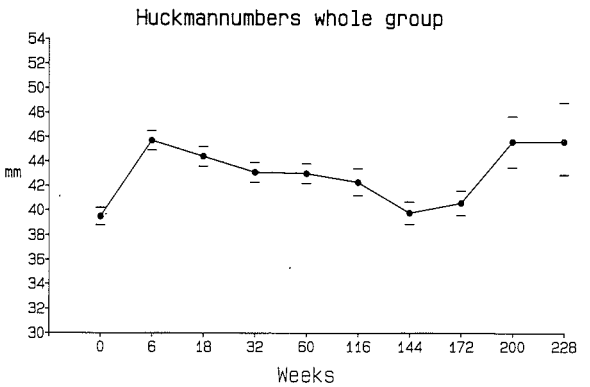
Within the risk groups, the same increase in the Huckmannumbers after induction treatment was found in the younger children as in the older ones. Over the next period, Huckmannumbers declined more and remained fairly stable thereafter in the younger children, while the older children showed the pattern as described above (table 7).

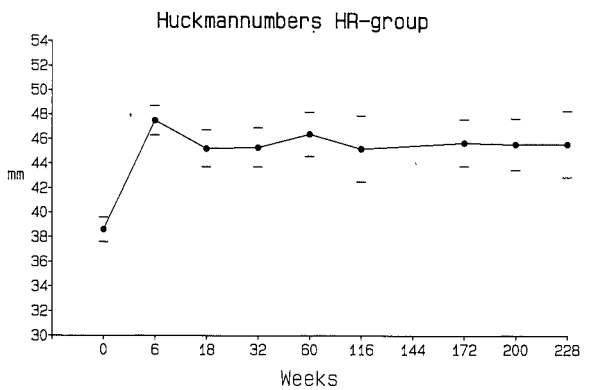
Table 7. Means of Huckmannumbers at different times
Agegroups 0 - 2 years and 2 years or over

	HR-ALL				NHR-ALL			
	0 - 2 years		>= 2 years		0 - 2 years		>= 2 years	
week	n	mean	n	mean	n	mean	n	mean
0	3	33.7	20	39.3	4	41.5	40	39.8
6	2	42.0	20	48.1	4	44.8	41	44.8
18	3	35.0	17	47.0	3	39.3	41	44.4
32	3	35.7	16	47.1	3	37.0	41	42.5
60	2	38.0	14	47.6	3	39.0	36	41.8
116	2	33.0	10	47.6	3	37.7	29	41.6
144					2	38.5	28	39.9
172			10	45.7	2	35.5	25	39.0
200			8	45.6				
228			7	45.6				

When all the children were grouped according to age at diagnosis (0 - 1.9, 2 - 3.9, 4 - 5.9, 6 - 9.9 and >= 10 years), an earlier diminishment and a tendency to lower values was present in the age group 2 - 3.9 years, especially during treatment. This was the case in children with a HR-ALL as well as in those with a NHR-ALL (figure 2 and tables 8 to 10).

Figure 1. Mean Huckmannumbers in all children and acc. to risk groups





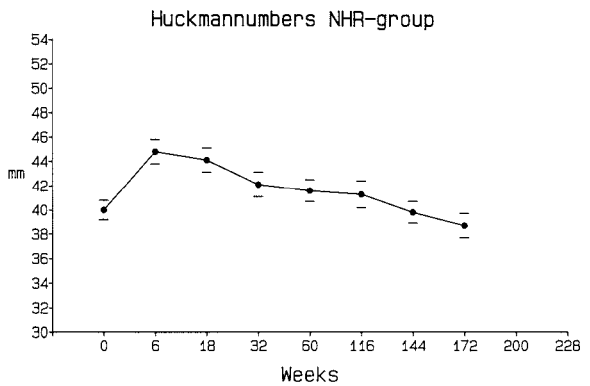


Figure 2. Mean Huckmannumbers according to agegroups

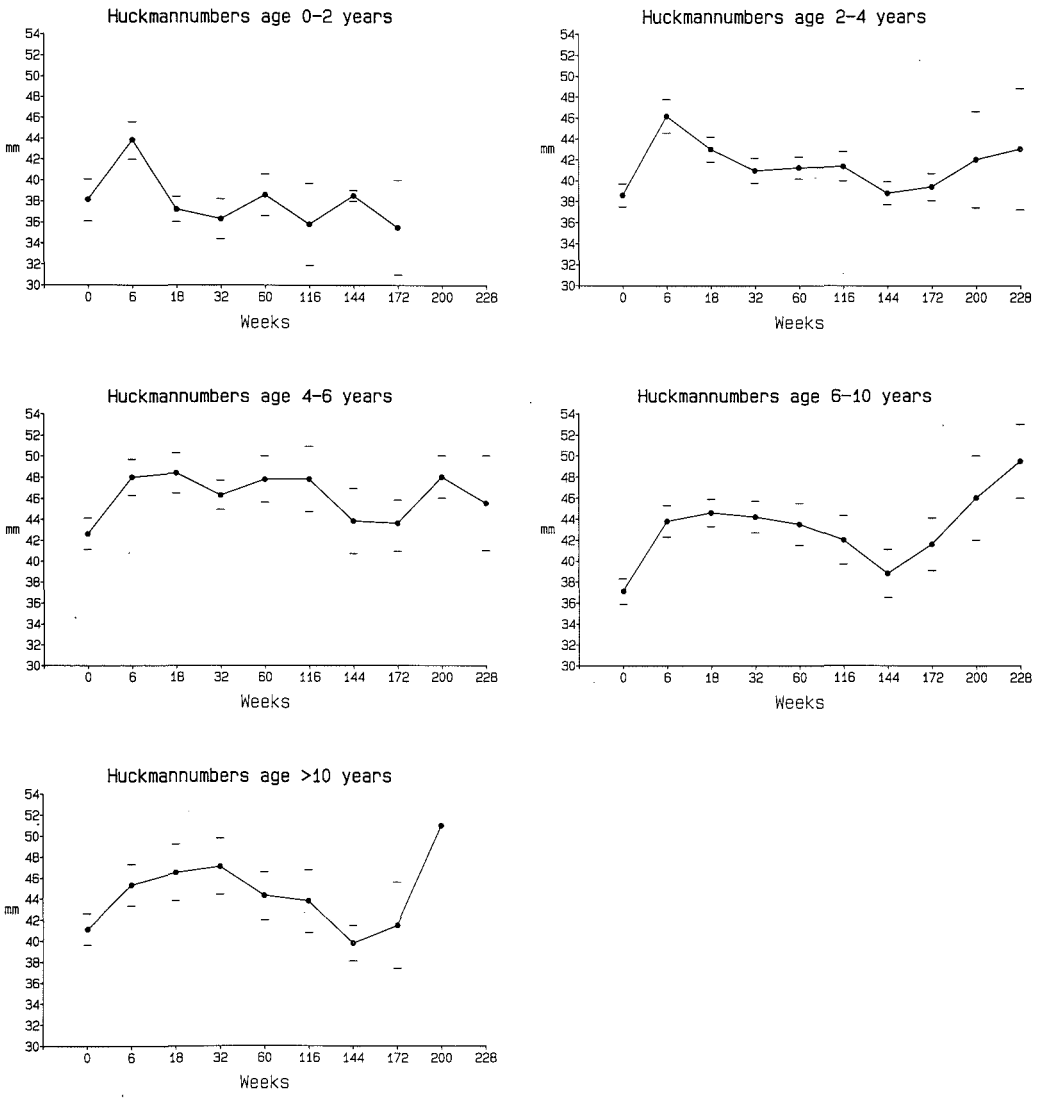


Table 8. Means of Huckmannumbers (mm) at different times
All children, several agegroups

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
week	n	mean	n	mean	n	mean	n	mean	n	mean
0	7	38.1	21	38.6	12	42.6	13	37.1	14	41.1
6	6	43.8	23	46.2	13	48.0	13	43.8	12	45.3
18	6	37.2	22	43.0	13	48.4	13	44.6	10	46.5
32	6	36.3	24	41.0	12	46.3	11	44.2	10	47.1
60	5	38.6	23	41.3	10	47.8	10	43.5	7	44.3
116	5	35.8	18	41.4	8	47.8	8	42.0	5	43.8
144	2	38.5	13	38.8	5	43.8	6	38.8	4	39.8
172	2	35.5	17	39.4	7	43.6	7	41.6	4	41.5
200			3	42.0	2	48.0	2	46.0	1	51.0
228			3	43.0	2	45.5	2	49.5		

Table 9. Means of Huckmannumbers (mm) at different times
Children with HR-ALL agegroups >= 2 years

	2 - 4 years		4 - 6 years		6 - 10 years		>= 10 years	
week	n	mean	n	mean	n	mean	n	mean
0	4	34.5	5	43.8	6	38.3	5	39.8
6	5	49.2	6	50.0	6	45.2	3	48.0
18	3	40.7	6	48.8	5	46.4	3	50.7
32	5	44.0	5	47.0	3	47.7	3	52.0
60	5	43.8	4	50.0	3	48.0	2	52.0
116	5	45.0	2	51.0	2	48.5	1	52.0
144								
172	5	42.2	2	48.0	2	49.0	1	52.0
200	3	42.0	2	48.0	2	46.0	1	51.0
228	3	43.0	2	45.5	2	49.5		

Table 10. Means of Huckmannumbers (mm) at different times
Children with NHR-ALL agegroups >= 2 years

	2 - 4 years		4 - 6 years		6 - 10 years		>= 10 years	
week	n	mean	n	mean	n	mean	n	mean
0	17	39.6	7	41.7	7	36.0	9	41.8
6	18	45.3	7	46.3	7	42.6	9	44.3
18	19	43.3	7	48.0	8	43.5	7	44.7
32	19	40.2	7	45.7	8	43.0	7	45.0
60	18	40.6	6	46.3	7	41.6	5	41.2
116	13	40.1	6	46.7	6	39.8	4	41.8
144	13	38.8	5	43.8	6	38.8	4	39.8
172	12	38.3	5	41.8	5	38.6	3	38.0

The differences between the values obtained for each child at the beginning as well as at the end of every period (delta) offer an impression about the variations over each interval. In one of the 61 children in whom measurements were made at diagnosis as well as after induction treatment (at week 6), the Huckmannumber became 4 mm smaller, remained the same in two and increased up to 19 mm in 58. Twenty-nine of the 59 children, measured at week 6 as well as at week 18, i.e. before and after irradiation, had lower values (1 to 11 mm less), 5 remained the same and 25 had higher values (1 to 10 mm more).
In the 19 children with HR-ALL who were measured both at week 0 and at week 6 all Huckmannumbers increased 1 to 19 mm with a mean of 7.6 mm. Over the next period, 9 values decreased maximally 8 mm, 2 remained the same and 6 increased up to 6 mm. The overall result was a mean decrease of 1.0 mm. Except for an increase in the second half year of therapy and in the second half year after treatment, a decrease in the means of the differences per interval was found. Children were also grouped according to age under 2 years and 2 years or older. Since only a few children were less than 2 years, no specific pattern emerged (tables IV.22 to IV.24).
In the 42 children with NHR-ALL, one Huckmannumber declined 4 mm, two remained the same and 39 increased up to 12 mm over the first 6 weeks, with a mean increase of 4.3 mm. After irradiation, at week 18, 20 Huckmannumbers had become 1 to 11 mm smaller, three remained the same and 19 had become up to 10 mm larger, with a mean decrease of 0.5 mm. In the next period, most numbers decreased. During further therapy, there was a slight increase in the values. After completion of treatment, a steady decline became evident (table IV.25). Again, children were grouped according to age under or over 2 years, but the number of children under 2 years was too small to show a specific pattern (tables IV.26 and IV.27).

Comparing the differences between values obtained at a certain time with those at diagnosis (cumulative delta (cumdelta)) in each child, an impression can be gained of the overall effects of the treatment and eventually, thereafter.
In the children with a HR-ALL, all, sometimes with the exception of one, had higher Huckmannumbers at each time during treatment compared with the ones at diagnosis. After therapy, most of the few evaluable children had still higher values. All children aged 2 years or older had higher values during therapy. The differences with the values at diagnosis, however, became gradually smaller. All the differences during treatment in this last group were significant

(p=0.012 or less)(tables IV.28 to IV.30).
In the children with NHR-ALL 17% to 28% of the Huckmannumbers during treatment from the postirradiation period on, were less than those at diagnosis and 7% to 10% were the same. All differences were significant (p=0.002 or less). After the end of therapy, more children proved to have values smaller than or equal to those at diagnosis. These differences were not significant any more. In the younger children the differences tended to be smaller and the means were most of the time negative. In the children aged 2 years and older, the differences were larger and the means were positive. All differences during treatment were significant (p=0.001 or less). At half a year after completion of treatment, the differences with the values at diagnosis were slightly significant (p=0.039). This proved not to be the case any more at one year after the end of treatment (tables IV.31 to IV.33).

Results of interpreted measurements

Coded Huckmannumber according to Meese

The interpreted codes for the Huckmannumber according to Meese are presented in table IV.13. At diagnosis, the mean of these codes for all patients proved to be 0.37 (SEM 0.09). This value increased significantly ($p < 0.001$) to 1.25 (SEM 0.12) at the end of the induction therapy. Thereafter, the mean value declined steadily untill week 60, but only the decline from week 18 to week 32 was significant (p=0.025). An outspoken lower mean value existed at week 144, at which moment only children with a NHR-ALL were examined.
In the children with HR-ALL, there was a great difference between the mean of the codes at diagnosis (0.22, SEM 0.13) and the one at the end of the induction treatment (1.61, SEM 0.16)(p 0.001). A slight decline in the mean value was found at week 18 (1.30, SEM 0.21). It remained at the same level in this group of children thereafter. No decline was found after treatment.
In the children with a NHR-ALL a less outspoken rise in the mean value of codes at diagnosis (0.44, SEM 0.12) and after induction (1.07, SEM 0.15) was observed, which however was still significant (p=0.001). The mean values declined thereafter untill week 60 was reached, with a slightly significant difference only between week 18 and week 32 (p=0.026). After the

second year of treatment the mean value proved to be the same, and dropped, although insignificantly, after stopping treatment (table 11).

Table 11. Mean codes of Huckmannumbers at different times
Whole group and according to risk groups

	Whole group		HR-ALL		NHR-ALL	
week	n	mean	n	mean	n	mean
0	68	0.37	23	0.22	45	0.44
6	68	1.25	23	1.61	45	1.07
18	64	1.00	20	1.30	44	0.86
32	63	0.76	19	1.26	44	0.55
60	55	0.64	16	1.25	39	0.39
116	44	0.66	12	1.33	32	0.41
144	31	0.26			31	0.26
172	37	0.57	10	1.30	27	0.30
200	8	1.25	8	1.25		
228	7	1.14	7	1.14		

In the children aged less than 2 years the mean codes were relatively high, the more so in the children with a NHR-ALL. These reverted soon to normal however. In the older children with a HR-ALL, the mean of the codes rose steadily after an initial fall during the postirradiation period. None of the differences between the consecutive means were significant however. In the group children with a NHR-ALL aged 2 years and older, the means declined during the first year of treatment and in the first half year after the end of therapy. Only the difference between week 18 and week 32 was found to be borderline significant (p=0.041)(table 12).

All children were grouped according to age at diagnosis (0 - 1.9, 2 - 3.9, 4 -5.9, 6 - 9.9, >= 10 years). A high mean value of the codes of 1.29 at diagnosis was found in the children under 2 years of age, with only a slight rise to 1.43 after induction therapy. This mean declined to 0 after one year of treatment and remained so thereafter.

In the older age groups, the mean values of the codes at diagnosis were equal to or lower than 0.50. These were all significantly risen in each age group at the end of induction with ± 1 point. The means were about the same or lower after radiation therapy at week 18 and tended to decline thereafter. Especially in the age groups 4 - 5.9 and 6 - 9.9 years, the mean values remained at high levels comparable with those at week 18. This resulted from a

relatively larger proportion of children with HR-ALL with higher mean values (table 13).

Table 12. Mean codes of Huckmannumbers at different times
Agegroups 0 - 2 years and 2 years or older

	HR-ALL				NHR-ALL			
	0 - 2 years		>= 2 years		0 - 2 years		>= 2 years	
week	n	mean	n	mean	n	mean	n	mean
0	3	0.67	20	0.15	4	1.75	41	0.32
6	3	1.33	20	1.65	4	1.50	41	1.02
18	3	1.00	17	1.35	3	0.67	41	0.88
32	3	0.67	16	1.38	3	0.0	41	0.59
60	2	0.0	14	1.43	3	0.0	36	0.42
116	2	0.0	10	1.60	3	0.0	29	0.45
144					3	0.0	28	0.29
172			10	1.30	2	0.0	25	0.32
200			8	1.25				
228			7	1.14				

Table 13. Mean codes of Huckmannumbers at different times
Whole group, several agegroups

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
week	n	mean	n	mean	n	mean	n	mean	n	mean
0	7	1.29	22	0.23	12	0.50	13	0.08	14	0.29
6	7	1.43	23	1.22	13	1.54	13	1.00	12	1.17
18	6	0.83	22	0.73	13	1.54	13	0.85	10	1.20
32	6	0.33	24	0.38	12	1.17	11	1.09	10	1.10
60	5	0.0	23	0.39	10	1.30	10	0.90	7	0.52
116	5	0.0	18	0.44	8	1.38	8	0.75	5	0.80
144	2	0.0	13	0.15	5	0.80	6	0.33	4	0.08
172	2	0.0	17	0.47	7	0.71	7	0.86	4	0.50
200			3	0.67	2	2.00	2	1.00	1	2.00
228			3	0.67	2	1.00	2	2.00		

With regard to the codes for the Huckmannumber acc. to Meese, 10 of 68 coded children (15%) were abnormal at diagnosis. After induction treatment, 42 of 68 tested children (62%) were coded as abnormal, while after radiation therapy only 31 of 64 tested children (48%) were found to be abnormal. These

percentages declined untill therapy had been given for one year and remained so thereafter. Half a year after stopping treatment a low value of 13% abnormal scans became evident in the children with NHR-ALL (week 144). Half a year and one year after stopping treatment, however, about 60% of the children with HR-ALL had abnormal cans (week 200 and 228)(table 14).

The proportion of children with abnormal scans at diagnosis was slightly lower in children with HR-ALL (2 of 23, 9%) than in children with NHR-ALL (8 of 45, 18%). After induction treatment 18 of 23 (78%) children with HR-ALL and 24 of 45 (53%) children with NHR-ALL had abnormal scans as defined by the Huckmannumber acc. to Meese.

In both groups the proportion of abnormal scans was less after radiation treatment (60% in HR-ALL and 43% in NHR-ALL) at week 18. Thereafter, the proportion of children with abnormal scans remained the same in the group with HR-ALL but reverted soon to the initial percentage in the group with NHR-ALL (table 15 and 16).

Table 14. Codes of Huckmannumbers at different times
Whole group

	code	0		1		2	
week	n	n	%	n	%	n	%
0	68	53	78	5	7	10	15
6	68	25	37	1	1	42	62
18	64	31	48	2	3	31	48
32	63	37	59	4	6	22	35
60	55	36	65	3	5	16	29
116	44	29	66	1	2	14	32
144	31	27	87			4	13
172	37	26	70	1	3	10	27
200	8	3	37			5	63
228	7	3	43			4	57

Table 15. Codes of Huckmannumbers at different times
Children with HR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	23	20	87	1	4	2	9
6	23	4	17	1	4	18	78
18	20	6	30	2	10	12	60
32	19	7	37			12	63
60	16	5	31	2	13	9	56
116	12	4	33			8	67
144							
172	10	3	30	1	10	6	60
200	8	3	38			5	63
228	7	3	43			4	57

Table 16. Codes of Huckmannumbers at different times
Children with NHR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	45	33	73	4	9	8	18
6	45	21	47			24	53
18	44	25	57			19	43
32	44	30	68	4	9	10	23
60	39	31	79	1	3	7	18
116	32	25	78	1	3	6	19
144	31	27	87			4	13
172	27	23	85			4	15

In the 3 children younger than 2 years of age with HR-ALL, one (33%) had an abnormal scan at diagnosis, as opposed to 1/20 (5%) aged 2 years or older. After induction treatment, these percentages were 67% and 80% resp. In the younger age group this percentage became 33% after irradiation and 0% after one year of treatment. In the older age group this percentage declined to 65% after irradiation and remained so during further follow-up (table IV.34 and IV.35).

In the 4 children younger than 2 years of age with NHR-ALL, 3 (75%) had abnormal scans at diagnosis, as opposed to 5/41 (12%) aged 2 years or older. At the end of the induction treatment the proportions of abnormal scans were

75% and 51% resp. In the young children, only one (33%) was still abnormal after irradiation. There were no abnormal scans after half a year of treatment. In the older age group 44% was still abnormal after irradiation. During further treatment about one-fifth of the children remained coded as abnormal. This proportion declined to about one-seventh after treatment had been completed (table IV.36 and IV.37).

The changes of codes in children, evaluated at the beginning as well as at the end of each interval, are presented in tables IV.38 - IV.40 for children with HR-ALL and in tables IV.41 - IV.43 for children with NHR-ALL.
Sixty percent of all children with a HR-ALL changed from normal to abnormal (i.e. +2 codes) during induction treatment. Thereafter, 71% to 91% of these patients remained unchanged. In the 3 younger children with HR-ALL one became abnormal after induction treatment. During the remainder of the first year of therapy none was upgraded and one was downgraded in each interval. In the older children, 11 of 17 (65%) changed from normal to abnormal during induction treatment. Thereafter, only one child changed one or two codes upwards in each interval except for the third year of therapy and the first year thereafter. In several periods only one, two or three children (7% to 14%) changed one or two codes downwards (tables IV.38 - IV.40).
Twenty-six percent of all children with a NHR-ALL changed from normal to abnormal (i.e. +2 codes) during induction treatment. Thereafter, 75% to 93% of these patients remained unchanged. In the 4 younger children with a NHR-ALL one changed one code downwards during induction treatment and one child changed from abnormal to normal in each of the next two periods. In the older children, 11 of 39 (28%) changed from normal to abnormal during induction treatment. Thereafter, only one to two children changed one or two codes upwards in each period except for the second half of the first year of therapy. In all periods after induction treatment, one to nine children (3% to 22%) changed one or two codes downwards (tables IV.41 - IV.43).

Comparing the codes at different times after induction therapy with those at diagnosis, a different pattern in children with HR and NHR-ALL became apparent.
In children with HR-ALL 25 - 38% of scans remained unchanged or became unchanged again during treatment in comparison with the code at diagnosis. Five to 10% of the scans were downgraded one or two codes and 60 - 75% were graded up for one or two codes. After completion of treatment the scans were found

to be unchanged in 33 - 40% of the children, compared with the scans at diagnosis. They were found to be upgraded for one or two codes in 60 - 67% of cases. The children younger than 2 years of age seemed to have changed less (tables IV.44 - IV.46).

In children with NHR-ALL however, 69 - 77% of scans remained unchanged or became unchanged again during treatment. Downgrading for one or two codes was found in 4 - 16% of scans and upgrading in 8 - 26%. After stopping treatment, the scans were coded as unchanged in 80 - 86% of the cases and were downgraded in 14 - 16%. In the children aged less than 2 years, codes seemed to have been graded downwards more often (tables IV.47 - IV.49).

Coded interpretation according to Meese

The coding according to Meese is based on the frontal horn index (F/A), cella media index (H/E) and the width of the 3d ventricle (C). The interpreted codes according to Meese are presented in table IV.14.

In all children the mean of the codes was 0.16 (SEM 0.06) at diagnosis, which increased significantly ($p < 0.001$) to 0.63 (SEM 0.11) after induction treatment. After irradiation, the mean was slightly lower but declined significantly ($p=0.013$) to 0.33 (SEM 0.09) over the next period. A just significant decline ($p=0.043$) was found between week 116 and week 144 in which period only the children with a NHR-ALL were evaluated. For the children with a HR-ALL the mean of the codes rose during induction treatment from 0.21 (SEM 0.12) to 0.44 (SEM 0.18)(not significant, $p=0.47$). This mean rose even further during treatment. In the children with a NHR-ALL, the mean of the codes rose significantly during induction treatment from 0.13 (SEM 0.07) to 0.73 (SEM 0.14)($p=0.001$). Thereafter, a decline to 0.32 (SEM 0.11) was found over the next two periods. In the last of these two periods, the difference approached significancy ($p=0.051$)(table 17).

In the children with HR-ALL aged less than 2 years all codes were 0.0 at diagnosis and remained so for the first year of treatment. In the older children the mean at diagnosis was 0.24 and rose after induction treatment to only 0.50. A further rise was found at the end of the irradiation, followed by a fall over the next period. Thereafter, the mean rose again.

In the children with NHR-ALL aged less than 2 years the mean code was 0.25 at diagnosis and rose to 0.50 after induction treatment. Thereafter, all codes

were 0.0. In the older children the mean rose from 0.12 to 0.76 during induction treatment, declined to 0.34 after half a year of therapy and remained so during treatment. After completion of therapy the mean became about the same as at diagnosis (table 18).

Table 17. Mean codes according to Meese at different times
Whole group and according to risk groups

	Whole group		HR-ALL		NHR-ALL	
week	n	mean	n	mean	n	mean
0	69	0.16	24	0.21	45	0.13
6	68	0.63	23	0.44	45	0.73
18	63	0.57	19	0.53	44	0.59
32	63	0.33	19	0.37	44	0.32
60	55	0.40	16	0.63	39	0.31
116	44	0.50	12	0.83	32	0.38
144	31	0.07			31	0.07
172	37	0.32	10	0.80	27	0.15
200	8	0.50	8	0.50		
228	7	1.00	7	1.00		

Table 18. Mean codes according to Meese at different times
Agegroups 0 - 2 years and 2 years or older

	HR-ALL				NHR-ALL			
	0 - 2 years		>= 2 years		0 - 2 years		>= 2 years	
week	n	mean	n	mean	n	mean	n	mean
0	3	0.0	21	0.24	4	0.25	41	0.12
6	3	0.0	20	0.50	4	0.50	41	0.76
18	3	0.0	17	0.63	3	0.0	41	0.63
32	3	0.0	16	0.44	3	0.0	41	0.34
60	2	0.0	14	0.71	3	0.0	36	0.33
116	2	1.00	10	0.80	3	0.0	29	0.41
144					3	0.0	28	0.07
172			10	0.80	2	0.0	25	0.16
200			8	0.50				
228			7	1.00				

In the different agegroups the mean codes rose during induction treatment slightly in children less than 2 years and in those older than 6 years, but substantially in the children aged 2 - 3.9 and 4 - 5.9 years (p=0.008 and p=

0.028 resp.). In children younger than 4 years the means were lower after the irradiation period, while in the older ones a further increase was found, which was most outspoken in the oldest group. In children aged 6 - 9.9 years a higher mean value was found after the next period, while the means in all other groups had become lower. Very low means were found at week 144, when only children with a NHR-ALL were evaluated (table 19).

Table 19. Mean codes according to Meese at different times
Whole group, several agegroups

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
week	n	mean	n	mean	n	mean	n	mean	n	mean
0	7	0.14	22	0.18	13	0.31	13	0.0	14	0.14
6	7	0.29	23	1.04	13	1.00	13	0.15	12	0.17
18	6	0.0	22	0.50	13	1.08	12	0.33	10	0.70
32	6	0.0	24	0.33	12	0.50	11	0.46	10	0.20
60	5	0.0	23	0.35	10	0.80	10	0.40	7	0.29
116	5	0.40	18	0.50	8	0.88	8	0.25	5	0.40
144	3	0.0	13	0.15	5	0.0	6	0.0	4	0.0
172	2	0.0	17	0.24	7	0.57	7	0.29	4	0.50
200			3	0.67	2	0.0	2	0.0	1	2.00
228			3	1.00	2	1.00	2	1.00		

At diagnosis, 4 of all 69 coded children (6%) were scored as abnormal and 3 (4%) as borderline. After induction treatment however, 20 of 69 coded children (29%) were found to be abnormal and 4 (4%) borderline (table 20).

Table 20. Codes according to Meese at different times
Whole group

	code	0		1		2	
week	n	n	%	n	%	n	%
0	69	62	90	3	4	4	6
6	68	45	66	3	4	20	29
18	63	43	68	4	6	16	25
32	63	52	83	1	2	10	16
60	55	42	76	4	7	9	16
116	44	31	70	4	9	9	20
144	31	30	97			1	3
172	37	31	84			6	16
200	8	6	75			2	25
228	7	3	43	1	14	3	43

Among the children with HR-ALL, one of the 24 coded at diagnosis was borderline (4%) and two were abnormal (8%). After induction treatment 5 (21%) were abnormal. During maintenance therapy this percentage rose to 40% and remained about the same after completion of treatment (table 21).

Table 21. Codes according to Meese at different times
Children with HR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	24	21	88	1	4	2	8
6	24	19	79			5	21
18	19	13	68	2	11	4	21
32	19	15	79	1	5	3	16
60	16	10	63	2	13	4	25
116	12	6	50	2	17	3	33
144							
172	10	6	60			4	40
200	8	6	75			2	25
228	7	3	43	1	14	3	43

All 3 children with a HR-ALL and aged 0 - 1.9 years at presentation were coded as normal at diagnosis. These children remained normal during the first year of treatment. At the end of the second year, one child was normal and the other abnormal.

One of the 21 children with HR-ALL and aged 2 years or older at presentation was coded as borderline (5%) and 2 as abnormal (9%). After induction treatment 5 of the 21 coded children (24%) had abnormal scans. This remained about the same during the first 2 years of treatment. One or two children were coded as borderline in that period. After stopping treatment, 2 resp. 3 children (25% resp. 43%) had abnormal scans (tables IV.50 and IV.51).

Among the children with NHR-ALL 2 of the 45 coded at diagnosis were borderline (4%) and 2 were abnormal (4%). After induction treatment 3 (7%) were borderline and 15 (33%) were abnormal. Already at week 32, only 16% of children had abnornal scans and 84% had normal scans. This distribution remained about the same during therapy. After stopping treatment, 97% resp. 93% of the children had normal scans (table 22).

Table 22. Codes according to Meese at different times
Children with NHR-ALL

		code	0		1		2	
week	n		n	%	n	%	n	%
0	45		41	91	2	4	2	4
6	45		27	60	3	7	15	33
18	44		30	68	2	5	12	27
32	44		37	84			7	16
60	39		32	82	2	5	5	13
116	32		25	78	2	6	5	16
144	31		30	97			1	3
172	27		25	93			2	7

One of the 4 children with a NHR-ALL aged 0 - 1.9 years at presentation was coded as borderline. After induction treatment this child became normal but another child became abnormal. Thereafter, all remaining 3 children remained normal. One of the 41 children with a NHR-ALL and aged 2 years or older at presentation was coded as borderline (2%) and 2 as abnormal (5%). After induction treatment 14 of the 41 coded children (34%) had abnormal scans. This percentage declined to 17% at week 32 and remained about the same during further treatment. Only two children were coded as borderline in that period. After stopping treatment only 1 resp. 2 children (4% resp. 8%) had abnormal scans (tables IV.52 and IV.53).

The changes of codes in children, evaluated at the beginning as well as the end of each interval, are presented in tables IV.54 - IV.56 for children with HR-ALL and in tables IV.57 - IV.59 for children with NHR-ALL.
Ten percent of all children with HR-ALL changed from normal to abnormal (i.e. +2 codes) during induction treatment. Thereafter, 57% to 88% of these patients remained unchanged. All 3 younger children with HR-ALL remained normal during induction treatment. No changes in the codes were found over the other evaluated periods. In the older children, 2 of 18 (11%) changed from normal to abnormal during induction treatment. Thereafter, one to three children (8% to 43%) changed one or two codes upwards in each period, except in the first half year after the end of treatment. In several periods, one to four children (7% to 30%) changed one to two codes downwards (tables IV.54 - IV.56).

Twenty-eight percent of all children with NHR-ALL changed from normal to abnormal (i.e. +2 codes) during induction treatment. Thereafter, 60% to 96% of this group of patients remained unchanged. In the 4 younger children with a NHR-ALL, one child changed one code downwards and one changed from normal to abnormal during the induction treatment; no changes were seen thereafter. In the older children, 11 of 39 (28%) changed from normal to abnormal during induction treatment. Thereafter, one to seven children changed one or two codes upwards in each period except for the first half year after stopping therapy. In several periods after induction treatment two to nine children (6% to 26%) changed one or two codes downwards (tables IV.57-IV.59).

Comparing the codes at different times after induction therapy with those at diagnosis the same pattern in children with HR and NHR-ALL was observed.
In children with HR-ALL 68 - 88% of scans remained unchanged or became so again during treatment in comparison with the code at diagnosis. Five to 17% of the scans were downgraded one or two codes and 12 - 21% were upgraded one or two codes. After stopping treatment the scans were found to be unchanged in 80 - 83% of these children. The scan of one child became normal from abnormal and one child was upgraded for one code compared with the scans at diagnosis. Only one of the children younger than 2 years changed to abnormal after 2 years of treatment (tables IV.60 - IV.62).
In children with NHR-ALL 62 - 79% of scans remained unchanged or became so again during treatment, while downgrading for one or two codes was found in 6 - 10% of scans and upgrading in 13 - 31%. After stopping treatment, the scans were coded as unchanged in 88 - 90% of cases, upgraded in 4% (one child) and downgraded in 8 - 10%. In the children aged less than 2 years, codes only went downwards (tables IV.63 - IV.65).

Coded interpretation according to Enzmann

The interpretation according to Enzmann is based on the frontal horn distance (A), frontal horn width (Al) and bicaudate distance (B). The interpreted codes according to Enzmann are presented in table IV.15 to IV.18.

In all children the mean of the codes was 0.15 (SEM 0.06) at diagnosis, and increased significantly ($p < 0.001$) to 0.87 (SEM 0.11) after induction treatment.

For the children with HR-ALL the mean of the codes rose during induction therapy significantly ($p=0.005$) from 0.08 (SEM 0.08) to 0.83 (SEM 0.19). Thereafter, this mean value remained about the same, even after completion of treatment.

In the children with NHR-ALL the mean of the codes rose significantly from 0.18 (SEM 0.07) at diagnosis to 0.89 (SEM 0.14) after induction treatment ($p < 0.001$). The mean was just significantly ($p=0.041$) lower at the end of the postirradiation period and declined again significantly ($p=0.033$) over the next period. It declined further over the following interval to equal at week 60 the value at diagnosis. A slight increase was found over the next year, which was followed by a decline in the first 6 months after stopping therapy. These differences, although substantial, proved to be not statistically significant (table 23).

Table 23. Mean codes acc. to Enzmann at different times
Whole group and according to risk groups

	Whole group		HR-ALL		NHR-ALL	
week	n	mean	n	mean	n	mean
0	69	0.15	24	0.08	45	0.18
6	68	0.87	23	0.83	45	0.89
18	64	0.64	20	0.80	44	0.57
32	63	0.46	19	0.79	44	0.32
60	55	0.38	16	0.88	39	0.18
116	44	0.46	12	0.83	32	0.31
144	31	0.13			31	0.13
172	37	0.32	10	0.80	27	0.15
200	8	0.63	8	0.63		
228	7	0.86	7	0.86		

All children aged 0 - 1.9 and 6 - 9.9 years had a normal ventricular size at diagnosis. In the other agegroups, the means of the codes were only just above 0. After induction treatment, the mean was only slightly raised in the children younger than two years of age and became 0 again immediately thereafter. In the older children, the means rose significantly (p=0.008, 0.043, 0.028 and 0.018 resp.) after induction therapy. The mean declined significantly (p=0.018) over the next period in the children aged 2 - 3.9 years. In the older ones, on the contrary, the means changed only slightly (table 24).

Table 24. Mean codes acc. to Enzmann at different times
Whole group, several agegroups

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
week	n	mean	n	mean	n	mean	n	mean	n	mean
0	7	0.0	22	0.18	13	0.31	13	0.0	14	0.14
6	7	0.29	23	1.04	13	0.85	13	0.77	12	1.00
18	6	0.0	22	0.36	13	1.00	13	0.69	10	1.10
32	6	0.0	24	0.17	12	0.58	11	0.73	10	1.00
60	5	0.0	23	0.13	10	0.90	10	0.50	7	0.57
116	5	0.0	18	0.22	8	1.13	8	0.38	5	0.80
144	3	0.0	13	0.08	5	0.40	6	0.17	4	0.0
172	2	0.0	17	0.18	7	0.43	7	0.43	4	0.75
200			3	0.33	2	0.0	2	1.00	1	2.00
228			3	0.67	2	0.50	2	1.50		

At diagnosis, the scans of 3 of all 69 coded children (4%) were scored as abnormal and 4 (6%) as borderline. After induction treatment however, 25 of 68 tested children (37%) were found to be abnormal, 9 (13%) borderline and only 34 (50%) normal. At the end of the postirradiation period, 18 of the 64 children (28%) were abnormal, 5 (8%) borderline and 41 (64%) normal (table 25).

In the children with HR-ALL, only 1 (4%) presented with an abnormal scan at diagnosis. After induction treatment, 30% were scored as abnormal and 22% as borderline, leaving only 48% of children with normal scans. Thereafter, about a third of children were found to have abnormal scans and one sixth of children were categorized as borderline. Thus, normal scans were present in about half of the children with HR-ALL after induction (table 26).

In the children with NHR-ALL two (4%) had abnormal scans at diagnosis and 4 (9%) were borderline. After induction, 40% of children had abnormal and 9% borderline scans, leaving 51% of children with normal scans. After irradiation 25% of scans were abnormal, 7% borderline and 68% normal. Over the next half year, the percentage of normal scans rose to 90% but declined to 81% after the second year of treatment. One year after stopping therapy only one scan (4%) was found to be abnormal (table 27).

Table 25. Codes acc. to Enzmann at different times
Whole group

	code	0		1		2	
week	n	n	%	n	%	n	%
0	69	62	90	4	6	3	4
6	68	34	50	9	13	25	37
18	64	41	64	5	8	18	28
32	63	46	73	5	8	12	19
60	55	43	78	3	5	9	16
116	44	32	73	4	9	8	18
144	31	27	87	4	13		
172	37	29	78	4	11	4	11
200	8	5	63	1	13	2	25
228	7	3	43	2	29	2	29

Table 26. Codes acc. to Enzmann at different times
Children with HR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	24	23	96			1	4
6	23	11	48	5	22	7	30
18	20	11	55	2	10	7	35
32	19	10	53	3	16	6	32
60	16	8	50	2	13	6	38
116	12	6	50	2	17	4	33
144							
172	10	5	50	2	20	3	30
200	8	5	63	1	13	2	25
228	7	3	43	2	29	2	29

Table 27. Codes acc. to Enzmann at different times
Children with NHR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	45	39	87	4	9	2	4
6	45	23	51	4	9	18	40
18	44	30	68	3	7	11	25
32	44	36	82	2	5	6	14
60	39	35	90	1	3	3	8
116	32	26	81	2	6	4	12
144	31	27	87	4	13		
172	27	24	89	2	7	1	4

Comparing the codes at different times with the former ones it was found that in the first 6 weeks of treatment 56% of all scans had not changed, 20% had changed one code and 23% had changed two codes (i.e. from normal to abnormal). This pattern was the same for HR-ALL and NHR-ALL. Thereafter, however, patterns proved to be different in these risk groups. After the irradiation period, 23% resp. 24% of scans changed backwards one or two codes in both groups. In the HR-ALL group 28% of scans gained one or two codes and 50% did not change. In the NHR-ALL group, however, only 4% of scans were graded upwards and 71% did not change.
In the following intervals 75 - 94% of codes did not change. The codes for some scans changed backwards and for others upwards. On the whole there was a tendency in the NHR-ALL group to change more often backwards (tables IV.66 and IV.67).

Comparing the codes at different times after induction therapy with those at diagnosis, a different pattern in children with HR and NHR-ALL was observed. In children with HR-ALL 50 - 60% of scans remained unchanged and 40 - 50% were graded upwards for one or two codes during treatment. After stopping treatment the scans of 40 - 67% of children with HR-ALL were found to be unchanged and in 33 - 60% of the cases these had been upgraded one or two codes compared with the scans at diagnosis. None of the scans were downgraded in comparison with the code at diagnosis (Table IV.68).
In children with NHR-ALL 71 - 86% of scans remained unchanged during treatment, 6 - 26% were upgraded for one or two codes and 2 - 9% of scans were downgraded.

After stopping treatment 92 - 93% of scans had the same code as at diagnosis and 6 - 8% were found to be downgraded for one or two codes (Table IV.69).

The percentages of normal, borderline and abnormal codes at different times and according to the three different methods of evaluation for the children with HR-ALL and NHR-ALL are presented in table 28 and 29 and in figure 3.

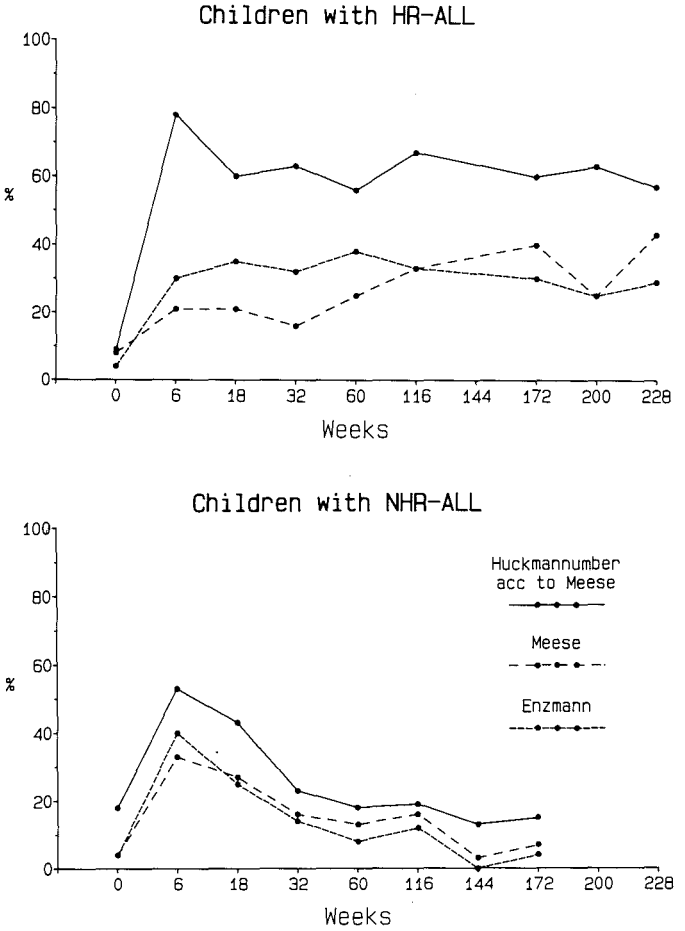
Table 28. Comparison of the evaluations of CT scans according to three different methods.
Percentages of codes for children with HR-ALL

		Normal			Borderline			Abnormal		
week	n	H	M	E	H	M	E	H	M	E
0	24	87	88	96	4	4		9	8	4
6	23	17	79	48	4		22	78	21	30
18	20	30	68	55	10	11	10	60	21	35
32	19	37	79	53		5	16	63	16	32
60	16	31	63	50	13	13	13	56	25	38
116	12	33	50	50		17	17	67	33	33
144										
172	10	30	60	50	10		20	60	40	30
200	8	38	75	63			13	63	25	25
228	7	43	43	43		14	29	57	43	29

Table 29. Comparison of the evaluations of CT scans according to three different methods.
Percentages of codes for children with NHR-ALL

		Normal			Borderline			Abnormal		
week	n	H	M	E	H	M	E	H	M	E
0	45	73	91	87	9	4	9	18	4	4
6	45	47	60	51		7	9	53	33	40
18	44	57	68	68		5	7	43	27	25
32	44	68	84	82	9		5	23	16	14
60	39	79	82	90	3	5	3	18	13	8
116	32	78	78	81	3	6	6	19	16	12
144	31	87	97	87			13	13	3	
172	27	85	93	89			7	15	7	4

Figure 3. Three different methods of evaluation of CT scans
Percentages of abnormal scans in children with HR-ALL and NHR-ALL



The codes as obtained by each of the different evaluation methods were compared for each patient.

The codes of the Huckmannumbers acc. to Meese were the same as the codes acc. to Meese in 63 - 90 % of all cases. The codes acc. to Huckman were lower than those acc. to Meese in 2 - 14% of cases and higher in 10 - 38%. Higher codes acc. to Huckman than those acc. to Meese were found more often in children with a HR-ALL than in children with a NHR-ALL. In the HR-ALL group codes acc. to Huckman were the same as acc. to Meese in 39 - 74% of cases, lower for Huckman in 8 - 14% and higher in 13 - 63%. These percentages were 69 - 92%, 2 - 9% and 7 - 26% respectively in children with NHR-ALL (table 30, IV.70, IV.71).

Table 30. Comparison of the coded evaluations of CT scans
Huckman compared with Meese.
Percentages of codes for all children with ALL

		Concordant			Huckm < Meese			Huckm > Meese		
week	n	00	11	22	01	02	12	10	20	21
0	68	71			2	6		7	12	3
6	68	34		29	3			2	31	2
18	63	48		25	2			3	18	5
32	63	59		14			2	5	19	2
60	55	66		15			2	4	7	7
116	44	57		11		9		2	11	9
144	31	87		3					10	
172	37	70		16				3	11	
200	8	38		25					38	
228	7	29		43	14				14	

The codes of the Huckmannumbers acc. to Meese were the same as the codes acc. to Enzmann in 63 - 87% of all cases. The codes acc. to Huckman were lower than those acc. to Enzmann in 2 - 4% of cases and higher in 13 - 38%. Higher codes acc. to Huckman than acc. to Enzmann were found more often in children with HR-ALL than in children with NHR-ALL again. In the HR-ALL group codes were the same in 39 - 91% of cases, lower for Huckman in 4 - 5% and higher in 8 - 56%. These percentages were 74 - 88%, 2 - 4% and 9 - 23% respectively in children with NHR-ALL (table 31, IV.72, IV.73).

Table 31. Comparison of the coded evaluations of CT scans
Huckman compared with Enzmann.
Percentages of codes for all children with ALL

		Concordant			Huckm < Enzm			Huckm > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	68	77	2	3		2		6	7	4
6	68	34		35	2	2		2	15	12
18	64	45		27	2	2		3	16	6
32	63	57		19	2			6	10	6
60	55	66		16				6	7	6
116	44	64		18	2			2	7	7
144	31	87								13
172	37	68		11	3			3	8	8
200	8	38		25					25	13
228	7	43		29						29

In all children the codes acc. to Meese and acc. to Enzmann were the same in 58 - 89 % of cases. The codes acc. to Meese were lower than those acc. to Enzmann in 5 - 23% of cases and higher in 3 - 28%. In children with a HR-ALL more different codes acc. to Meese than acc. to Enzmann were found in comparison with children with a NHR-ALL. In the HR-ALL group codes were the same in 57 - 83% of cases, lower for Meese in 4 - 34% and higher in 5 - 28%, while these percentages were 76 - 93%, 4 - 15% and 3 - 12% respectively in children with NHR-ALL (table 32, IV.74, IV.75).

Table 32. Comparison of the coded evaluations of CT scans Meese compared with Enzmann.
Percentages of codes for all children with ALL

		Concordant			Meese < Enzm			Meese > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	69	81	1		4	4		3	6	
6	68	46		24	9	12	2	3	2	4
18	63	57		19	6	5	3	3	5	2
32	63	68		8	5	10	2		5	3
60	55	73		7	2	2	7		6	4
116	44	61		11	7	2	5	5	7	2
144	31	87			10					3
172	37	78		11	5					5
200	8	63		13		13				13
228	7	29		29	14			14		14

Coded interpretation of sulci

The mean of the codes for sulci at diagnosis concerning all children was 0.23 (SEM 0.07). This value increased significantly ($p < 0.001$) to 1.66 (SEM 0.08) after induction treatment. After irradiation the mean was slightly lower, but declined significantly ($p=0.018$) to 1.44 (SEM 0.11) over the next period. The mean at the end of the first year of treatment (1.31, SEM 0.12) was just significantly lower ($p=0.048$) than half a year earlier. A significant difference ($p=0.001$) was found between the means at week 116 and week 144, i.e. in the first half year after stopping treatment in the children with NHR-ALL. Over the corresponding period in children with HR-ALL,

week 172 to week 200, a tendency to significancy (p=0.068) was seen. The means of the risk groups are comparable in the period of treatment. In both groups the mean declined after therapy had been completed (table 33).

Independent of risk group, the means increased somewhat less in the children aged less than 2 years, and tended to become normal earlier (table 34).

The pattern of the means for sulci was the same in the different age groups. However, the means in the youngest age group tended to be lower (table 35).

Table 33. Mean codes of sulci at different times
Whole group and to risk groups

	Whole group		HR-ALL		NHR-ALL	
week	n	mean	n	mean	n	mean
0	69	0.23	24	0.17	45	0.27
6	68	1.66	23	1.74	45	1.62
18	63	1.64	19	1.68	44	1.61
32	62	1.44	19	1.42	43	1.44
60	55	1.31	16	1.38	39	1.28
116	44	1.18	12	1.33	32	1.13
144	31	0.48			31	0.48
172	37	0.70	10	1.40	27	0.44
200	8	1.25	8	1.25		
228	7	0.57	7	0.57		

Table 34. Mean codes of sulci at different times
Agegroups 0 - 2 years and 2 years or oder

	HR-ALL				NHR-ALL			
	0 - 2 years		>= 2 years		0 - 2 years		>= 2 years	
week	n	mean	n	mean	n	mean	n	mean
0	3	0.33	21	0.14	4	0.25	41	0.27
6	3	1.33	20	1.80	4	1.50	41	1.63
18	2	1.00	17	1.77	3	1.00	41	1.66
32	3	0.33	16	1.63	3	0.33	40	1.53
60	2	0.0	14	1.57	3	0.0	36	1.39
116	2	1.00	10	1.40	3	0.0	29	1.24
144					3	0.0	28	0.54
172			10	1.40	2	0.0	25	0.48
200			8	1.25				
228			7	0.57				

Table 35. Mean codes of sulci at different times
Whole group, several agegroups

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
week	n	mean	n	mean	n	mean	n	mean	n	mean
0	7	0.29	22	0.46	13	0.0	13	0.08	14	0.21
6	7	1.43	23	1.74	13	1.77	13	1.77	12	1.42
18	5	1.00	22	1.68	13	1.62	13	1.69	10	1.80
32	6	0.33	23	1.52	12	1.42	11	1.55	10	1.80
60	5	0.0	23	1.39	10	1.30	10	1.60	7	1.57
116	5	0.40	18	1.11	8	1.38	8	1.63	5	1.20
144	3	0.0	13	0.54	5	0.40	6	0.33	4	1.00
172	2	0.0	17	0.59	7	0.71	7	1.00	4	1.00
200			3	1.33	2	1.00	2	1.00	1	2.00
228			3	0.67	2	0.0	2	1.00		

The codes for sulci were borderline abnormal in 6 (9%) of the 69 children and were abnormal in 5 (7%). After induction treatment, only 6 (9%) were still normal, 11 (16%) were borderline abnormal and 51 (75%) were abnormal. During treatment, a slow shift towards more normal codes was seen, which was more evident among the children with NHR-ALL. After therapy had been completed a definite shift towards normal sulci was found. This took one year in children with HR-ALL and half a year in those with NHR-ALL (table 36 - 38).

Table 36. Codes of sulci at different times
Whole group

	code	0		1		2	
week	n	n	%	n	%	n	%
0	69	58	84	6	9	5	7
6	68	6	9	11	16	51	75
18	63	9	14	5	8	49	78
32	62	14	23	7	11	41	66
60	55	15	27	8	15	32	58
116	44	15	34	6	14	23	52
144	31	22	71	3	10	6	19
172	37	22	59	4	11	11	30
200	8	1	13	4	50	3	38
228	7	5	71			2	29

Table 37. Codes of sulci at different times
Children with HR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	24	21	87	2	8	1	4
6	23			6	26	17	74
18	19	2	11	2	11	15	79
32	19	4	21	3	16	12	63
60	16	4	25	2	13	10	63
116	12	4	33			8	67
144							
172	10	3	30			7	70
200	8	1	13	4	50	3	38
228	7	5	71			2	29

Table 38. Codes of sulci at different times
Children with NHR-ALL

	code	0		1		2	
week	n	n	%	n	%	n	%
0	45	37	82	4	9	4	9
6	45	6	13	5	11	34	76
18	44	7	16	3	7	34	77
32	44	10	23	4	9	29	67
60	39	11	28	6	15	22	56
116	32	11	34	6	19	15	47
144	31	22	71	3	10	6	19
172	27	19	70	4	15	4	15

One of the 3 children less than 2 years of age with HR-ALL had borderline abnormal sulci at diagnosis. One of the 21 (5%) children aged 2 years or older had borderline abnormal and one (5%) had abnormal sulci.

After induction treatment, none of the children with HR-ALL had normal sulci. In the younger age group, there seemed to be a tendency to become normal again earlier. In the older age group, most children remained abnormal as long as therapy was given. During the one year of observation after treatment sulcal dilatation diminished gradually (table IV.76 and IV.77).

One of the 4 children less than 2 years of age with NHR-ALL had borderline abnormal sulci at diagnosis. The sulci of 3 of the 41 (7%) children aged 2

years or older were borderline and 4 (10%) were abnormal. At the end of the induction treatment, the proportions of abnormal scans were 75% and 76% resp. One of the young children had borderline sulci and one had abnormal sulci after irradiation. There were no abnormal scans after half a year of treatment. In the group of older children, 80% had abnormal sulci after irradiation. During further treatment, a steady decline in the proportion children with abnormal sulci was seen untill after two years 52% was reached. A relatively large number of children had borderline sulci after one or two years of treatment. Immediately after stopping therapy, a shift to a high number with normal sulci was observed (table IV.78 and IV.79).

The changes of codes in children, evaluated at the beginning as well as the end of each interval, are presented in tables IV.80 - IV.82 for children with HR-ALL and in tables IV.83 - IV.85 for children with NHR-ALL.
The sulci of one of the 3 younger children with a HR-ALL became borderline abnormal and of another one became abnormal after induction treatment. During the remainder of the first year of therapy, none were upgraded and one was downgraded in each period. In the older children, 13 of 18 (72%) changed from normal to abnormal during induction treatment. Thereafter, only one or two children changed one code upwards in some periods. In several periods during therapy, only one or two children (7% to 14%) changed one or two codes downwards (tables IV.80 - IV.82).
One of the 4 younger children with a NHR-ALL changed one code upwards and another one changed two codes upwards during induction treatment. In each of the next three periods, one child changed backwards. In the older children 23 of 39 (59%) changed from normal to abnormal during induction treatment. After irradiation, gain and loss of codes was balanced (five children each). Thereafter, more children, although in small numbers, changed one or two codes downwards in each period during therapy. In the first half year after treatment had been completed, 13 (46%) of 28 children showed a return to borderline or normal sulci (table IV.83 - IV.85).

Comparing the codes at different times after induction therapy with those at diagnosis, a slightly different pattern in children with HR-ALL and NHR-ALL was observed. In general, a higher proportion of children with HR-ALL had abnormal sulci during treatment.
In children with HR-ALL, 5 - 38% of scans remained unchanged or became so again during treatment in comparison with the codes at diagnosis. Seven or

10% of the scans (each in one patient younger than 2 years of age at diagnosis) were downgraded one code and 60% - 96% were graded up for one or two codes. After stopping treatment, the sulci were found to be unchanged in 17 and 60% of these children, 20% were downgraded for two codes and 20% - 84% were upgraded for one or two codes, compared with the scans at diagnosis. The children younger than 2 years of age seemed to have changed less (table IV.86 -IV.88).

In children with NHR-ALL however, 21% - 40% of sulci remained unchanged or became so again during treatment, while downgrading for one or two codes was found in 2 - 7% of scans (one or two children) and upgrading in 53 - 77% of scans. After stopping treatment, the sulci were coded as unchanged in 68 or 69% of cases, downgraded in 10 or 12% and upgraded in 20 or 21%. In the children younger than 2 years of age codes changed less (table IV.89 - IV.91).

In order to evaluate ventricular and sulcal dilatation on the same scans, the codes according to the different methods of interpretation for the ventricles were combined with the codes for the sulci.

The results for the interpretation for the ventricles according to Huckman and for the sulci were concordant in 38% - 72% of the scans. The ventricles were considered to be relatively too wide in relation to the sulci in 6 - 38% of cases. The opposite, sulci interpreted as relatively too wide in relation to the ventricles was the case in 14% - 47% (table 39).

The same codes for the ventricles as well as for the sulci were more often allocated to the children with HR-ALL, in particular during treatment. The sulci were more often enlarged in relation to the ventricles in the children with NHR-ALL during therapy (tables IV.92 and IV.93).

With the interpretation of the ventricles according to Meese, the sulci were found to be more often enlarged, in particular during the first year of treatment. This discrepancy was more evident in the children with a HR-ALL (tables 40, IV.94 and IV.95).

Table 39. Comparison of the coded evaluations of CT scans
Sulci with ventricles acc. to Huckman.
Percentages of codes for all children with ALL

		Concordant			Sulci < Huckm			Sulci > Huckm		
week	n	00	11	22	01	02	12	10	20	21
0	68	66	2		4	13	2	6	6	2
6	68	7	2	50		2	10	4	25	
18	63	8	2	43		6		6	33	2
32	62	16		29	2	5	2	10	32	5
60	55	24	2	20		4	6	7	35	4
116	44	25		21	2	7	5	9	32	
144	31	65		3		7	3	7	16	
172	37	54		16		5	5	5	11	3
200	8	13		25			38	13	13	
228	7	43		29		29				

Table 40. Comparison of the coded evaluations of CT scans
Sulci with ventricles acc. to Meese.
Percentages of codes for all children with ALL

		Concordant			Sulci < Meese			Sulci > Meese		
week	n	00	11	22	01	02	12	10	20	21
0	69	75		1	4	4		9	6	
6	68	9		27			3	13	44	4
18	62	15		26				8	45	7
32	62	21		15		2		11	50	2
60	55	24	4	13	2	2	2	9	44	2
116	44	32	2	16	2		5	7	32	5
144	31	71		3				10	16	
172	37	60		14			3	8	16	
200	8	13		25				50	13	
228	7	43		29	14	14				

Comparing the codes for the ventricles according to Enzmann and Lane with those for the sulci, about the same incidence of concordant codes was found as with the interpretation according to Meese, and a slightly lower incidence of concordant codes compared with the Huckman interpretation, in particular during the first half year of treatment. With this evaluation, sulci were more often enlarged than the ventricles at the end of induction treatment in the children with a HR-ALL. At week 32 till week 116 however, sulci were more often enlarged in the children with a NHR-ALL (tables 41, IV.96 and IV.97).

Table 41. Comparison of the coded evaluations of CT scans
Sulci combined with ventricles acc. to Enzmann.
Percentages of codes for all children with ALL

		Concordant			Sulci < Enzm			Sulci > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	69	77	1	1	4	3		7	6	
6	68	9	3	34			3	10	31	10
18	63	14	2	29				6	43	6
32	62	21	3	18		2		8	44	5
60	55	24	2	11	2	2	4	9	46	2
116	44	32	2	14		2	2	9	32	7
144	31	65	3		7			7	16	3
172	37	57	3	11	3			8	14	5
200	8	13		13			13	38	13	13
228	7	43		29	29					

Children with initial borderline abnormal or abnormal codes

With the interpretation of the Huckmannumbers according to Meese, the codes of one child with HR-ALL and of four patients with NHR-ALL were borderline abnormal at diagnosis. The codes of two children with HR-ALL and of eight with NHR-ALL were abnormal. Except for the code of one child (#59), which became normal, all other codes (93%) were found to be abnormal after induction therapy. At the end of the irradiation period the codes of two of the tested children (#59, #42)(15%) were normal, one (#33)(8%) borderline and the other 10 (77%) abnormal. After the next period, the child with the borderline code (#33) and three children with abnormal codes (#49, #68, #47) had become normal; one abnormal child (#53) became coded as borderline. Thus, at this time (week 32), 6 of the 13 tested children (46%) were coded as normal, 1 (8%) as borderline and 6 (46%) as abnormal. All children with an abnormal code at this time kept that code during further follow-up. The others got or kept a normal code (Table 42).

According to Meese, the codes of one child with HR-ALL and of two with NHR-ALL were borderline abnormal. The codes of two children with HR-ALL and of two with NHR-ALL were abnormal at diagnosis. After induction treatment, the codes of two children (#47, #65)(29%) became normal, of one (#30)(14%) borderline and of the four others (57%) these became or remained abnormal.

At the end of the irradiation period, the code of one of the children (#47) remained normal and three (#41, #30, #61)(57%) became normal, one (#65) (14%) became borderline and the other two (#66, #21)(28%) remained abnormal. Over the next period, the abnormal codes remained so and the other ones became normal. At this time (week 32), 5 of the 7 tested children (71%) had normal codes and 2 (28%) abnormal ones. Both children with an abnormal code at this time kept that code during further follow-up; one other became abnormal again and remained so (Table 43).

Table 42. Children with initial borderline or abnormal codes
Interpretation of Huckmannumbers according to Meese

pt	weeknumber										
nr	0	6	9	18	32	60	116	144	172	200	228
056	1	2		2	2	2	2		2	2	2
049	1	2		2	0	0					
053	1	2		2	1	0	2	0	0		
057	1	2									
059	1	0		0	0	0	0	0			
033	2	2		1	0		0				
034	2	2		2	2	2					
023	2	2									
042	2	2		0	0	0	0	0	0		
050	2	2		2	2						
068	2	2		2	0	0					
015	2	2		2	2	2					
045	2	2		2	2	2	2	2	0		
047	2	2		2	0	0	0	0	0		
066	2	2		2	2	2	2	2	2		

Table 43. Children with initial borderline or abnormal codes
Interpretation of measurements according to Meese

pt	weeknumber										
nr	0	6	9	18	32	60	116	144	172	200	228
041	1	2		0	0						
047	1	0		0	0	0	0	0	0		
066	1	2		2	2	2	2	0	2		
021	2	2		2	2	2	2		2	0	2
065	2	0		1	0	2	2		2	2	
030	2	1		0	0	0					
061	2	2		0	0	0	0	0	0		

With the interpretation according to Enzmann, the codes of four children with NHR-ALL were borderline abnormal, and of one child with HR-ALL and of two with NHR-ALL abnormal at diagnosis. After induction treatment the codes of all children (100%) were abnormal. At the end of the irradiation period, the code of one of the children (#46)(14%) became normal, one (#66) (14%) became borderline abnormal and the other five (71%) remained abnormal. Over the next period the abnormal codes of three children remained so while two (#53, #68) became normal; one child (#46) became coded as borderline abnormal. Thus, at that time (week 32), 3 of the 7 tested children (43%) had normal codes, one (14%) was borderline abnormal and 3 (43%) were abnormal. One of the children with a normal code at this time remained so and two of them became borderline abnormal during further follow-up; the one who was borderline abnormal became normal ultimately. Of the other three children with abnormal codes, one (#50) was not tested again, one (#45) became normal one year after stopping treatment and one (#34) remained abnormal (Table 44).

Table 44. Children with initial borderline or abnormal codes
Interpretation of measurements according to Enzmann

pt	weeknumber										
nr	0	6	9	18	32	60	116	144	172	200	228
050	1	2		2	2						
053	1	2		2	0	0	2	0	1		
045	1	2		2	2	2	2	1	0		
066	1	2		1	0	1	2	1	1		
034	2	2		2	2	2					
068	2	2		2	0	0					
046	2	2		0	1	0	1	0	0		

Comparing the three different methods of evaluation no concordant codes of either borderline abnormal or abnormal were found at diagnosis.
Four of the five children with borderline codes acc. to Huckman were found to be normal with the other evaluations. The fifth child (#53) was borderline acc. to Enzmann also. One (#66) of the three children borderline acc. to

Meese was also borderline acc. to Enzmann and at the same time abnormal acc. to Huckman. One other (# 47) was abnormal acc. to Huckman and one (#41) was normal with the other evaluations. Two (#53, #66) of the four children, borderline acc. to Enzmann were already mentioned and two (#45, #50) were abnormal acc. to Huckman.
Two (#50, #45) of the ten children coded as abnormal acc. to Huckman, were borderline acc. to Enzmann, one (#47) was borderline acc. to Meese and one (#66) was borderline in both the Meese and Enzmann evaluations. Two (#34, #68) were abnormal acc. to Enzmann as well. The other four were normal acc. to Meese as well as acc. to Enzmann. All four children, abnormal acc. to Meese, were normal in both the Huckman and the Enzmann evaluations. Two (#34, #68) of the three children, abnormal acc. to Enzmann, are mentioned above and the other one was normal in the other two evaluations.

The sulci were interpreted as borderline abnormal in 2 children with HR-ALL and in 4 children with NHR-ALL. After induction treatment one child with a HR-ALL remained borderline abnormal while the other 5 became abnormal. The former child became normal after one year of treatment and remained so over the next year. Three of the latter five had no further investigations because of death or of resistance to induction therapy. One (#51) became borderline abnormal after one year of treatment and normal half a year after completion of therapy. Another one (#53) became borderline abnormal at one year of treatment and normal thereafter.
Four children with a NHR-ALL had abnormal sulci at diagnosis. All remained so after induction treatment. One (#46) became borderline abnormal already after irradiation and remained so during treatment; half a year after stopping therapy, the sulci were interpreted as normal but half a year later as borderline again. One child (#49) had normal sulci at week 32 and week 60, another one (#18) had abnormal sulci untill half a year after stopping therapy and normal sulci half a year later. The last child (#30) kept abnormal sulci untill the last evaluation at week 60 (table 45).

Table 45. Children with initial borderline or abnormal codes
Interpretation of measurements of sulci

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
016	1	1			1	0	0				
038	1	2									
023	1	2									
051	1	2		2	2	1	1	0			
053	1	2		2	2	1	0	0	0		
031	1	2									
030	2	2		2	2	2					
049	2	2		2	0	0					
018	2	2		2	2	2	2	2	0		
046	2	2		1	1	1	1	0	1		

Children with a CNSL as a first relapse.

Nine children, 3 with HR-ALL and 6 with NHR-ALL, had a central nervous system leukemia as a first relapse. At first presentation, one (#49)(11%) was interpreted as borderline with the Huckmannumber acc. to Meese and two (#33, #50)(22%) as abnormal. These three had abnormal ventricles after induction therapy, as was the case in three other children. Only one of the children with originally abnormal ventricles (#50) was found to be abnormal at week 32 after recovery of the postirradiation syndrome. Two (#20, #48) of the 3 children, who became abnormal after induction treatment, were still abnormal at that time. At the last examination before the CNSL was diagnosed, seven of the children were coded as normal, one (#20) as borderline and one (#50) as abnormal.

All 3 children with a HR-ALL (#20, #33, #48) were interpreted as abnormal after induction treatment, while this was the case in only 3 of the 6 children with NHR-ALL (table 46).

Table 46. Children with CNSL as first relapse
Interpretation of Huckmannumbers according to Meese

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
020	0	2		1	2	1					
033	2	2		1	0		0				
048	0	2		2	2	0					
030	0	0		0	0	0					
049	1	2		2	0	0					
050	2	2		2	2						
054	0	2		2	0						
060	0	0		0	0	0	0	0			
022	0	0		0	0	0					

According to Meese only one child with a CNSL as a first relapse was coded as abnormal (#30)(11%). This child and one other (#22)(22%) became borderline abnormal after induction treatment, while two others became abnormal (22%). At week 32, after recovery of the postirradiation syndrome, all children were coded as normal. At the last examination before the CNSL was diagnosed only one child (#33) was found to be abnormal and all others normal (table 47).

Table 47. Children with CNSL as first relapse
Interpretation of measurements according to Meese

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
020	0	0		0	0	0					
033	0	0		0	0		2				
048	0	0		0	0	0					
030	2	1		0	0	0					
049	0	2		2	0	0					
050	0	0		2	0						
054	0	2		0	0						
060	0	0		1	0	0	0	0			
022	0	1		0	0	0					

Table 48. Children with CNSL as first relapse
Interpretation of measurements according to Enzmann

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
020	0	1		0	0	0					
033	0	0		0	0		0				
048	0	0		0	0	0					
030	0	0		0	0	0					
049	0	1		0	0	0					
050	1	2		2	2						
054	0	2		0	0						
060	0	0		0	0	0	0	0			
022	0	0		0	0	0					

According to Enzmann none of the 9 children with a CNSL as a first relapse was classified at presentation as abnormal and only one (11%) as borderline abnormal. This child and one other became abnormal after induction treatment (22%), while two became coded as borderline abnormal (22%). At the end of the postirradiation period, only one child (#50 with the borderline code at diagnosis) was still abnormal, while all others were normal. These codes remained the same during further follow-up including at the last examination before a CNSL was diagnosed. (Table 48).

Comparing the evaluations according to the three different methods in the same child, no clear correlation was evident. The Huckmannumber showed the most abnormal findings (table 49).

Table 49. Children with CNSL as first relapse
Interpretation according to three different methods

pt nr	method	weeknumber 0	6	9	18	32	60	116	144	172
020	H	0	2		1	2	1			
020	M	0	0		0	0	0			
020	E	0	1		0	0	0			
033	H	2	2		1	0		0		
033	M	0	0		0	0		2		
033	E	0	0		0	0		0		
048	H	0	2		2	2	0			
048	M	0	0		0	0	0			
048	E	0	0		0	0	0			
030	H	0	0		0	0	0			
030	M	2	1		0	0	0			
030	E	0	0		0	0	0			
049	H	1	2		2	0	0			
049	M	0	2		2	0	0			
049	E	0	1		0	0	0			
050	H	2	2		2	2				
050	M	0	0		2	0				
050	E	1	2		2	2				
054	H	0	2		2	0				
054	M	0	2		0	0				
054	E	0	2		0	0				
060	H	0	0		0	0	0	0	0	
060	M	0	0		1	0	0	0	0	
060	E	0	0		0	0	0	0	0	
022	H	0	0		0	0	0			
022	M	0	1		0	0	0			
022	E	0	0		0	0	0			

H = coded Huckmannumber acc. to Meese

M = code acc. to Meese

E = code acc. to Enzmann

The percentages of normal, borderline abnormal and abnormal codes according to the three different methods of evaluation in the children with CNSL as a first relapse, taking the small numbers into account, show the same pattern as found in all children within the two risk groups. Only the finding, that all scans in the 3 children with a HR-ALL during the first year of treatment were normal according to Meese differed from the general pattern (tables 50 and 51).

Seven children, 3 with HR-ALL and 4 with NHR-ALL had normal sulci at diagnosis. Two of them (#20, #48) were borderline abnormal after induction treatment. One (#48) became normal after irradiation and remained so untill the last examination before a CNSL was diagnosed and the other returned to normal after half a year of therapy but became borderline abnormal again at the last evaluation before a CNSL occurred. One (#60) of the four children with NHR-ALL became borderline abnormal at the end of induction treatment, abnormal after irradiation and borderline abnormal after half a year of therapy; she had normal sulci thereafter. The other three had abnormal sulci after induction treatment; one (#54) became normal after irradiation, the other two (#50, #22) remained abnormal at the subsequent evaluations before a CNSL was diagnosed.

Two children with a NHR-ALL (#30, #49) had abnormal sulci at diagnosis. One (#49) became normal at week 32 and remained so untill the last evaluation before a CNSL was diagnosed. The other (#30) remained abnormal untill the last evaluation before the CNSL occurred.

Thus, at the last examination before a CNSL was diagnosed, four children- one (#48) with HR-ALL and three (#49, #50, #60) with NHR-ALL - had normal sulci. One (#20) with a HR-ALL had borderline abnormal sulci. Four children - one (#33) with a HR-ALL and three (#30, #50, #22) with a NHR-ALL - had abnormal sulci (table 52).

Table 50. Comparison of the evaluations of CT scans according to three different methods in children with CNSL as a first relapse. Percentages of codes for children with HR-ALL

		Normal			Borderline			Abnormal		
week	n	H	M	E	H	M	E	H	M	E
0	3	67	100	100	–	–	–	33	–	–
6	3	–	100	67	–	–	33	100	–	–
18	3	–	100	100	67	–	–	33	–	–
32	3	33	100	100	–	–	–	67	–	–
60	2	50	100	100	50	–	–	–	–	–
116	1	100	–	100	–	–	–	–	100	–

Table 51. Comparison of the evaluations of CT scans according to three different methods in children with CNSL as a first relapse. Percentages of codes for children with NHR-ALL

		Normal			Borderline			Abnormal		
week	n	H	M	E	H	M	E	H	M	E
0	6	67	83	83	17	–	17	17	17	–
6	6	50	33	50	–	33	17	50	33	33
18	6	50	50	83	–	17	–	50	33	17
32	6	83	100	83	–	–	–	17	–	17
60	4	100	100	100	–	–	–	–	–	–
116	1	100	100	100	–	–	–	–	–	–
144	1	100	100	100	–	–	–	–	–	–

Table 52. Children with CNSL as first relapse
Interpretation of measurements of sulci

pt					weeknumber						
nr	0	6	9	18	32	60	116	144	172	200	228
020	0	1		1	0	1					
033	0	2		2	0		2				
048	0	1		0	0	0					
030	2	2		2	2	2					
049	2	2		2	0	0					
050	0	2		2	2						
054	0	2		0							
060	0	1		2	1	0	0	0			
022	0	2		2	2	2					

Hypodense areas

Hypodense areas were seen in 18 children, 8 with a HR-ALL and 10 with a NHR-ALL. Sixteen children were younger than 6 years of age at initial diagnosis. In 2 children (#2, #19) hypodense areas were already present after induction treatment. In 6 patients (#48, #7, #10, #42, #45, #46) these were first seen at the end of the irradiation period. In 6 children (#1, #34, #70, #79, #49, #35) they first appeared at week 32, in 1 child at week 60 (#28) and at week 116 (# 69) and in 2 patients (#47, #66) at week 144. Hypodense areas disappeared but reappeared later in 3 children (#1, #2, #70) and disappeared definitely in 6 patients (#7, #10, #42, #35, #45, #46)(table IV.20).

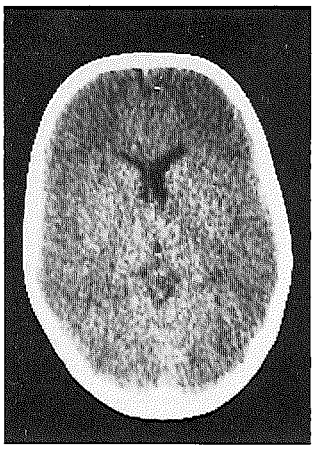
In three children, hypodense areas were present before calcifications were noticed: in child #1 at week 32 around the frontal horns (transitory), in child #48 from week 18 onwards around the frontal and occipital horns and at the cella media level and in child #10 around the frontal horns from week 18 till week 116 and also around the occipital horns from week 32 till week 116.

Calcifications

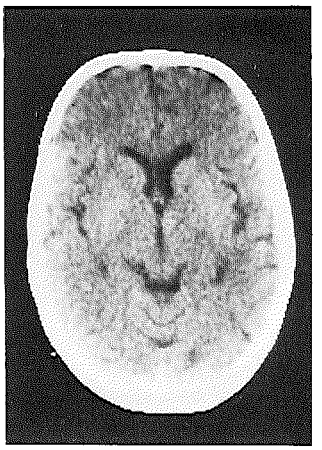
Calcifications were found on the CT scans of four children, three with a HR-ALL (#1, #33, #48) and one with a NHR-ALL (#10). All were younger than 4 years of age at diagnosis. Calcifications were noticed for the first time at week 32 in one child (#48) and at week 116 in the other three children (#1, #33, #10). Two children (#33, #48) experienced a CNS relapse as a first event two and fourteen months later resp.. The other two remained in first remission from their leukemia; one child (#10) however, developed a mediastinal Hodgkins lymphoma 6 years after the first presentation with leukemia.

The calcifications were found subcortically in the left frontal area in child #1, in both frontal lobes in child #33, at the cella media level in child #48 and in both occipital areas in patient #10; in child #48 calcifications were also found in the basal ganglia (table IV.21).

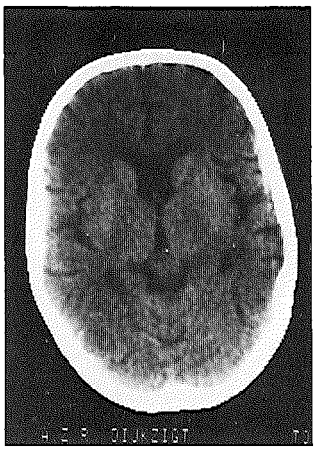
Figure 4. Follow-up of child #39; CT scans with different foveal distances
weeknumbers and codes acc. to Huckman/Meese/Enzmann



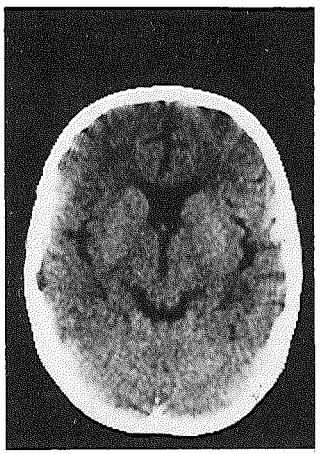
week 0
0/0/0



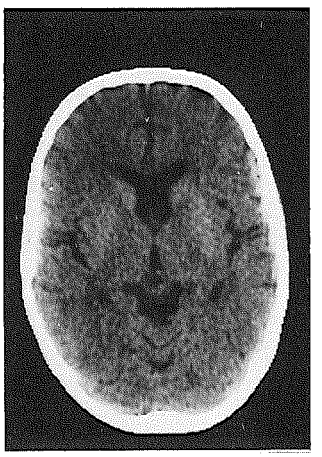
week 6
1/0/0



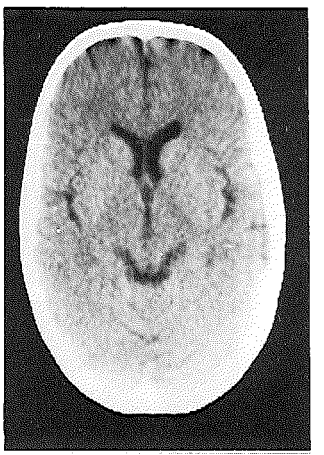
week 18
2/0/2



week 32
2/0/2

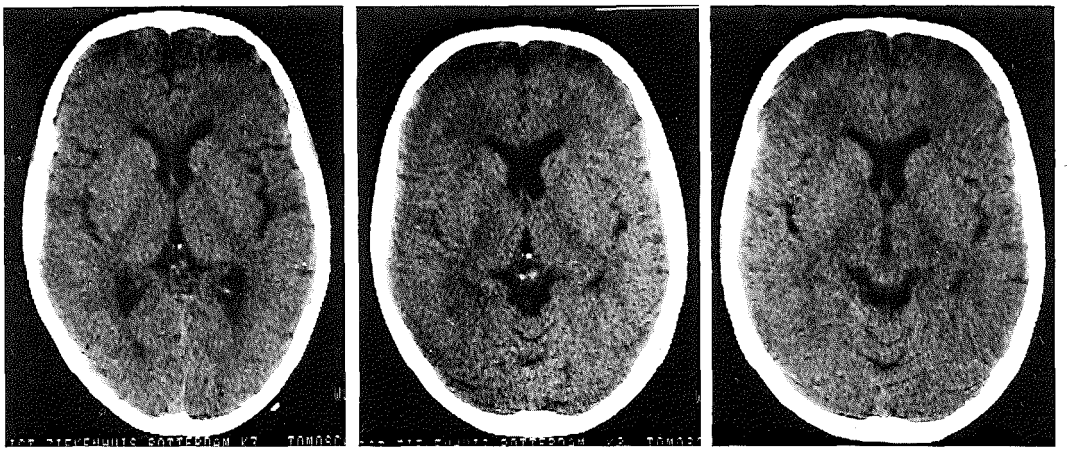


week 60
2/0/1



week 116
2/0/1

Figure 4. Follow-up of child #39; CT scans with different foveal distances weeknumbers and codes acc. to Huckman/Meese/Enzmann (cont.)

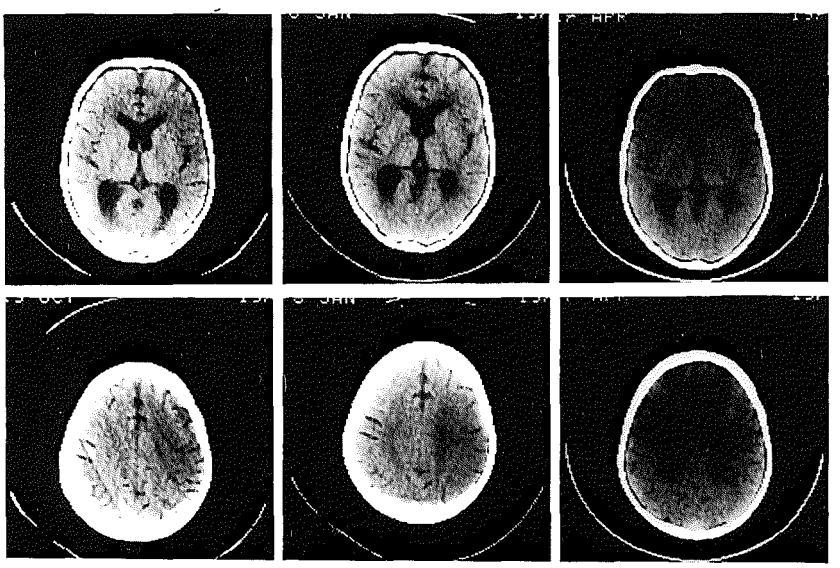


week 172
2/0/1

week 200
0/0/0

week 228
2/0/1

Figure 5. Follow-up showing dilated CSF spaces, hypodense areas and calcifications (child #10) weeknumbers and codes acc. to Huckman/Meese/Enzmann

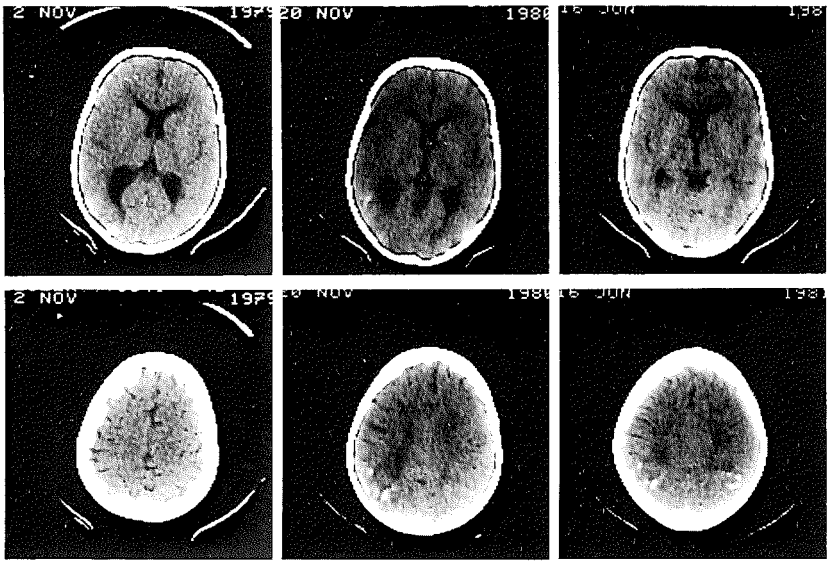


week 6
2/2/2

week 18
2/2/2

week 32
1/2/0

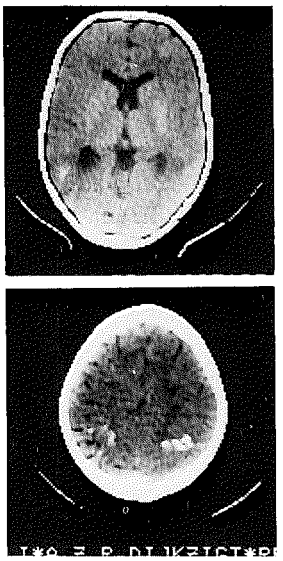
Figure 5. Follow-up showing dilated CSF spaces, hypodense areas and calcifications (child #10) weeknumbers and codes acc. to Huckman/Meese/Enzmann (cont.)



week 60
1/2/0

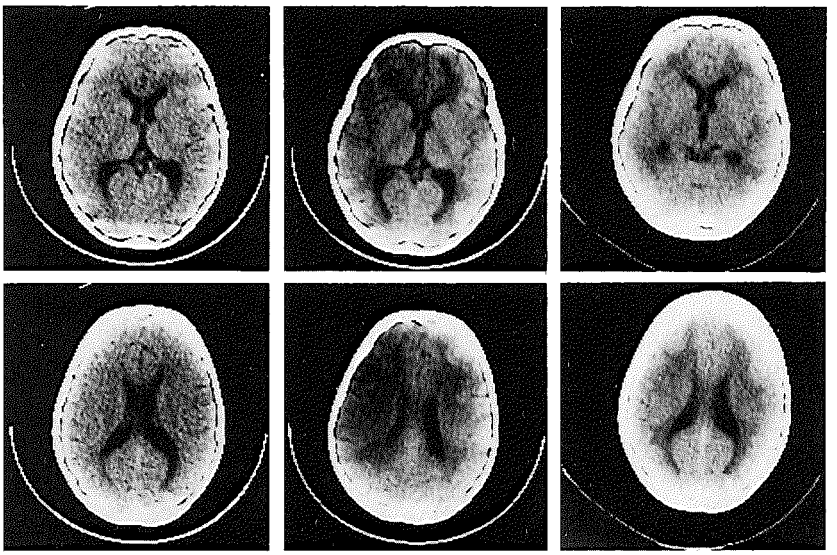
week 116
0/2/0

week 144
2/2/1



week 172
2/2/2

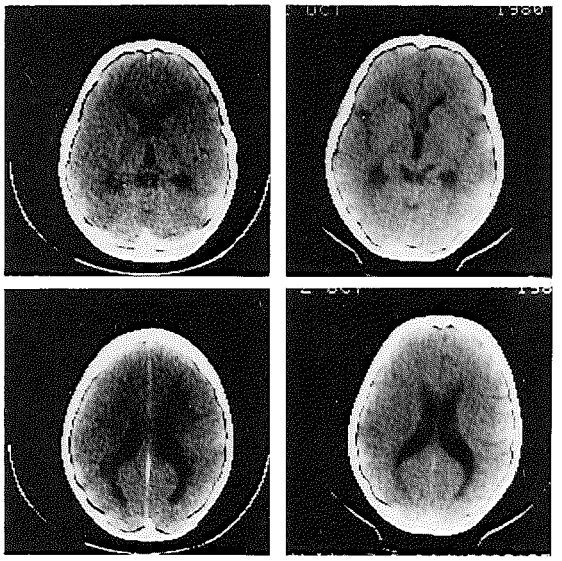
Figure 6. Transient severe periventricular hypodensities without clinical symptoms (patient #7)
weeknumbers and codes acc. to Huckman/Meese/Enzmann



week 6
2/0/2

week 18
2/0/0

week 32
2/0/1



week 60
2/1/2

week 116
2/1/0

C H A P T E R 5

Results of EEG evaluation

Results of visual interpretation

The interpretations in each child are presented in table V.1.
At diagnosis, EEG's were obtained in 71 children (table 1). Fourty-eight (68%) of them had normal or borderline normal/abnormal background rhythms, 15 (21%) had slightly abnormal, 7 (10%) moderately abnormal and 1 (1%) severely abnormal background rhythms. The mean of these coded values was 1.86 (SEM 0.14).
After induction treatment (week 6) a slight tendency towards less abnormal background rhythms was seen. The mean was not significantly lower than at diagnosis (p=0.341).
At the end of the postirradiation period (week 18), however, a definite shift towards more severe abnormalities in the background rhythm was seen. The mean of the codes rose from 1.63 (SEM 0.12) at week 9 to 2.06 (SEM 0.16) at week 18 (p=0.006). A subsequent shift to normalization was seen at week 32. The mean at week 32 was 1.60 (SEM 0.11), which was significantly lower than the mean at week 18 (p=0.003). Thereafter, the distribution of normal and abnormal background rhythms among the children and consequently the mean values remained about the same.

These same variations were present in the groups of children with HR-ALL and NHR-ALL (table 2). Statistically however, the changes were less significant in the children with HR-ALL than in those with NHR-ALL. The rise in the mean value from week 9 till week 18, although in the same order of magnitude, showed only a tendency to significancy in the children with HR-ALL (p=0.141). This was significant in the children with NHR-ALL (p=0.016). The decrease in the mean values from week 18 till week 32 was significant in both groups of children (p=0.043 in HR-ALL and p=0.026 in NHR-ALL).

Table 1. Distribution of codes for background rhythms at different times in all patients.

week nr	pts n	code 1	2	3	4	5	nd	mean	SEM
0	71	42	6	15	7	1	2	1.859	0.136
6	67	43	7	13	3	1	6	1.687	0.126
9	59	38	7	12	2		14	1.627	0.121
18	65	35	5	14	8	3	8	2.062	0.161
32	63	41	8	12	2		10	1.603	0.114
60	55	38	3	12	1	1	18	1.618	0.136
116	44	30	2	11	1		29	1.614	0.143
144	31	20	4	7			42	1.581	0.152
172	37	25	3	9			36	1.568	0.143
200	8	5	2	1			65	1.500	0.267
228	7	4	1	2			66	1.714	0.360

Table 2. Means of codes for background rhythms at different times in children with HR and NHR-ALL.

week nr	HR-ALL pts	mean	SEM	NHR-ALL pts	mean	SEM
0	26	1.846	0.205	45	1.867	0.181
6	22	1.636	0.233	45	1.711	0.151
9	21	1.667	0.187	38	1.605	0.158
18	22	2.091	0.308	43	2.047	0.188
32	20	1.500	0.212	43	1.651	0.137
60	17	1.882	0.283	38	1.500	0.150
116	12	1.333	0.225	32	1.719	0.175
144				31	1.581	0.152
172	10	1.600	0.306	27	1.556	0.163
200	8	1.500	0.267			
228	7	1.714	0.360			

Focal abnormalities

The codes for focal abnormalities in each child are presented in table V.2. At diagnosis, 56 of the 71 (79%) children with interpretable EEG's had no focal abnormalities, 10 (14%) had focal abnormalities in one (one or

double-sided) area and 5 (7%) in two or more areas (table 3). The mean of the coded values at that time was 0.28 (SEM 0.07).

After induction treatment no focal abnormalities were found in 55 of 67 (82%) children. In 9 (13%) children one area and in 3 (4%) children two areas with focal signs were seen. The mean of the codes was 0.22 (SEM 0.06), not significantly different from the one at diagnosis.

At the end of the postirradiation period 49 of 65 (75%) children had a code of 0, ten (15%) of 1 and six (9%) of 2 with a mean of 0.34 (SEM 0.08). This slight tendency towards an increase of abnormalities was also not significant (p=0.142 for week 18 compared with week 6). After the next 14 weeks, 52 of 63 (83%) children had a code of 0, ten (16%) of 1 and only one (2%) of 2 with a mean of 0.19 (SEM 0.06). However, this shift towards less focal abnormalities, probably as a result of recovery from the postirradiation syndrome, was also not significant (p=0.089 for week 32 compared with week 18). The distribution of focal abnormalities remained about the same thereafter.

Table 3. Distribution of codes for focal abnormalities at different times in all patients.

week	pts	code				mean	SEM
nr	n	0	1	2	nd		
0	71	56	10	5	2	0.282	0.070
6	67	55	9	3	6	0.224	0.063
9	59	47	10	2	14	0.237	0.065
18	65	49	10	6	8	0.338	0.080
32	63	52	10	1	10	0.190	0.055
60	55	45	9	1	18	0.200	0.060
116	44	38	6		29	0.136	0.052
144	31	26	5		42	0.161	0.067
172	37	34	3		36	0.081	0.045
200	8	7	1		65	0.125	0.125
228	7	6	1		66	0.143	0.143

At diagnosis, a mean of the codes of 0.22 (SEM 0.08) was calculated for the children with NHR-ALL as opposed to a mean of 0.39 (SEM 0.13) for those with HR-ALL. At the end of the induction period this had changed only slightly in the NHR-ALL group. There was a definite although not significant (p=

0.46) change in the HR-ALL group. Neither the changes in the mean values from week 6 to week 18, nor those from week 18 to week 32 were found to reach significancy. Comparison of the means at week 6 and week 18 did not show a significant difference either. Only in the children with HR-ALL a near significant difference was found between the means of week 18 and week 32 (p=0.06). None of the other changes in the means were significant in each group of children (table 4).

Table 4. Means of codes for focal abnormalities at different times in children with HR and NHR-ALL.

week nr	HR-ALL pts	HR-ALL mean	HR-ALL SEM	NHR-ALL pts	NHR-ALL mean	NHR-ALL SEM
0	26	0.385	0.125	45	0.222	0.083
6	22	0.273	0.117	45	0.200	0.075
9	21	0.333	0.105	38	0.184	0.083
18	22	0.409	0.142	43	0.302	0.097
32	20	0.100	0.069	43	0.233	0.073
60	17	0.118	0.118	38	0.237	0.070
116	12	0.0	0.0	32	0.188	0.070
144				31	0.161	0.067
172	10	0.0	0.0	27	0.111	0.062
200	8	0.125	0.125			
228	7	0.143	0.143			

Children with initial moderately or severely abnormal background rhythms

Eight children showed moderately or severely abnormal background rhythms at diagnosis. Two of them had HR-ALL, the other 6 were classified as NHR-ALL (table 5). The latter children had all been randomized to protocol ALL VB. A definite tendency towards improvement of background rhythms after induction treatment was observed in 6 of the 7 tested children. After cranial irradiation, 3 children showed further improvement, 2 remained the same and the other 2 (#22, #45) changed from normal to slightly abnormal. Surprisingly, only one (#46) of these children showed slowing of the background rhythm at the end of the postirradiation period. One child (#34), who had not been tested in between, showed further deterioration at the end of this period. He, however, had suffered from a viral meningitis between week 15 and week

18. This could have influenced his EEG findings, which were recorded shortly after his illness. So, 7 of the 8 children with moderately or severely abnormal background rhythms at diagnosis showed improvement of background rhythms at the end of the postirradiation period. Four children were classified as normal and 3 as slightly abnormal. At week 32, however, all 8 children were found to have normal or borderline normal background rhythms. In the next six months the background rhythms remained normal in 4 children, changed slightly (one code) in two (#44, #80) and changed from normal to slightly abnormal in one (#45). One child (#34) showed a deterioration from a borderline normal to a severely abnormal background rhythm. All 5 children tested after the second year of treatment showed slightly or moderately abnormal background rhythms. One child (# 44) showed the same slightly abnormal background rhythm as before, three (#46, #66, #74) changed from normal to slightly abnormal and one (#45) from slightly to moderately abnormal. In one child (#46) only, the EEG reverted to normal after stopping treatment.

Table 5. Follow-up of children with definite abnormal background rhythms at diagnosis.

pt nr	sex	age	treat ment	weeknumber 0	6	9	18	32	60	116	144	172
34	M	5	HR	4	nd	nd	5	2	5			
80	M	11	HR	4	3	3	1	1	2			
22	F	2	VB	4	1	3	3	1	1			
44	F	8	VB	4	3	1	1	2	3	3	3	3
46	F	3	VB	4	4	1	3	1	1	3	1	1
66	M	5	VB	4	3	2	1	1	1	3	3	3
74	M	5	VB	4	3	3	3	1	1	3		
45	M	4	VB	5	1	3	1	1	3	4	3	3

Children with focal abnormalities at diagnosis

In 15 children focal abnormalities were noted in the EEG recordings at diagnosis (table 6). Only one area with focal abnormalities was seen in 10 children (6 with a HR-ALL and 4 with a NHR-ALL) and two or more areas in 5 children (2 with HR-ALL and 3 with NHR-ALL). After induction treatment 7 of

14 tested children (4 with code 1 and 3 with code 2 at diagnosis) did not show focal abnormalities anymore (figure 1 and 2), one had improved to only one area with focal signs. The other 6 children presented the same recordings. After CNS prophylaxis improvement was found in 3 and deterioration in 2 of the 12 tested children. At the end of the postirradiation period 3 children showed a change to more focal abnormalities compared with their recordings at week 9. Compared with the findings at diagnosis 7 children showed an improvement, 3 a deterioration and 3 the same focal abnormalities. At this time 6 patients had no abnormalities anymore, 4 had grade 1 and 3 grade 2 focal abnormalities. After resolution of the PRS 3 children had focal abnormalities in one area and 10 showed no focal signs anymore. The children with HR-ALL who are not shown after week 172 remained without focal abnormalities.

Table 6. Follow-up of children with focal abnormalities at diagnosis.

pt nr	sex	age	treat ment	weeknumber 0	6	9	18	32	60	116	144	172
21	M	4.8	HR	1	1	1	2	0	0	0		0
34	M	5.1	HR	1	nd	nd	2	0	0			
40	M	12.8	HR	1	0	0	0	0				
65	F	14.1	HR	1	1	0	1	0	0	0		0
69	M	2.3	HR	1	0	0	1	0	0	0		0
79	F	4.0	HR	1	1	1	1	0	0			
26	F	5.2	VA	1	0	0	0	0				
19	F	10.5	VB	1	1	2	2	1				
61	M	2.9	VB	1	0	0	0	0	0	0	0	0
73	M	3.5	VB	1	1	0	0	1	1	0	0	0
55	M	2.9	HR	2	0							
80	M	11.4	HR	2	0	1	0	0	0			
57	M	10.3	VA	2	1							
45	M	4.0	VB	2	0	0	0	1	1	1	1	1
46	F	3.2	VB	2	2	1	1	0	0	1	1	0

Figure 1. Example of the EEG of a 4-year old boy
a. at diagnosis: abnormal background rhythm and focus (↓)
b. after induction: normal background rhythm and no focus

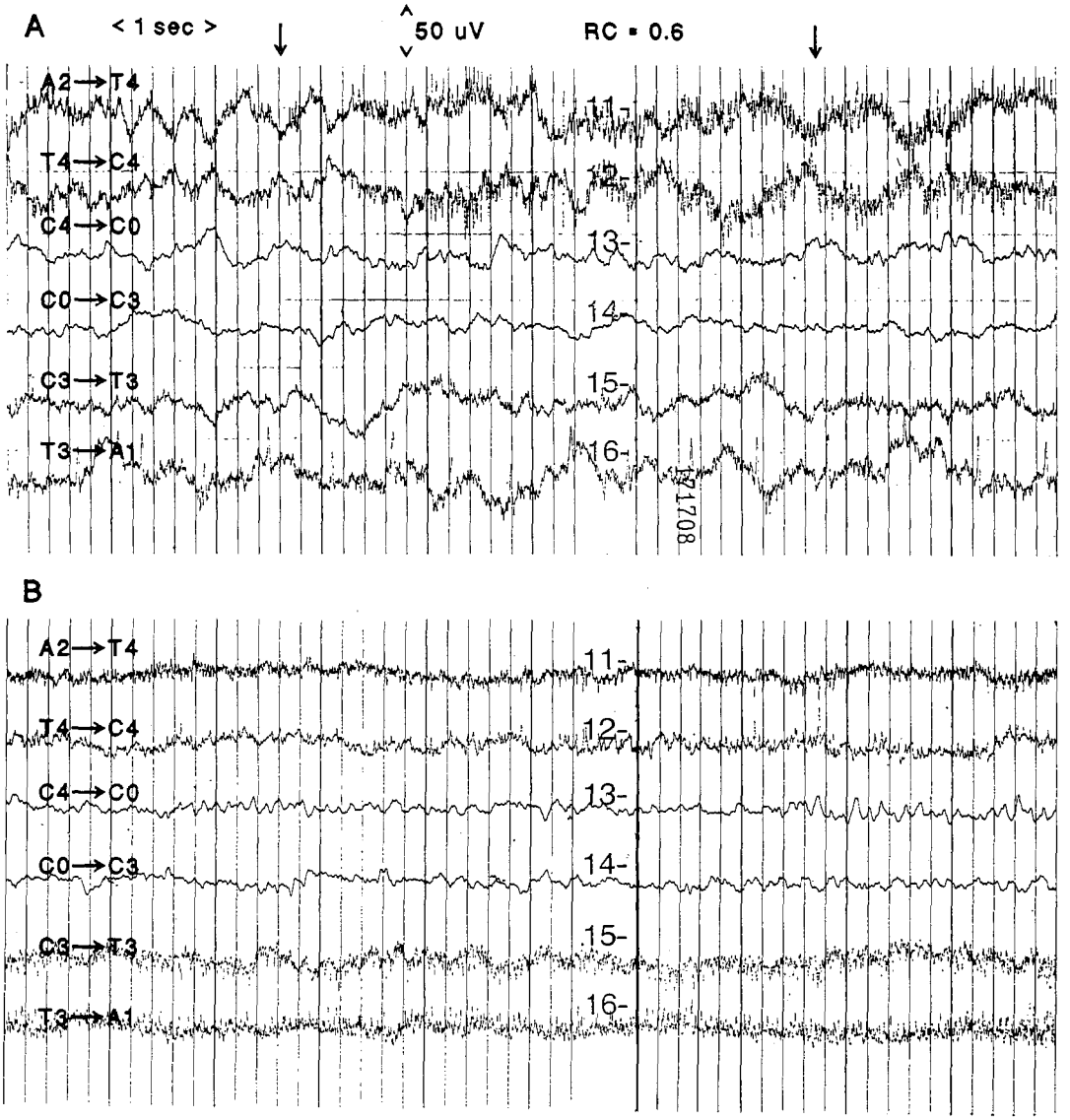
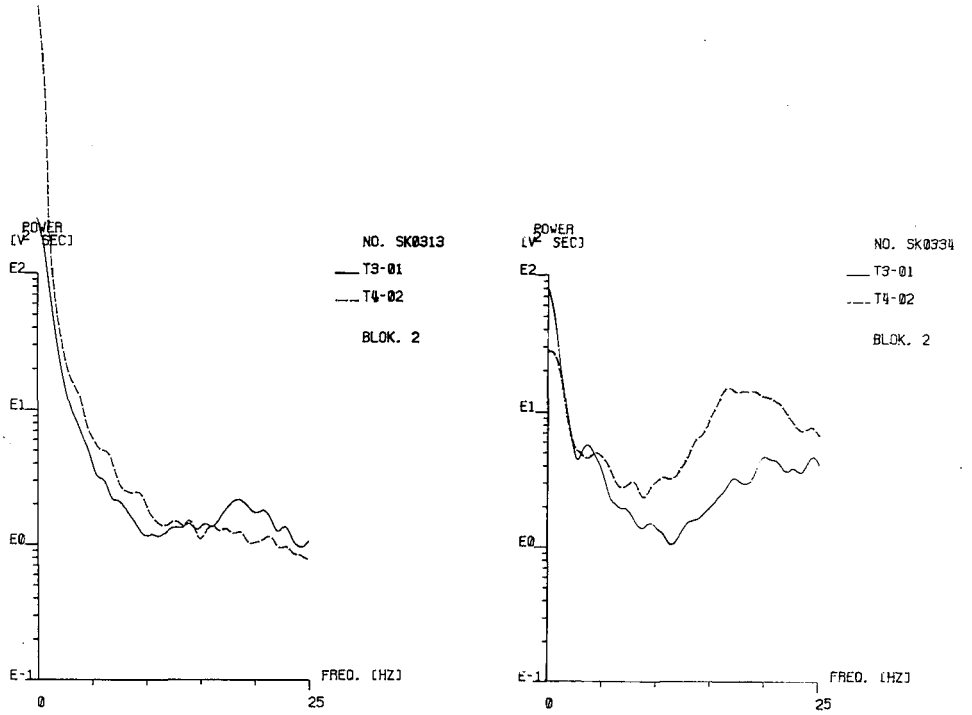


Figure 2. Spectral analysis of the same patient as in figure 1. at diagnosis (left) and after induction treatment (right)



Children with a CNSL as a first relapse

Relapse in the CNS terminating first complete remission occurred in 9 children, 3 with a HR-ALL and 6 with a NHR-ALL (table 7). Four girls and 5 boys were involved. Age at initial diagnosis ranged from 1.3 to 10.2 years with a median of 2.9 years. At initial diagnosis 6 children had a normal background rhythm, 2 showed a slightly abnormal and 1 a moderately abnormal background rhythm. These abnormal background rhythms were all found in children younger than 3 years of age at diagnosis. None of the 9 children presented focal abnormalities.

Table 7. Children with first relapse in the CNS
Initial findings on visual EEG interpretation

pt nr	sex	age	treat ment	code vis	code foc	month CR
20	F	8.1	HR	1	0	13
33	M	1.6	HR	1	0	25
48	M	1.3	HR	3	0	22
30	M	2.9	VA	1	0	13
49	M	2.9	VA	3	0	16
50	M	10.2	VA	1	0	9
54	F	3.8	VA	1	0	22
60	F	3.2	VA	1	0	32
22	F	2.0	VB	4	0	16

With respect to background rhythms, all EEG's remained normal or became so again after induction treatment. Two children in first complete remission showed slightly abnormal background rhythms in the postirradiation period; one of them reverted to normal at the next investigation.

At the last investigation before the CNS relapse was diagnosed, 7 children had normal background rhythms and 2 slightly abnormal background rhythms. In two children (#20, #30), in whom the EEG's were obtained one week before CNSL was diagnosed, normal background rhythms had been found (table 8).

Table 8. Follow up of children with first relapse in the CNS. Codes for background rhythms.

pt	weeknumber									
nr	0	6	9	18	32	60	116	144	172	200
20	1	1	1	1	1	1				
33	1		1	1	1	1	1			
48	3	1	1	1	1	1				
30	1	1	1	1	1	1				
49	3	1	2	1	1	3				
50	1	1	3	3	3					
54	1	1	1	1	2	1				
60	1	1	1	1	1	1	1	1		
22	4	1	3	3	1	1				

With respect to focal abnormalities, the EEG of one child showed bilateral foci after induction treatment, which remained till after the postirradiation period. One other child had a single focus on his EEG after completion of the prophylactic irradiation, which proved to have disappeared on later EEG's. At the last investigation before a CNSL was diagnosed, the child with bilateral foci after induction treatment had only one focus on the EEG. The other 8 had no focal abnormalities (table 9).

Table 9. Follow up of children with first relapse in the CNS. Codes for focal abnormalities.

pt	weeknumber									
nr	0	6	9	18	32	60	116	144	172	200
20	0	0	0	0	0	0				
33	0		0	0	0	0	0			
48	0	0	1	0	0	0				
30	0	0	0	0	0	0				
49	0	0	0	0	0	0				
50	0	0	0	0	0					
54	0	0	0	0	0	0				
60	0	0	0	0	0	0	0	0		
22	0	2	2	2	0	1				

Results of spectral analysis.

The frequencies and proportions of delta, theta, alpha and rest waves as derived by the spectral analysis in each individual child are presented in the tables V.3 - V.7.

The mean frequency, as determined by spectral analysis (table 10), was 4.34 (SEM 0.16) with a median of 4.13 for 71 children investigated at diagnosis. After completion of induction treatment the mean frequency rose to 5.92 (SEM 0.24)($p < 0.001$) with a median of 5.51 for 63 investigated children. A slight decrease in the mean frequency was seen directly after cranial irradiation (p=0.094), which became more evident 9 weeks later at the end of the postirradiation syndrome. The mean frequency at this time was significantly lower than at week 6 (p=0.001), but significantly higher than at diagnosis (p=0.001). Thereafter, a gradual increase in the mean frequency was observed till one year after the start of treatment. This then remained about the same till three years after diagnosis. At 3.5 and 4 years after diagnosis, only children with HR-ALL were investigated. The very small number of children available for evaluation at that time must be taken into account for the interpretation of the large differences in mean frequencies at those times.

Essentially, the same variations in frequencies were observed in the different groups of patients. In the two risk groups the mean frequencies were significantly higher at the end of induction treatment than at diagnosis (p= or < 0.005). At week 18, however, the children with HR-ALL did not show lower frequencies compared with week 9, such in contrast to the children with NHR-ALL, although the differences in the latter group were not statistically significant. Only in children with NHR-ALL the frequencies at week 18 were significantly lower than those at week 6 (p=0.001). In children with HR-ALL as well as in children with NHR-ALL, the frequencies at week 18 were higher than those at diagnosis (p=0.03 and 0.015 resp.). The children with HR-ALL showed a decrease in the mean frequency at 3 years after diagnosis which was not evident in the other children.

At diagnosis, the mean percentages of delta, theta, alpha and rest waves were 64.78 (SEM 1.43), 21.11 (SEM 0.81), 6.51 (SEM 0.51) and 7.69 (SEM 0.71) respectively, with medians of 65.60, 20.20, 5.53 and 6.03.

At the end of induction treatment the delta percentage was significantly decreased to 52.77 (SEM 1.38)($p < 0.001$). The theta percentage was slightly increased to 22.98 (SEM 0.90)(p=0.076). The alpha and rest percentages

had significantly risen to 9.41 (SEM 0.89)($p < 0.001$) and 14.83 (SEM 1.34)($p < 0.001$) resp..

After cranial irradiation the delta percentage had slightly risen at the expense of alpha and rest percentages, the theta percentage showing the smallest change.

At the end of the postirradiation period, delta percentage was 59.30 (SEM 1.64), which was significantly lower than at diagnosis ($p=0.001$), but significantly higher than at the end of induction treatment ($p < 0.001$). Theta percentage was 22.11 (SEM 0.96), not significantly different from the values at diagnosis nor from those at week 6. Alpha percentage was 6.82 (SEM 0.43), not different from the one at diagnosis ($p=0.071$), but significantly different if compared with the value at week 6 ($p < 0.001$). The rest percentage was 11.77 (SEM 1.27), significantly higher than at diagnosis ($p=0.004$) although lower than at the end of induction treatment ($p=0.028$).

In the next 3 months (week 18 to 32) the percentage of delta and rest waves decreased slightly while that of alpha waves increased significantly ($p=0.001$). The percentages of delta, theta and rest waves showed only slight nonsignificant changes during further follow-up. The percentage of alpha waves however continued to rise significantly during the following half a year (week 32 to 60) and one year (week 60 to 116)($p=0.005$ and $p=0.044$ resp), remaining about the same thereafter.

The same variations were found in the different risk groups (tables 10 - 12 and figure 3) as well as in the groups of children treated according to protocol VA or VB (tables V.8 and V.9)

Table 10. Spectral analysis of the EEG
Means , whole group

wknr	n	freq	delta	theta	alpha	rest
0	71	4.336	64.782	21.015	6.507	7.693
6	63	5.919	52.771	22.981	9.414	14.833
9	57	5.402	55.691	23.377	8.667	12.263
18	64	5.119	59.300	22.106	6.822	11.769
32	63	5.137	57.708	22.537	8.925	10.830
60	55	5.374	57.891	20.062	9.853	12.915
116	43	5.347	56.651	20.795	11.395	10.958
144	30	5.413	56.207	21.523	10.423	11.833
172	37	5.165	56.624	21.654	12.070	9.654
200	8	4.414	62.450	20.563	10.500	6.475
228	7	5.193	54.800	21.043	15.857	8.314

Figure 3. Spectral analysis of the EEG, all children and risk groups Mean frequencies and contributing proportions of different wavetypes

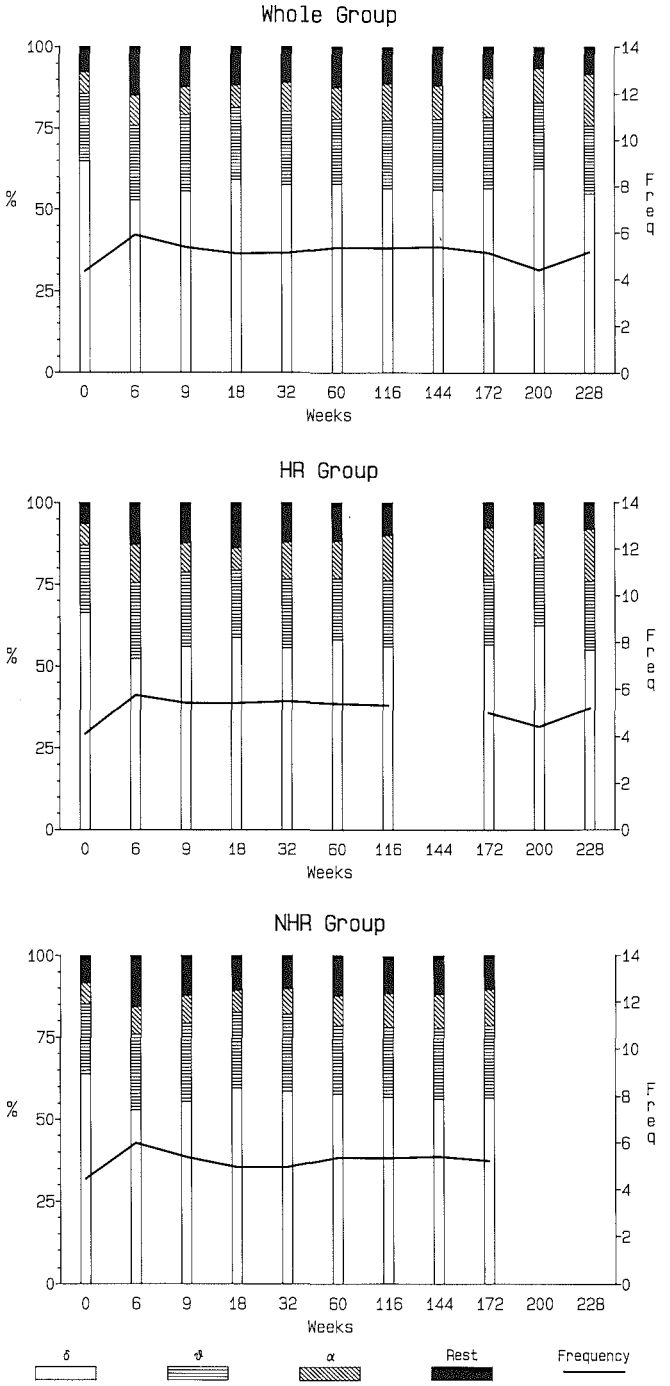


Table 11. Spectral analysis of the EEG
Means , HR group

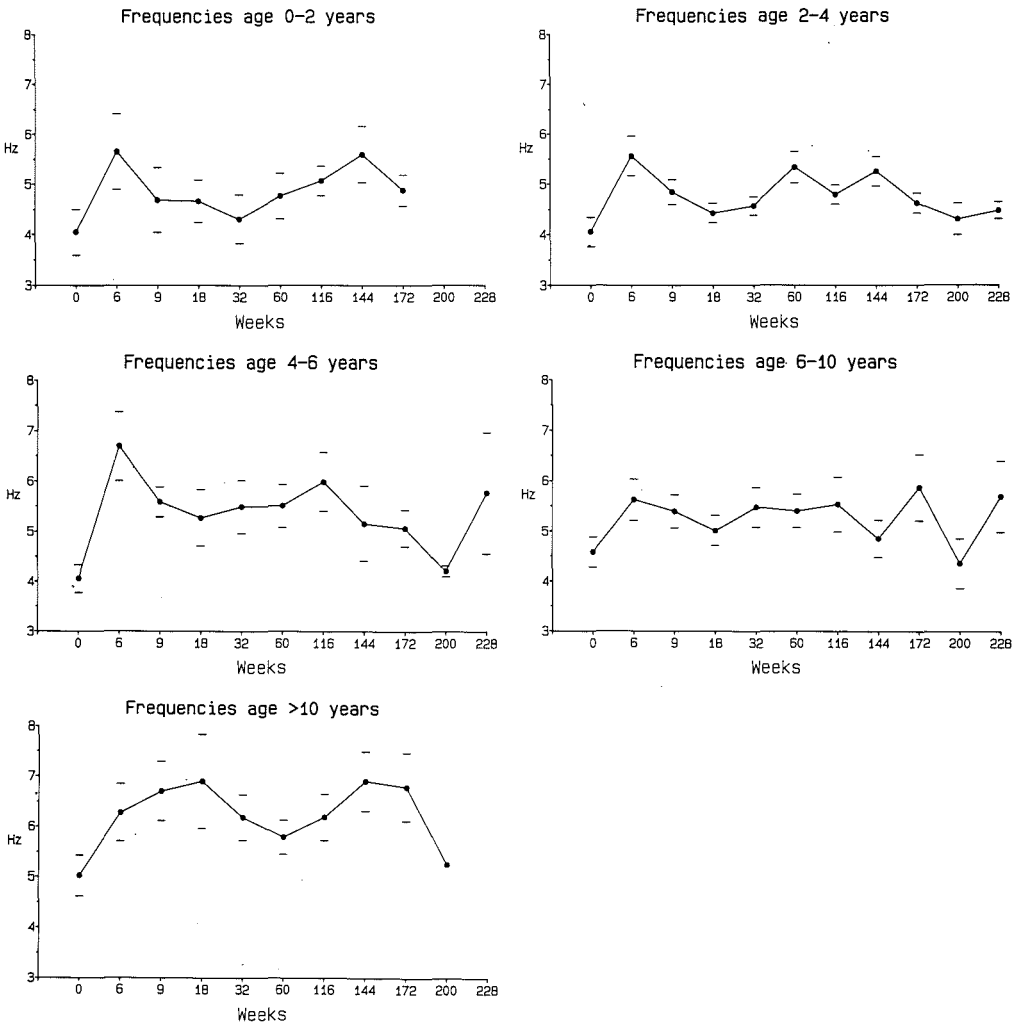
wknr	n	freq	delta	theta	alpha	rest
0	26	4.115	66.396	20.550	6.535	6.519
6	19	5.762	52.316	23.126	11.700	12.858
9	20	5.415	55.960	22.730	8.945	12.360
18	22	5.414	58.800	20.436	6.868	13.891
32	20	5.497	55.580	20.905	11.300	12.215
60	16	5.386	58.119	18.587	11.444	11.850
116	12	5.318	55.983	20.092	13.817	10.100
144						
172	10	4.997	56.500	21.090	14.530	7.870
200	8	4.414	62.450	20.563	10.500	6.475
228	7	5.193	54.800	21.043	15.857	8.314

Table 12. Spectral analysis of the EEG
Means , NHR group

wknr	n	freq	delta	theta	alpha	rest
0	45	4.464	63.849	21.284	6.491	8.371
6	44	5.988	52.968	22.918	8.427	15.686
9	37	5.396	55.546	23.727	8.516	12.211
18	42	4.965	59.562	22.981	6.798	10.657
32	43	4.970	58.698	23.295	7.821	10.186
60	39	5.369	57.797	20.667	9.200	12.336
116	31	5.357	56.910	21.068	10.458	11.290
144	30	5.413	56.207	21.523	10.423	11.833
172	27	5.228	56.670	21.863	11.159	10.315

With respect to age lower frequencies were found in the younger agegroups. This was mainly due to a higher percentage of deltawaves in the these age-groups. Remarkebly, the mean frequencies in the agegroups 0 - 2, 2 - 4 and 4 - 6 years did not differ very much. The variations in frequencies at the different times showed the same pattern as described before (table V.10-V.17 and figure 4).

Figure 4. Spectral analysis of the EEG
Mean frequencies in different agegroups



In the children with a first relapse in the CNS, the same pattern in the mean frequency and in the proportions of the wavetypes was found as in the whole group. At the last investigation before a CNSL was diagnosed a mean frequency equal to or lower than at initial diagnosis was seen in 4 patients (tables 13 and 14, V.18 - V.21)

Table 13. Follow up of children with first relapse in the CNS. Mean frequency derived from spectral analysis.

pt	weeknumber								
nr	0	6	9	18	32	60	116	144	172
20	5.47	8.22	6.07	6.18	5.73	7.36			
33	6.62			4.86	4.40	5.36	4.96		
48	3.80	6.82	3.22	4.32	4.70	6.31			
30	6.44	9.08	5.22	3.85	3.80	3.64			
49	2.57	4.23	4.23	3.50	4.54	5.08			
50	4.28	9.08	9.60	6.82	5.35				
54	4.72	6.18	4.63	4.57	2.67	6.67			
60	4.84	4.72	4.16	5.27	4.81	5.10	5.86	4.00	
22	3.73	4.12	4.51	4.73	3.56	3.25			

Table 14. Spectral analysis of the EEG Means , children with first relapse in the CNS

wknr	n	freq	delta	theta	alpha	rest
0	9	4.72	63.9	19.8	5.5	10.8
6	8	6.56	49.9	22.2	9.1	18.8
9	8	5.21	55.5	26.1	7.0	11.4
18	9	4.90	59.1	24.3	6.0	10.6
32	9	4.40	61.9	24.1	6.5	7.5
60	8	5.35	59.1	16.5	6.8	11.7
116	2	5.41	57.1	20.95	12.6	11.6
144	1	4.00	67.5	19.2	7.6	5.7

Comparing the evaluations of the CT scans and the EEG visual interpretations, no consistent correlation could be observed. At diagnosis, 78% of CT scans evaluated acc. to Huckman and 59% of EEG's were normal. Eight percent of CT scans and 10% of EEG's were borderline and 15% of CT scans and 35% of EEG's were abnormal. The 78% of normal CT scans are composed of 46% normal EEG's, 6% borderline and 26% abnormal EEG's. The 15% of abnormal CT scans consist of 8% normal EEG's, 2% borderline and 7% abnormal EEG's. After induction treatment more EEG's than CT scans were normal (67% vs 36%). At the end of the postirradiation period about the same proportions of normal EEG's and CT scans were found (53% vs 49%). At this time EEG's and CT scans were both interpreted as normal in only 29% of patients. This percentage of normal EEG's as well as of normal CT scans in the same patient rose during follow-up (table 15).

The same pattern was seen when the CT scans were evaluated acc. to Enzmann and were compared with the EEG interpretations. The percentages of normal CT scans were most of the time higher than that of normal EEG's (table 16).

Table 15. Comparison between CT evaluation and EEG interpretation
Huckman code versus code for visual interpretation
Percentages in all children

week	Huckm code	Code for visual interpretation 1	2	3	4	5	total
	0	46	6	18	8		78
0	1	5	2	2			8
	2	8	2	2	3	2	15
	0	27	3	5		2	36
6	1	2					2
	2	38	6	14	5		63
	0	29	5	11	3	2	49
18	1	3					3
	2	21	3	11	10	3	48
	0	39	10	8	3		60
32	1	3	2	2			7
	2	23	2	10			34
	0	51	2	13	2		68
60	1	2	2				4
	2	15	2	9		2	28
	0	46	5	16			66
116	1	2					2
	2	21		9	2		32
	0	61	10	16			87
144	1						
	2	3	3	7			13
	0	50	6	17			72
172	1	3					3
	2	14	3	8			25
	0	13	13	13			38
200	1						
	2	50	13				63
	0	14	14	14			43
228	1						
	2	43		14			57

Table 16. Comparison between CT evaluation and EEG interpretation
Enzmann code versus code for visual interpretation
Percentages in all children

week	Enzm code	Code for visual interpretation 1	2	3	4	5	total
	0	57	7	19	6		90
0	1	2	2		2	2	6
	2			2	3		4
	0	39	3	5	2	2	50
6	1	5	2	6			13
	2	22	5	8	3		38
	0	37	6	16	5	2	65
18	1	5			3		8
	2	11	2	6	5	3	27
	0	48	11	11	3		74
32	1	7		2			8
	2	10	2	7			18
	0	57	4	15	2		77
60	1	4		2			6
	2	8	2	6		2	17
	0	55	5	14			73
116	1	5		5			9
	2	9		7	2		18
	0	61	10	16			87
144	1						
	2	3	3	7			13
	0	53	6	19			78
172	1	6		6			11
	2	8	3				11
	0	25	25	13			63
200	1	13					13
	2	25					25
	0	14	14	14			43
228	1	14		14			29
	2	29					29

C H A P T E R 6

Postirradiation syndrome

In february 1981 the records of 37 children, up till then enrolled in this study, were examined retrospectively for symptoms of the postirradiation syndrome. Even in retrospect, most children had shown signs of PRS. The most difficult symptom to interprete was fever. In a lot of children fever was attributed to an upper respiratory infection, even when the recorded findings were not convincing to substantiate such a conclusion. Most convincingly, the recording of somnolence, nausea and vomiting, anorexia and weight loss coincided with the occurrence and severity of a PRS. It was noted from the records, that a more or less dull expression of the eyes in particular seemed to be related to the PRS. Other symptoms of the PRS proved to be recorded in a haphazard way. Thus, a questionaire for a prospective evaluation of the occurrence of a PRS was designed. Symptoms and signs had to be registered at consultation in the outpatient department or at regular times during hospitalization and had to be coded for single symptoms as well as for the overall impression (i.e. grade) about the existence of PRS. Attempts were also made at the different times of evaluation to determine the moments of beginning and end of this syndrome, as well as of the moment of maximal symptomatology. The questionaire asked for slowness, lethargy, somnolence, headache, ataxia, irritability, nausea, vomiting, anorexia, fever without apparent cause, dull expression of the eyes, acrocyanosis, paleness, physical impression and overall interpretation of the severity of the PRS. The beginning and end, as well as the moment of maximal symptomatology was recorded by weeknumber. Moreover, exact dates for beginning and end of symptoms were tried to be obtained, from which the duration of symptoms could be calculated.

Codes for this evaluation are as follows:

0 no signs or symptoms

1 very slight signs or symptoms

2 slight signs or symptoms

3 moderate signs or symptoms

4 severe signs or symptoms, just manageable at home

5 very severe signs or symptoms, hospitalization necessary

6 life threatening signs or symptoms

7 not interpretable because of intercurrent infections, early

relapse or insufficient data (grade only)

9 not interpretable because of intercurrent infections, early relapse or insufficient data (for signs or symptoms only)

The severity of the PRS was expressed by the highest score obtained at successive visits. The children who had been investigated retrospectively were reevaluated using this questionnaire. All other children were evaluated prospectively.

The Student t test was applied for age and duration of symptoms. The Wilcoxon test was used for the coded items.

The codes for each child are presented in table VI.1. Results, expressed as mean values, together with a comparison between the groups evaluated retrospectively and prospectively are shown in table 1.

Table 1. Comparison of mean values in groups with retrospective and prospective evaluation of PRS

	whole group	retrospect	prospect	p value
n children	73	37	36	
age	5.9	5.9	5.9	0.93
risk factor	1.06	1.10	1.02	0.37
slowness	1.3	0.9	1.7	0.02
lethargy	1.6	1.3	2.0	0.05
somnolence	2.3	1.5	3.1	0.0005
headache	0.3	0.3	0.3	0.56
ataxia	0.5	0.3	0.8	0.03
irritability	0.5	0.1	1.0	0.0001
nausea	0.7	0.5	0.9	0.34
vomiting	1.2	1.2	1.2	0.25
anorexia	2.5	2.2	2.9	0.10
fever eci	1.4	1.3	1.5	0.88
dull eyes	1.1	0.6	1.6	0.0004
acrocyanosis	0.9	0.3	1.4	0.0000
paleness	0.9	0.7	1.0	0.19
worn-out	1.0	1.0	1.0	0.40
grade	2.7	2.4	3.1	0.03
begin WEEKNR	14.3	14.5	14.1	0.79
end WEEKNR	17.3	17.1	17.4	0.41
maximum WKNR	15.5	15.6	15.5	0.33
duration DAYS	20.3	18.0	22.4	0.06
range DAYS	4-41	4-41	4-36	
weightloss KG	1.4	1.6	1.3	0.85

Lower mean values for codes were in general found in the group of patients evaluated retrospectively. This difference was highly significant for the means concerning somnolence, irritability, dull eyes and acrocyanosis. A significant difference was also found for slowness, ataxia and grade. A trend towards significancy was present for lethargy and for duration of the PRS. This was undoubtedly a result of the difference in accuracy in recording symptoms retrospectively or prospectively.

Results for all children and for different agegroups are shown in table 2.
There were 7 children in the agegroup 0 - 2 years. One (#23) could not be evaluated because of an interstitial pneumonitis.
Twenty-five children were in the agegroup 2 - 4 years. One (#55) had been refractory to the initial treatment, three (#11, #18, #63) had an interstitial pneumonitis. One other child (#68) with a pneumonia during the period under investigation was evaluable for signs or symptoms of PRS before the occurrence of the infection, but not for the overall grading of the PRS.
In the agegroup 4 - 6 years all 13 children were evaluable.
There were 14 children in the agegroup of 6 - 10 years. One (#84) had not received radiotherapy and one (#17) had an interstitial pneumonitis.
One (#57) of the 14 children older than 10 years of age had been refractory to the initial treatment, one (#58) had died due to infection and one (#31) had an interstitial pneumonitis.
With regard to agegroups, a tendency to more severe symptoms was found with increasing age, in particular with regard to lethargy, nausea, vomiting, anorexia, and paleness. Under the age of six, symptoms became more outspoken in each higher agegroup. In the two older agegroups (6 - 10 years and older than 10 years) severity of symptoms was about the same, except for nausea and vomiting, which were more severe among children in the oldest group.
For all ages symptoms of PRS were first noticed between the 10th and the 17th week (mean 14th week) and were last recorded between the 13th and the 20th week (mean 17th week). The mean duration of PRS in the different agegroups ranged from 17 to 24 days (range 4 - 41 days). As was to be expected weight loss increased with increasing age. The differences between the highest and lowest bodyweights in the period of PRS were significant (paired Wilcoxon) in all agegroups.

Table 2. Mean values for postirradiation syndrome.
All children and per agegroup

Agegroup YRS	0 - 16	0 - 2	2 - 4	4 - 6	6 - 10	>= 10
n patients	73	7	25	13	14	14
n pts coded	62	6	20	13	12	11
slowness	1.3	0.5	1.1	1.2	1.8	1.7
lethargy	1.6	0.7	1.2	1.7	2.3	2.2
somnolence	2.3	2.3	2.0	1.8	3.3	2.5
headache	0.3	0	0.3	0.5	0.3	0.2
ataxia	0.5	0.8	0.4	0.5	0.8	0.6
irritability	0.5	0.5	0.5	0.6	0.8	0.2
nausea	0.7	0	0.3	0.6	1.0	1.6
vomiting	1.2	0.3	0.6	1.6	1.2	2.2
anorexia	2.5	2.0	2.0	2.8	3.1	2.8
fever eci	1.4	1.7	1.1	1.1	1.6	2.1
dull eyes	1.1	0.8	0.9	1.2	1.8	1.0
acrocyanosis	0.9	0.2	1.0	0.3	1.2	1.3
paleness	0.9	0.5	0.8	0.9	1.6	0.5
worn-out	1.0	0.5	0.6	1.2	1.5	1.3
grade	2.7	2.0	2.4	2.6	3.3	3.2
begin WEEKNR	14.3	13.8	14.1	14.6	14.0	14.7
end WEEKNR	17.3	16.7	17.0	17.1	17.8	17.8
maximum WKNR	15.5	14.8	15.3	15.8	15.9	15.8
duration DAYS	20.3	20.7	19.6	16.8	24.3	21.2
range DAYS	4-41	5-32	8-31	4-41	6-37	12-34
weightloss KG	1.4	0.6	0.8	1.2	1.8	2.9

A code for the PRS could be attributed to 62 children. One child (2%) had not shown signs of a PRS. Nine children (15%) had shown very slight symptoms and 17 (27%) had shown slight symptoms attributed to a PRS. A moderate PRS had been found in 19 patients (31%) and a severe PRS in 11 (18%). A very severe PRS necessitating hospitalization was observed in 5 children (8%). The mean frequencies derived from spectral analysis did not show a clear inverse relation with the grading for the PRS: 4.26 in the child without PRS, 5.27 for grade 1, 5.37 for grade 2, 4.90 for grade 3, 4.71 for grade 4 and 6.42 for grade 5.

The distribution of the grades for PRS over the different agegroups within the risk groups showed a tendency towards a more severe PRS in the older children (tables 3 and 4).

In the children destined to suffer from a CNSL as a first relapse the grading for the PRS was not different from that in the other children (table 5).

Table 3. Grades for PRS at week 18 according to agegroups
Children with HR-ALL

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
grade	n	%	n	%	n	%	n	%	n	%
0										
1	2	67	1	20	2	33				
2			2	40	1	17	1	20	2	50
3					1	17	2	40		
4	1	33	2	40	1	17	2	40	1	25
5					1	17			1	25
Total	3	13	5	22	6	26	5	21	4	17

Table 4. Grades for PRS at week 18 according to agegroups
Children with NHR-ALL

	0 - 2 yrs		2 - 4 yrs		4 - 6 yrs		6 - 10 yrs		>= 10 yrs	
grade	n	%	n	%	n	%	n	%	n	%
0			1	7						
1			2	13	1	14	1	14		
2	3	100	4	27	3	43			1	14
3			7	47	1	14	4	57	4	57
4			1	7	2	29			1	14
5							2	29	1	14
Total	3	8	15	39	7	18	7	18	7	18

Table 5. Postirradiation syndrome in children with first relapse in the CNS.
Codes for symptoms, signs and overall severity; days duration.

pat nr	S	L	So	H	A	I	N	V	An	F	D	C	P	W	dur	G*)
20	2	0	2	0	0	0	0	0	3	2	0	0	0	2	15	2
33	0	2	0	0	2	0	0	0	0	0	0	0	0	2	5	1
48	2	2	4	0	0	0	0	2	4	2	2	0	1	0	32	4
30	0	0	0	0	0	0	0	2	3	0	0	0	0	0	31	1
49	2	2	4	0	0	2	0	0	2	2	1	2	0	0	22	3
50	2	2	4	2	0	0	0	0	2	2	2	2	2	2	15	3
54	0	0	3	0	2	4	0	0	3	0	2	1	0	1	24	3
60	2	2	2	0	0	0	0	2	2	2	2	0	0	1	14	3
22	2	2	1	0	0	0	0	2	3	2	2	0	2	2	17	3

*) For legend see table VI.1

C H A P T E R 7

Discussion

In this longitudinal study three different methods for the evaluation of the CT scans were applied. These consisted of:

1) the calculation of the sum of the frontal horn distance and the bicaudate distance as performed by Huckman et al (1975); the results were interpreted according to the normal values for children as established by Meese et al (1980) and referred to as " Huckmannumber " or " acc. to Huckman ".

2) the evaluation of the combination of the frontal horn index F/A, the cella media index H/E and the width of the 3d ventricle using the normal values proposed by the same authors and referred to as " acc. to Meese " and

3) the evaluation of the frontal horn distance, the frontal horn width and the bicaudate distance according to the criteria of Enzmann and Lane (1977) and referred to as " acc. to Enzmann ".

The evaluations acc. to Huckman consistently showed higher percentages of borderline or abnormal values in comparison with the results obtained by the other two methods. This could be due to a too low upper value of normal of 35 and 45 mm (90th percentile) as established by Meese in two groups of only 10 and 40 healthy children respectively. It is also possible that this was the result of too high upper values of normal as derived from the two other methods. For instance, the upper limit of normal of the Huckmannumber using the criteria of Enzmann is 49 mm. The interpretations acc. to Huckman acc. to Meese et al probably overestimate the amount of abnormal ventricular dilatations. Even if this is the case it offers a better impression of the fluctuations in the ventricular dimensions, in the same order as can be seen with the real Huckmannumbers.

By our definition, abnormality according to Meese is composed of the finding of at least two abnormal interpretations out of two indices and of one absolute value. These indices were chosen because they were expected to be obtainable in almost all patients. They could also offer an impression of the relative width of the ventricles at two different levels of the CT scans. The additional interpretation of the absolute value of the width of the 3d ventricle was chosen because an abnormal dilatation of this ventricle only occurs when a substantial dilatation of the ventricles is present. This could compensate for an overestimation of ventricular enlargement. Rather frequent-

ly however, the cella media distance could not be measured and consequently its index could not be calculated. In those cases, only two of three parameters needed for an interpretation were available. If one of these parameters was abnormal, an overall code "normal" was attributed. It may therefore be possible that the number of normal scans acc. to Meese was overestimated. In general, the interpretations acc. to Meese were more often normal than those acc. to Enzmann. Furthermore, they also seemed to be more inconsistent.
The measurements for the interpretation acc. to Enzmann and consequently also those for the calculation of the Huckmannumber are more easily and more reliably obtained in comparison with those needed for the more complicated evaluations acc. to Meese. It is then a matter of choice which one of the two former methods of evaluation are applied. Since evaluations which use the normal values of Enzmann and Lane are most of the time referred to in the literature these are to be preferred for comparison. However, the use of the Huckmannumber according to the criteria presented by Meese may sometimes yield more information.

At diagnosis, 15% of all children had abnormal scans and 7% borderline abnormal scans acc. to the Huckmannumber. These figures were 6% and 4% acc. to Meese and 4% and 6% acc. to Enzmann respectively. The percentage of abnormal scans acc. to Enzmann is rather low compared with the percentages obtained by others who found values in the order as reported by Enzmann and Lane (1978) for children with non-CNS-malignancies (18%): Clausen and Pedersen (1982) found dilated CSF spaces in 2 of 11 children scanned at diagnosis. Ochs et al (1980) scanned 13 children before therapy was started and found 2 abnormal CT scans. The number of children in these two reports however is very small. Jankovic et al (1989) published a report about 40 children in whom CT scans were obtained before any treatment was given and who had been examined in a single hospital. They found 40% abnormal CT scans already at that time. These authors postulated, that the dilated CSF spaces might reflect clinically unsuspected lesions secondary to leukemia. In comparison with our findings as well as those by Ochs et al and Clausen and Pedersen this proportion of abnormal scans is unexpectedly high. The reason for this discrepancy is not clear. In our patients even with the most sensitive method of evaluation acc. to Huckman, only 15% of scans proved to be abnormal at diagnosis.
At the end of the induction treatment with a.o. prednisone, 62% of scans of 68 children were abnormal and 1% borderline abnormal according to the Huckmannumber. With the interpretation acc. to Meese these figures were 29% and

4% respectively and acc. to Enzmann 37% and 13%.
The proportion of abnormal scans as determined with the interpretation according to Enzmann is somewhat higher than reported by most other authors. Kretzschmar et al (1980) found scans with widened ventricles and sulci in 10 children (31%) before CNS prophylaxis. These scans were made in the first two weeks of induction therapy which also included prednisone. It has been shown, that prednisone in sufficiently high dosages can give rise to dilatation of the CSF spaces (Momose et al 1971, Heinz et al 1977, Bentson et al 1978). This could be the cause of the widening of the ventricles and sulci in their study, as well as in those by others. Kretzschmar et al stated however, that this widening was still present in almost all children on scans repeated 1 year after CNS prophylaxis. Therefore, their conclusion was:
""late" damage seems principally to be damage that was diagnosed too late".
Ochs et al (1983) found mild ventricular dilatation and/or sulcal dilatation in approximately 30% of children. CT scans had also been made during induction treatment. The authors attributed this finding to steroid therapy since on repeat scans 6 weeks after the completion of the CNS prophylaxis, no widening of the CSF spaces was found, and it was not found any more during further follow-up. O'Hare et al (1988) reported also widening of CSF spaces in 16% of scans obtained during induction treatment. This low proportion was found despite a mean treatment period of 5 weeks prior to the scanning, even though prednisone and in some instances also i.th. MTX had been given. Jankovic et al (1988) however reported a high incidence of 62% abnormal scans in their multi-centre study. These scans were made during the first 2 weeks of therapy and were evaluated according to the criteria of Enzmann and Lane. Their proportion of abnormal scans could only be matched by our results obtained by the sensitive evaluation according to the Huckmannumber.

In the postirradiation phase, the number and percentages of abnormal scans had declined in comparison with those in the post induction scans. This was the case regardless of the method of interpretation. Abnormal scans acc. to Huckman were found in 48%, acc. to Meese in 25% and acc. to Enzmann in 28%. The decline in these percentages was more outspoken in the group of children with NHR-ALL.

During treatment the proportions of abnormal scans remained about the same in children with HR-ALL. In contrast, these values declined in patients with NHR-ALL. Pulses of prednisone are rather frequently incorporated in our treatment protocols. Widening of the CSF spaces due to the use of this ster-

oid may not have diminished sufficiently in the interval periods. It is quite possible that these dilatations had remained visible up till at least 4 weeks after the prednisone pulse. This interval was dictated by the protocol. Even if these widenings of the CSF spaces are caused by prednisone, it is remarkable that the course of the dilatations proved to be different between the children with HR-ALL and those with NHR-ALL.

In the majority of children with NHR-ALL, diminishing ventricular dimensions were seen after stopping treatment. This may indicate that prednisone is indeed the cause of the widening and that the interval between the pulses was too short to reestablish normal dimensions. In contrast, diminution after completion of treatment was not evident in the children with HR-ALL, suggesting that other mechanisms may play a role.
One year after completion of therapy, 4 (57%) of the children with HR-ALL and 4 (15%) of the children with NHR-ALL were coded abnormal acc. to the Huckmannumber. According to Meese, these figures were 3 (43%) and 2 (7%) and acc. to Enzmann 2 (29%) and 1 (4%) respectively. In children with NHR-ALL these percentages are within the range as has been reported for children with other malignancies (Enzmann and Lane 1978) or in control children (Ochs 1980, Allen 1981). The proportions of abnormal scans in children with HR-ALL are much higher with all three methods of interpretation.

In this study widening of ventriculi and sulci was found after induction therapy and before any CNS prophylaxis was administered. Whether L-asparaginase and/or daunorubicin was added to the vincristine and prednisone regimen did not influence the occurrence of widening of the CSF spaces. Prednisone was incremented to be the cause of sulcal and ventricular widening in a CT scan study performed on adult patients treated for immunological diseases like SLE etc., especially when a dose of more than 30 mg/m^2 per day had been given. Also, a decrease of widening was seen when a high prednisone dose was tapered to a dose less than 10 mg per day (Bentson et al 1978). In the treatment of leukemia rather high dosages of prednisone are administered. In our study, children received a dosage of 40 mg/m^2/day. Therefore, one should expect that all children would show ventricular dilatation at the end of the induction treatment.
Fifty-eight of the 61 children who were measured at diagnosis and at the end of induction therapy, and for whom the Huckmannumber was calculated, did show dilatation, varying between 1 and 19 mm. Thirty-nine children (64%) showed

a widening of 4 mm or more. Sixteen of the 61 children (26%) had a widening of even 8 mm or more. In one child the Huckmannumber was 4 mm smaller after induction therapy. Two children had the same Huckmannumber before and at the end of induction treatment. These last 3 NHR-ALL patients did not differ from the others. Differences of less than 4 mm could have been the result of measuring errors due to the dimensions of the pixels on the CT scans.

A difference in the size and pattern of ventricular enlargement was found between children with HR-ALL and NHR-ALL. Already in the first six weeks, i.e. during induction treatment, a greater mean enlargement of the ventricles was evident in the children with HR-ALL. A mean dilatation of the ventricles of 7.6 mm was found in contrast to a mean dilatation of 4.3 mm in children with NHR-ALL. Sixteen out of 19 children with HR-ALL (84%) and 23 out of 42 with NHR-ALL (55%) showed a dilatation of 4 mm or more. Eight of the children with HR-ALL (42%) and 8 of those with NHR-ALL (19%) had a widening of 8 mm or more. The HR-ALL patients had received the same dosages of vincristine, prednisone and l-asparaginase as the children with NHR-ALL. No intrathecal therapy was administered during induction in both groups. Gutjahr et al (1980) also noticed more abnormal scans in children with a higher mean WBC than in children with lower WBC, although the difference was not significant. Other authors found no correlation between CT scan abnormalities and WBC (O'Hare et al 1988, Jankovic et al 1989).
In the five children who received only vincristine and prednisone as induction treatment, the same pattern of ventricular widening was found as in the others. Also, the pattern proved to be the same in the children who received four injections of daunorubicin in addition (protocol VB).
Thus, differences in treatment can not be implicated as a cause for the differences found between both risk groups. Most probably the leukemia itself is responsible for this different behaviour.

Earlier reports stated, that up to 80% of children with ALL would experience a CNS relapse when no "prophylactic" CNS treatment was given, provided sufficient time in continuous hematological remission could elapse. It is most likely that infiltration of leukemic cells in the arachnoidea does occur in up to 80% of children before ALL is diagnosed. If this infiltration disrupts the BBB an increased diffusion of certain drugs into the brain or CSF will occur. One may postulate, that there exists a correlation between the infiltration by leukemic cells and the diffusion of systemic drugs. A high tumor load as in children with HR-ALL may be accompanied by an increased infiltra-

tion and consequently an increased diffusion of drugs. This may explain why children with a HR-ALL show more dilatation after induction treatment.

Widening of the CSF spaces has been attributed to CNS irradiation (Peylan-Ramu et al 1978), in particular since such dilatation was not found in children who had received i.v. and/or i.th. MTX (Peylan-Ramu et al 1978, Kolmannskog et al 1979, Ochs et al 1980). Other authors however, could not establish such a relation (Day et al 1978, Gutjahr and Kretschmar 1979, Clausen and Pedersen 1982, Brecher et al 1985, O'Hare et al 1988). Our observation that the dimensions diminished after irradiation had been given renders irradiation also less probable as a cause for the widening. This is in particular so in children with NHR-ALL. In children with HR-ALL however, the dilatation of the CSF spaces proved to be more stable. Supposedly the damage inflicted by the initial leukemic infiltration was more extensive. Repair could have taken longer with consequently an increased diffusion of drugs over an extended time. Vascular changes induced by irradiation will a.o. cause reductions in cerebral blood flow, resulting in small necrotic foci. All these mechanisms together may result in real cerebral atrophy, manifested by a permanent widening of the CSF spaces.

The four children who showed calcifications on their CT scans during the follow-up period of this study, were all young (1.3 - 3.0 years) at the time of initial diagnosis. Seventeen other children were also younger than 3 years at diagnosis but showed no calcifications. There was a higher prevalence among children with HR-ALL: three of the nine children aged less than 3 years got calcifications as opposed to one of the twelve children with a NHR-ALL. This difference could be due to the fact that children with HR-ALL received more intrathecal therapy with MTX during the first year of treatment. In one child, however, calcifications were already present at week 32, i.e. after only 3 additional i.th. injections. This renders the additioned i.th. MTX a less probable cause of the calcifications. This particular child experienced a CNS relapse as a first event 14 months after the calcifications had been recorded for the first time, suggesting another explanation.
The EEG's were normal at the time calcifications were seen on the CT scan in 3 children and borderline abnormal in one. None showed focal abnormalities. Thus, the presence of calcifications seemed to have no bearing on the EEG's.

Calcifications have been reported to occur in children, who had been irradiated for medulloblastoma. Pearson et al (1983) performed CT scans on 5 chil-

dren, at least 5 years after treatment with surgery and radiotherapy with more than 30 Gray. Calcifications were found in 3 of them who had been irradiated while being younger than 5 years of age. These children had not received i.th. medication, nor MTX orally or parenterally. This suggests that irradiation alone may be implicated as the cause of the calcifications. Moreover, there seems to be a correlation between the age at which the child had received irradiation and the presence of calcifications. The interval between irradiation and the detection of calcifications was long, 6 to 13 years. In one of these patients however, a scan was performed one year after treatment and was found to be normal. In other reports intervals of 3 to 14 years are mentioned (Harwood et al 1970, Numaguchi et al 1975, Lee and Suh 1977, Murphy 1979). However, since CT scans were not performed in a prospective study, a precise interval between irradiation and the occurrence of calcifications in children with brain tumours cannot be established.

Price and Birdwell (1978) found calcifications in their autopsy series of children with ALL, who had received cranial irradiation and who had survived longer than 10 months after diagnosis. Especially children irradiated under the age of 10 years seemed at risk. They concluded that the mineralizing microangiopathy resulted from cranial irradiation, and was potentiated by systemic and intrathecal chemotherapy, in particular with MTX. Bowles et al (1982) could find no abnormalities on CT scans in children treated for osteosarcoma with high cumulative dosages (up to 95 g/m²) of MTX intravenously, suggesting that MTX alone does not cause calcifications. McIntosh et al (1977) also found calcifications in children with ALL surviving for more than 9 months after CNS irradiation. These children were also treated with fairly high dosages of i.v. MTX. In one of the children in our series, calcifications were already present 5 months after irradiation had been completed. This suggests, that chemotherapy indeed potentiates the effects of irradiation for the development of calcifications. Calcium is deposited in necrotic brain areas whatever the cause may be. If one assumes leukemic infiltrates to be present in and around the vessel walls already at diagnosis, one may also postulate that during induction treatment with a.o. prednisone these infiltrates are eradicated, leaving a necrotic area, which then will become calcified. Disruption of the BBB by leukemic infiltration may then be the underlying cause. This may be corroborated by the more frequent finding of calcifications in children after treatment for CNS leukemia (Gastaut et al 1978, Pedersen and Clausen 1981, Metz et al 1983). In our own experience calcifications became visible in children with CNSL not treated with irradiation but

with a.o. intrathecal injections of MTX and i.v. infusions of MTX. Russo et al (1987) also reported the finding of calcifications in a child with CNSL treated with i.th. MTX only. This is compatible with the assumption that the successful treatment of leukemic infiltrations may be an important cause of the development of calcifications.

In this study hypodense areas around the frontal or occipital horns of the lateral ventricles or around the ventricles in the cella media region were seen. This occurred in 8 of the 26 children with a HR-ALL and in 10 of the 47 children with a NHR-ALL. In some children, the hypodense areas disappeared on follow-up. In a proportion of these children hypodense areas reappeared on the next scans. Reversibility of hypodensities has also been reported by others (Wendling et al 1978), and sometimes had occurred even a long time after CNS prophylaxis (Ochs et al 1983, Riccardi et al 1985).
Ochs et al (1983) observed abnormal scans in a group of 108 children, serially evaluated over a 2 year period. In 14 out of the 15 children with abnormal scans, focal or diffuse white-matter hypodensities had been found, which reverted to normal in most cases. The hypodensities were detected as early as six weeks after CNS prophylaxis, regardless whether this consisted of crXRT or of i.v. infusions of MTX, both in combination with i.th MTX. In our series hypodense areas were already present at the end of the induction period in two children and at week 18 in 6 patients. This last time is comparable with the six weeks after CNS prophylaxis of Ochs et al. Hypodensities are assumed to be the result of demyelination. The reversibility of these abnormalities suggests that alternative explanations should be sought. Hypodensities may also be caused by (transient) edema.
In three of our children, hypodense areas were present before calcifications became visible on CT scan. Calcifications were seen at the earliest time half a year after the end of the CNS prophylaxis. No calcifications had been found in children who had shown hypodense areas in the series of Riccardi nor of Ochs. The combination of these abnormalities was noticed in one child treated for CNSL by Pedersen and Clausen (1981).

The fluctuations in the dimensions of the CSF spaces as well as the transient nature of the hypodensities make single CT scans less valuable, in particular those obtained during treatment. For correct interpretation a CT scan obtained before therapy was started is necessary in order to be informed about pre-existing abnormalities. Knowledge of the treatment employed and whether the

patient is on or off therapy is necessary. Abnormalities, which are present one year after therapy has been completed may be irreversible. However, Riccardi et al (1985) have shown that after longer follow-up some abnormalities may revert to normal or others may still appear.

Two methods for the evaluation of the EEG's were applied. These consisted of evaluation in the usual visual way for background rhythm and focal abnormalities and of evaluation with computer aided spectral analysis.
At diagnosis and before treatment was started 42 of 71 tested children (60%) had a normal EEG. Fifteen had a slightly abnormal EEG (21%), seven a moderate abnormal (10%) and one a severely abnormal EEG (1%).
This proportion of normal EEG's is within the range reported in the literature: Korinthenberg et al found 24% normal EEG's before treatment, Mahoney et al 40%, Stephani et al 53% and Hässler et al even 80%.
The cause for the high proportions of abnormal EEG's at diagnosis is not clear. The initial slowing of the EEG has been attributed to leukemic infiltration of the CNS, although this was not confirmed by lumbar puncture (Hanefeld and Riehm 1980). Since we assumed that more leukemic infiltration is present in children with HR-ALL, one should expect more abnormal EEG's in these children. However, this was not the case. Thirty-one percent of children with HR-ALL and 33% of those with NHR-ALL had initially abnormal background rhythms. Mahoney et al (1981) could not establish a correlation with age, hemogram, bleedings, infections or metabolic derangements. However, in their study, EEG abnormalities at diagnosis appeared to be associated with subsequent early transient neurotoxicity including the postirradiation syndrome.
At the end of the induction period, 43 of 67 (65%) children had a normal EEG, 13 (20%) a slightly abnormal, 3 (5%) a moderately abnormal and one (1%) a severely abnormal EEG. Thus, a very slight tendency to less abnormal EEG's was observed. This is contrary to the findings of Stephani et al (1980) who found a higher proportion of abnormal EEG's after 4 weeks of induction treatment. Korinthenberg et al (1979) and Hässler et al (1976) also reported an increase in abnormal EEG's at the end of induction. They implicated the chemotherapeutic drugs to be the cause. Indeed, L-asparaginase has been reported to cause a reduced frequency of the basal rhythm and the presence of diffuse slow waves in a high proportion of patients (75 - 85%) studied (Moure et al 1970, Land et al 1972). Prolonged administration of prednisone has also been associated with a gradual increase in the 4 - 7 Hz activity (

Butcher et al 1970). In our treatment protocols, with the exception of protocol III, L-asparaginase is given daily during the last 2 weeks of induction therapy. In all protocols, prednisone is tapered during the same period from 40 mg/m²/day to 0 in 10 days. Four children, treated according to protocol III proved to have a normal EEG before as well as at the end of induction treatment. The fifth was tested only at the end of induction and had a slightly abnormal EEG at that moment. None of these five children had focal abnormalities after induction therapy. Due to these small numbers, it is not possible to determine whether with this treatment protocol another pattern of EEG interpretations would have emerged.

Spectral analysis showed that the mean frequency had risen from 4.3 to 5.9 Hz during the induction treatment. This was due to a lower proportion of delta waves after induction therapy (52.8%) than before (64.8%). At the same time the proportion of alpha waves had risen from 6.5% to 9.4%. The theta activity did not rise significantly (from 21.1% to 23.0%) during the induction period. The children treated according to protocol III showed also an increase in the mean frequency as a result of a decrease in the proportion of delta waves and an increase in alpha waves. The improvement in the EEG's may be attributed to the eradication of leukemic infiltrations.

Immediately after CNS irradiation, 64% of EEG's were normal, 20% slightly abnormal and 3% moderately abnormal. Thus, the distribution of normal and abnormal EEG's was about the same as immediately before CNS prophylaxis. Korinthenberg et al (1979) on the contrary, reported a higher proportion of normal EEG's after irradiation. In view of their already low number of normal recordings at diagnosis, they could hardly have had more abnormal EEG's. Garwicz et al (1975) also found about the same proportions of normal EEG's before and after irradiation. According to the spectral analysis the mean frequency after irradiation was slightly decreased to 5.4 Hz with a rise in the proportion of delta waves to 55.7% and a decline in alpha waves to 8.7%.

The EEG's obtained at week 18, while most of the children suffered from the postirradiation syndrome, proved to be normal in 52%, slightly abnormal in 21%, moderately abnormal in 12% and severely abnormal in 5%. This deterioration is also evident in the low mean frequency of 5.1 Hz, which is made up by 59.3% delta waves and 6.8% alpha waves. A drop in the mean frequencies was also reported by Ch'ien et al (1980), in particular in the children suffering from the PRS.

A specific pattern in the mean frequency derived from spectral analysis was

observed. The mean frequency was low at diagnosis, and rose during induction treatment. Immediately after irradiation, the mean frequency was slightly lower than before. At the time of the PRS, the mean frequency had declined further, but was still higher than at diagnosis. Thereafter, a slight increase occurred untill one year after diagnosis, and remained fairly stable thereafter. These patterns were the same for children with HR-ALL or NHR-ALL. The variable mean frequencies in the HR group, obtained after treatment may be due to the small numbers of children involved.

The mean frequency was influenced most by the percentage of deltawaves as calculated by spectral analysis. Variations in the percentages of deltawaves were generally inversely related to those of alpha and rest waves. Theta waves were fairly stable over the period of study. Normally, the mean frequency becomes higher with age. Such a developmental rise in the mean frequency was not observed in our series. This indicates that a gradual relative decrease in mean frequency with age occurs in the children treated for leukemia. The percentage of alpha waves however did show a slight increase after the first half year of therapy. Since the follow-up in our patients was ended one year after treatment was stopped, it is not possible to know whether catch-up will take place. However, no trend for a rising mean was seen after stopping therapy. Therefore, it seems unlikely that a catch-up will occur later on.

No correlation between the interpretations of the EEG's and the results of the CT scans could be established. This was also reported by Carli et al (1985).

The children who eventually developed a CNS relapse as a first event did not differ from the other patients with respect to the outcome of their EEG's at initial diagnosis. Six (67%) had normal background rhythms, two (22%) had slightly abnormal and one (11%) moderately abnormal background rhythms. In the children who did not develop a CNS relapse the corresponding values were 58%, 21% and 10% respectively. None of the children with a CNSL as a first relapse had shown focal abnormalities at the EEG at initial diagnosis. Among the 62 other patients, 47 (76%) had no focal abnormalities, 10 (16%) had focal abnormalities in one area and 5 (8%) in two or more areas.

At the end of the induction period, all 8 tested children, destined to suffer from a CNSL, had normal background rhythms. One of them showed focal abnormalities in two or more areas. Among the 59 other children, 42 (74%) had a normal or borderline EEG at that time. Twelve (20%) showed focal abnormali-

ties.

Immediately after irradiation as well as at the time of the PRS, 7 (78%) of the 9 children with a CNSL as a first relapse had a normal EEG. In the other children 76% and 59% of normal EEG's were found at those times resp. Thus, no specific pattern in the first 4 EEG's of children who developed a CNS relapse could be established.

Hässler et al (1976) and Mahoney et al (1981) also stated that initial EEG's did not predict for the development of a later CNSL. The latter authors also remarked, that the occurrence of a postirradiation syndrome was not related with the eventual development of a CNS relapse. Ch'ien et al (1980) noticed that the presence of a somnolence syndrome predicted for later cerebral dysfunctions. As we did not perform psychological tests as part of this study, we are unable to substantiate such a relationship.

The last EEG's obtained before a CNS relapse was diagnosed were normal in most instances. Only 2 EEG's showed slightly abnormal background rhythms. Only one focus was found to be present in one child with a normal background rhythm. In our study serial EEG's did not predict an imminent CNS relapse.

In the same 9 children with a CNSL as a first relapse, six (67%) had normal ventricles acc. to the Huckmannumber, one (11%) was borderline abnormal and two (22%) were abnormal when initially diagnosed. According to Meese, these proportions were 89%, 0% and 11%, and acc. to Enzmann 89%, 11% and 0% respectively. For all children, these figures were in the same order of magnitude. Thus, CT scans at initial diagnosis have no predictive value for the development of a CNSL.

At the end of the induction period these figures were 33%, 0% and 67% for the Huckmannumber, and 56%, 22% and 22% for both Meese and Enzmann resp. in the children developing a CNSL. In all children the distribution acc. to the Huckmannumber was about the same. The proportion of normal scans according to Meese was a bit higher and of borderline scans a bit lower. There were proportionally somewhat less borderline and more abnormal scans acc. to Enzmann. However, these differences were too small for clinical use.

At the time of the PRS, these proportions were 33%, 22% and 56% acc. to the Huckmannumber, 67%, 11% and 22% acc. to Meese and 89%, 0% and 11% acc. to Enzmann resp. in the children with a later CNSL. Again, there were small differences in these distributions in the whole group of children, but these were too small to be of clinical significance.

Therefore, the scans made early during treatment also did have no predictive

value for the development of a later CNSL.
The last scans made before the diagnosis of CNSL were most of the time normal: according to Huckman, one was borderline abnormal and one abnormal, acc. to Meese one was abnormal and acc. to Enzmann also one was abnormal. Only one child interpreted as abnormal acc. to Huckman was also abnormal acc. to Enzmann. Thus, scans made regularly can not indicate an imminent CNS relapse.

The postirradiation syndrome was evaluated retrospectively in 37 children and prospectively in the other 36. The PRS was considered to be less severe in the children evaluated retrospectively due to a less systematic recording of symptoms. Nevertheless, almost all children had shown some signs of the PRS. Only one child among the 62 evaluable children had shown no signs of the syndrome. Nine had shown very slight symptoms. Clear signs and symptoms were found in 52 (83%) children. Five of them needed hospitalization. This frequency of occurrence of the PRS is higher than reported by others (Freeman et al 1973, Terheggen and Rado 1978) as a result of the specific searching or questioning for the syndrome. The PRS proved to be more severe in older children. Symptoms were first noticed at a mean of 5 weeks after the end of the cranial irradiation i.e. in week 14 of our treatment protocol. This is in concordance with the literature. The use of a prednisone pulse in week 11 and 12 in our protocols could have postponed the first occurrence of symptoms. The mean duration of symptoms was 20 days (range 4 - 41 days). This is in the same order as reported by others (Freeman et al 1973, von Lieven et al 1976, Terheggen and Rado 1978). The mean could have been higher since the duration of symptoms had been shortened in some of our children due to the start of a prednisone pulse at week 18. The percentage of abnormal CT scans had not become higher than that before irradiation. Fourty percent of the EEG's were interpreted as abnormal during the PRS. At the evaluations at week 9 and week 32 the percentage of abnormal EEG's was 26% and 23% resp. The mean frequencies derived from spectral analysis did not show a relation with the grades of severity of the PRS. The children who later developed a CNSL did not show more severe symptoms.

In conclusion, the evaluations of the dimensions of the ventricular system according to the Huckmannumber, as defined for children by Meese, proved to be the most sensitive of the three methods applied. However, for practical purposes those according to Enzmann are to be preferred.

Already at diagnosis before any treatment was delivered some children showed an abnormal ventricular system and dilated sulci on the CT scan. Abnormal background rhythms were found in one third of children and focal abormalities in one fifth. Spectral analysis revealed a mean frequency of 4.3 Hz with 64.8% delta waves and 6.5% alpha waves.

Widening of the CSF spaces was already present at the end of induction treatment, which was more obvious in the children with HR-ALL. This is caused by prednisone, which effect is probably enhanced by more damage inflicted by a higher tumor load in children with HR-ALL. After CNS prophylaxis with cranial irradiation and i.th. MTX a decline in the percentage of children with dilated CSF spaces was found. In children with NHR-ALL the proportion of abnormal scans declined during therapy and even more thereafter. The use of prednisone pulses may have influenced this process. In the children with HR-ALL however, the same proportions of enlarged CSF spaces proved to be present during the further treatment and for one year thereafter. This may represent real atrophy.

Calcifications were found in 4 children aged less than 3 years at initial diagnosis.Three of them suffered from HR-ALL. The successful treatment of leukemic infiltrations may be an important factor in the development of calcifications.

The dynamic process of ventricular and sulcal widening renders the interpretation of a single CT scan difficult, in particular during therapy.

The EEG's showed improvement with a higher mean frequency after induction treatment. After worsening of the EEG's together with a decline in the mean frequencies during the postirradiation period, improvement was again observed. After one year of treatment the mean frequencies remained stable.

No correlation between the interpretations of the EEG's and the results of the CT scans could be established.

Almost all children suffered from the postirradiation syndrome. Unequivocal signs and symptoms of the PRS were established in 83% of the evaluable children. Symptoms were more severe in older children. No correlation between the mean frequency and the grade of severity of the PRS was seen.

The children who developed a CNS relapse did not differ from the others. Neither initial nor serial CT scans and EEG's did predict an imminent CNS relapse.

Summary

This longitudinal study was initiated in order to examine the nature and sequence of structural and functional cerebral abnormalities in children with acute lymphocytic leukemia (ALL).
For this purpose computer assisted tomography scans of the brain (CT scans) and electroencephalograms (EEG's) were obtained at diagnosis before treatment was instituted, after induction therapy, at specific times during maintenance treatment and till one year therafter.
An other obiective was to investigate retrospectively whether children who first relapsed in the central nervous system (CNS) could be identified at initial diagnosis or shortly thereafter.

Cerebral CT scans were performed with an EMI 1010 or a Philips 300 or 310 scanner.
Linear measurements of the ventricles, sulci and skull on the röntgen films were performed three times. The means thereof were multiplied by the minification factor in order to obtain the actual dimensions. The frontal horn and cella media indices were calculated.
The results were compared with the reference values of each of three evaluation methods: with those of Enzmann and Lane, with those of Meese et al and with the Huckmannumber as defined for children by Meese et al. The results were coded. CT scans were also examined for the presence of hypodense areas and calcifications.

Electroencephalograms were obtained with a 16-channel Elema-Schönander apparatus. The electrodes were placed according to the international 10 - 20 system.
The EEG's were interpreted in the usual way and were coded for background rhythm and for focal abnormalities.
Spectral analysis was performed with a PDP 11/34 computer after the EEG's had been recorded on magnetic tape. Three artifact-free epochs of 100 seconds in the leads T3 - O1 were analyzed. A Fast Fourier Transformation was used to yield a weighted mean frequency and the percentages of delta-, theta-, alpha- and rest waves.

Seventy-three children with ALL consecutively admitted to the Sophia Children's Hospital between february 1978 and february 1984 were taken into this

study. Twenty-six of them suffered from a high-risk ALL (HR-ALL) and 47 from a non-high-risk ALL (NHR-ALL). NHR-ALL was defined as an ALL with less than 50 * 10^9 leucocytes/liter, no mediastinal enlargement or no central nervous system leukemia (CNSL) at initial diagnosis. The group of children with a HR-ALL comprised all others except those with an initial CNSL.
Children with a NHR-ALL were treated for 2 years according to national protocols of the Dutch Childhood Leukemia Study Group and children with a HR-ALL were treated for 3 years according to the institutional protocol HR77.

Initially, patients were examined by a pediatric neurologist at the same day as the EEG's and CT scans were performed. Since it turned out that these examinations did not yield additional information than already obtained by pediatric oncologists, they were discarded after two years.

With regard to the ventricles, the evaluations according to the Huckmannumber consistently showed abnormal values more frequently than by the other two methods. The measurements needed for the calculation of the Huckmannumber and for the interpretation according to Enzmann could be obtained most reliably. The cella media index could rather frequently not be calculated, which made the interpretations according to Meese less reliable.
For practical purposes, the normal values of Enzmann and Lane must be preferred, not in the least since those are most often used as a reference. The interpretations according to Huckman however give a far better insight in the fluctuations of the ventricular dimensions.

At diagnosis before treatment was started, a small proportion of children had an abnormal or borderline abnormal ventricular system on the CT scans. This amounted to 15% abnormal and 7% borderline abnormal ventricles according to the Huckmannumber, 6% and 4% acc. to Meese and 4% and 6% acc. to Enzmann resp. After induction therapy, before CNS prophylaxis, enlargement of the ventricles as expressed by the absolute Huckmannumbers was seen in almost all children. This dilatation was more outspoken in the children with HR-ALL than in those with NHR-ALL. The children with HR-ALL not only showed a higher mean dilatation (8 mm vs 4 mm) but also a higher proportion of abnormal scans than those with NHR-ALL (78% vs 53% with the coded Huckmannumber). The interpretations acc. to Meese and acc. to Enzmann however, did not show such a difference in the proportion of abnormal scans in children with HR-ALL or NHR-ALL.

After CNS prophylaxis, the proportion of abnormal scans acc. to the Huckmannumber had become slightly lower in children in both groups.
During maintenance treatment, the proportion of abnormal CT scans remained about the same (60% acc. to the Huckmannumber) in the children with HR-ALL. In those with NHR-ALL however, less than 20% abnormal scans were found already after one year of treatment.
After therapy had been completed, the percentage of abnormal CT scans remained about the same in the children with HR-ALL but declined further in those with NHR-ALL. One year after the end of treatment, 4 of 7 children with HR-ALL were still abnormal acc. to the Huckmannumber in contrast to 4 of 27 children with NHR-ALL.
In 2 of the 5 children with HR-ALL, investigated both at diagnosis and at one year after treatment, the interpretations of the ventricular system with the Huckmannumber were the same (i.e. normal) but these had changed from normal or borderline to abnormal in the other three. Among the 25 children with NHR-ALL 20 remained the same (i.e. 19 normal and 1 abnormal), 4 had become normal (3 from abnormal and 1 from borderline) and only one had changed from normal to abnormal.

At diagnosis, sulci were abnormal in 4% of children with HR-ALL and in 9% of children with NHR-ALL. Sulci showed widening after induction treatment also. At that moment, about 75% of children had abnormal sulci in both groups.
During maintenance treatment this percentage of abnormal sulci was about 67% in the children with HR-ALL, but declined to 47% in the children with NHR-ALL. In both groups, the percentages of abnormal sulci became much lower after treatment was completed. The return to normal occurred faster in the children with NHR-ALL.

The most probable cause for the initial widening is the use of high doses of prednisone during induction treatment. The regression of this ventricular widening as seen in the children with NHR-ALL during the first year of treatment may be retarded by the use of prednisone pulses. The further diminution of the ventricular dimensions after treatment was stopped is compatible with this notion. This argues against irradiation as the primary cause of the ventricular widening. In the children with HR-ALL however, the widening proved to be more stable and may represent real atrophy.

Hypodense areas, in particular around the frontal horns, were seen in 8 children with a HR-ALL and in 10 with a NHR-ALL. Sixteen of these children were younger than 6 years at diagnosis. Hypodense areas were noted at different times: in 8 children (2 HR-ALL and 6 NHR-ALL) already as early as at week 6 or at week 18. In 9 children (3 HR-ALL and 6 NHR-ALL) the hypodensities disappeared, but became again apparent in 3 (3 HR-ALL).

Calcifications were found in 4 children (3 HR-ALL and 1 NHR-ALL). All were younger than 4 years at initial diagnosis. Three of them had also shown hypodense areas. Calcifications were first seen half a year (1 HR-ALL) and 2 years (2 HR-ALL and 1 NHR-ALL) after the start of treatment in the others. Two of the children with HR-ALL developed a CNS leukemia later on. Irradiation alone can give rise to the occurrence of calcifications in the cerebrum. The use of MTX contributes to the development of calcifications. The successful treatment of leukemic infiltrations may be the principal cause.

With regard to the visual interpretation of the EEG's, abnormal background rhythms were present in 32% of children at diagnosis and focal abnormalities in 21%. After induction treatment and prior to CNS prophylaxis 25% of the EEG's showed abnormal background rhythms and 18% showed focal abnormalities. Immediately after irradiation, these percentages were about the same. In the postirradiation period however, these percentages rose significantly to 38% and 25% respectively. After recovery from the postirradiation syndrome, these percentages became of the same order as those after induction treatment and remained so thereafter. There were no differences in the patterns between children with HR-ALL and NHR-ALL.

The mean frequency, calculated by spectral analysis, was 4.3 Hz at diagnosis and rose to 5.9 Hz after completion of induction therapy. During the postirradiation syndrome, the mean frequency proved to have declined significantly to 5.1 Hz. This value was still significantly higher than the one at diagnosis. The mean frequency rose slightly over the next half year and remained stable during further follow-up. Most of the time the mean frequencies were about the same in children with HR-ALL and NHR-ALL. Only during the postirradiation syndrome and 3 months thereafter, the means were lower in children with NHR-ALL.
With spectral analysis, the distribution over delta, theta, alpha and rest waves, contributing in the calculation for the mean frequency, was obtained

also. The differences in the percentages of the delta waves between two observations were reflected in the differences between the percentages of alpha and rest waves. The mean percentages of the theta waves remained about the same during this study.
The percentage of delta waves was highest at initial diagnosis (64.8%) and decreased significantly to 52.7% after induction treatment. At the end of the postirradiation period this percentage proved to have risen significantly to 59.3%. After the next 3 months the mean percentage of delta waves became 57.7% and remained fairly stable thereafter. In the first six months, the mean percentages of the alpha waves showed the same fluctuations as the delta waves, although in the opposite directions. After the first half year of therapy however, the mean percentage of alpha waves continued to rise significantly. These patterns were the same in children with HR-ALL and NHR-ALL.

No correlation between the interpretations of the EEG's and the results of the CT scans could be established at any time. Spectral analysis did not contribute to a better interpretation of the EEG's.

Almost all children suffered from the postirradiation syndrome. Unequivocal signs and symptoms of the PRS were established in 83% of the evaluable children. Symptoms were more severe in older children. Fourty percent of the EEG's were abnormal. The mean frequency was only 5.1 Hz. No correlation between the mean frequency and the grade of severity of the PRS was found. The children who later developed a CNSL did not show more severe symptoms.

Nine children experienced a central nervous system leukemia as a first relapse. They did not show different patterns in the CT scan evaluations nor in the EEG visual interpretations or with spectral analysis. Serial investigations of CT scans and EEG's proved not to be helpful for the early identification of children at high risk for the development of a CNS relapse.

Samenvatting

Dit longitudinaal onderzoek werd opgezet om inzicht te krijgen in het optreden en beloop van anatomische en functionele afwijkingen van de hersenen bij kinderen met een acute lymphatische leukemie (ALL).
Hiertoe werden met de computer berekende tomografische scans van de hersenen (CT scans) en electroencephalogrammen (EEG's) vervaardigd bij eerste presentatie van de patient voordat met therapie werd begonnen, aan het eind van de aanvalsbehandeling, op gezette tijden tijdens de onderhoudsbehandeling en tot een jaar na het beeindigen daarvan.
Daarnaast werd retrospectief nagegaan of kinderen, die een recidief in het centraal zenuwstelsel (CZS) kregen, reeds bij eerste diagnose of kort daarna geidentificeerd konden worden.

CT scans van de hersenen werden vervaardigd met een EMI 1010 of een Philips 300 of 310 scanner.
Metingen van de ventrikels, sulci and schedel op de röntgenopnamen werden op drie verschillende momenten verricht. De gemiddelden van de drie metingen werden telkens berekend en vermenigvuldigd met de verkleiningsfactor om de werkelijke maat te verkrijgen. Tevens werden de frontaal hoorn en cella media indices berekend. De uitkomsten werden vergeleken met 3 sets referentie waarden: die volgens Enzmann en Lane, die volgens Meese et al en met die van het Huckmangetal zoals voor kinderen door Meese et al was vastgesteld. De resultaten werden gecodeerd. De CT scans werden tevens beoordeeld op het aanwezig zijn van hypodense gebieden en verkalkingen.

Electroencephalogrammen werden afgeleid met behulp van een 16-kanaals Elema-Schönander encephalograaf. De electroden werden overeenkomstig het internationale 10 - 20 systeem geplaatst. De EEG's werden op de gebruikelijke manier beoordeeld. Daarna werden deze gecodeerd voor achtergrond ritme en focale afwijkingen.
De EEG's werden tevens op een magnetische band vastgelegd. Spectraal analyse met behulp van een PDP 11/34 computer werd op een later tijdstip verricht. Hiertoe werden drie artefact vrije perioden van 100 seconden in de temporo-occipitale afleiding T3 - O1 geanalyseerd. Met behulp van een "Fast Fourier transformation" werden een gewogen gemiddelde frequentie en de percentages delta-, theta-, alpha- en overige golven berekend.

Drieenzeventig kinderen met ALL, achtereenvolgens tussen februari 1978 en februari 1984 in het Sophia Kinderziekenhuis opgenomen, werden in deze studie betrokken. Zesentwintig hadden een ALL met verhoogd risico op een recidief (HR-ALL) en 47 een ALL zonder verhoogd risico (NHR-ALL). NHR-ALL was volgens nationale criteria gedefinieerd als een ALL met minder dan 50 * 10^9 leucocyten/liter, zonder mediastinale verbreding of zonder een CZS leukemie (CZSL) bij eerste presentatie. Alle overige kinderen, behalve die met een initiële CZSL, vormden de groep HR-ALL. De kinderen met NHR-ALL werden gedurende 2 jaar behandeld volgens de vigerende protocollen van de Nederlandse Werkgroep Leukemie bij Kinderen. De kinderen met HR-ALL werden gedurende 3 jaar behandeld volgens het SKZ-protocol HR77.

Aanvankelijk werden de kinderen op dezelfde dag waarop de EEG's en CT's werden vervaardigd ook onderzocht door een kinderneuroloog. Aangezien bij tussentijdse evaluatie bleek, dat deze onderzoekingen niet méér informatie opleverde dan al door de kinderoncologen verkregen was, werden deze na de eerste twee jaar beëindigd.

Voor de ventrikelgrootte werden met de beoordelingen volgens het Huckmangetal telkens in hogere percentages abnormale waarden gevonden dan met de twee andere methoden. Het bleek, dat de maten benodigd voor de berekening van het Huckmangetal evenals die benodigd voor de interpretatie volgens Enzmann, het meest frequent en meest betrouwbaar verkregen konden worden. Daarentegen kon de cella media afstand vaak niet gemeten worden en derhalve de index niet berekend worden. Dientengevolge was de interpretatie volgens Meese minder betrouwbaar. Uit practische overwegingen voldoen de normaalwaarden volgens Enzmann en Lane het beste, mede omdat deze in de literatuur het meest als referentie gebruikt worden. Toepassing van de beoordeling volgens Huckman geeft daarentegen een veel beter inzicht in de veranderingen van de ventrikel afmetingen.

Bij presentatie, voor therapie werd begonnen, toonde slechts een minderheid van de kinderen abnormaal of grenswaarde abnormaal wijde ventrikelruimten. Beoordeeld volgens Huckman kwam dit respectievelijk voor bij 15% en 7%, volgens Meese bij 6% en 4% en volgens Enzman bij 4% en 6% van de kinderen. Na inductie behandeling en nog vóór CZS prophylaxe bleken vrijwel alle kinderen wijdere ventrikelruimten te hebben, tot uiting komend in hogere Huckmangetallen. Deze verwijding was meer uitgesproken bij kinderen met HR-ALL dan met

NHR-ALL. Dit was niet alleen duidelijk door een grotere gemiddelde toename in de wijdte (8 mm tegenover 4 mm) maar ook doordat méér kinderen met een HR-ALL een abnormale CT scan (78% tegenover 53% volgens het Huckmangetal) kregen. Met de andere methoden kon een dergelijk verschil in abnormale scans tussen kinderen met HR-ALL en NHR-ALL echter niet aangetoond worden.
Na de CZS prophylaxe was het percentage abnormale scans volgens Huckman iets lager in beide groepen patienten. Gedurende de onderhoudsbehandeling bleef het percentage abnormale CT scans vrijwel gelijk (60%) bij kinderen met HR-ALL, doch werd allengs lager bij kinderen met NHR-ALL. In deze laatste groep werd reeds na één jaar behandeling minder dan 20% abnormale scans gevonden.
Nadat de behandeling electief was beëindigd, bleef het percentage abnormale CT scans vrijwel gelijk bij de kinderen met HR-ALL, maar daalde verder bij de kinderen met NHR-ALL. Een jaar na beëindiging van de behandeling toonden 4 van de 7 kinderen met een HR-ALL nog een vergrote ventrikelruimte in tegenstelling tot slechts 4 van de 27 kinderen met een NHR-ALL.
Van de 5 kinderen met een HR-ALL, onderzocht bij diagnose evenals een jaar na beëindiging van de behandeling, bleken er 2 in beide gevallen als normaal beoordeeld te zijn, doch waren er 3 abnormaal geworden. Van de 25 kinderen met NHR-ALL waren er 20 gelijk gebleven (19 normaal en 1 abnormaal), 4 waren normaal geworden (3 van abnormaal en 1 van randwaarde) en slechts één was van normaal naar abnormaal veranderd.

De sulci bleken ook verwijd te zijn na inductiebehandeling: ongeveer 75% van de kinderen in beide groepen hadden wijde sulci. Gedurende de onderhoudsbehandeling bleef dit percentage abnormale sulci rond de 67% bij kinderen met HR-ALL, doch daalde gestaag tot 47% bij de kinderen met NHR-ALL. In beide groepen patienten werden de percentages verwijde sulci veel lager nadat de therapie was beeindigd. De terugkeer naar normale sulci verliep veel sneller bij de kinderen met NHR-ALL.

De meest waarschijnlijke oorzaak van de verwijding is de toepassing van hoog gedoseerd prednison gedurende de inductie behandeling. Het kleiner worden van de ventrikel ruimten gedurende het eerste jaar van behandeling bij de kinderen met NHR-ALL is waarschijnlijk vertraagd verlopen door het periodiek gebruik van prednison. De verdere verkleining na het staken van de therapie past hierbij. Dit pleit tegen de opvatting dat bestraling de belangrijkste oorzaak van de verwijding van de liquorruimten is. Bij kinderen met HR-ALL bleken de verwijdingen echter stabieler en zouden deze een uiting kunnen zijn

van echte atrofie.

Hypodense gebieden, in het bijzonder rond de frontaal hoornen, werden waargenomen bij 8 kinderen met een HR-ALL en bij 10 kinderen met een NHR-ALL. Zestien van hen waren jonger dan 6 jaar bij initiële diagnose. De hypodense gebieden werden op diverse tijdstippen waargenomen: bij 8 kinderen (2 HR-ALL en 6 NHR-ALL) reeds na inductiebehandeling (week 6) of na bestraling (week 18). Bij 9 patienten (3 HR-ALL en 6 NHR-ALL) waren de hypodense gebieden niet meer waarneembaar op latere scans, bij 3 (3 HR-ALL) werden deze echter opnieuw zichtbaar.

Verkalkingen werden bij 4 kinderen (3 HR-ALL en 1 NHR-ALL) waargenomen. Al deze kinderen waren jonger dan 4 jaar bij eerste diagnose. Bij 3 van hen waren ook hypodense gebieden op de CT scans gezien. Verkalkingen werden voor het eerst na een half jaar (1 HR-ALL) en na 2 jaar (2 HR-ALL en 1 NHR-ALL) behandeling waargenomen. Twee van deze kinderen kregen later een CZS leukemie. Bestraling alleen kan al verkalkingen in de hersenen veroorzaken. Toepassen van MTX draagt hieraan bij. Het met succes behandeld zijn van occulte leukemische infiltraties zou wel eens de meest belangrijke oorzaak voor het ontstaan van verkalkingen kunnen zijn.

Bij eerste diagnose toonden 32% van de EEG's een abnormaal achtergrond ritme en 21% focale afwijkingen. Na inductiebehandeling waren deze percentages respectievelijk 25% en 18%. Deze waren in dezelfde orde van grootte direct na de bestralingsperiode. Tegen het eind van het postirradiatie syndroom waren de percentages afwijkingen duidelijk gestegen tot respectievelijk 38% en 25%. Na herstel van dit postirradiatie syndroom keerden deze percentages terug tot de waarden zoals gezien aan het eind van de inductie en bleven daarna op gelijk niveau. Er waren geen verschillen in deze patronen tussen kinderen met HR-ALL of NHR-ALL.

De gemiddelde frequentie, berekend met spectraal analyse, was 4.3 Hz bij diagnose en steeg tot 5.9 Hz aan het eind van de inductie. Gedurende het postirradiatie syndroom daalde dit gemiddelde significant tot 5.1 Hz. Deze waarde bleek echter nog significant hoger dan die bij diagnose. Hierna steeg de gemiddelde frequentie enigszins gedurende een half jaar om daarna ongeveer gelijk te blijven. Bij de meeste onderzoekingen waren de gemiddelde frequenties ongeveer gelijk bij de kinderen met HR-ALL en NHR-ALL. Alleen bij het onder-

zoek in de postirradiatie fase en dat 3 maanden later was de gemiddelde frequentie lager bij de kinderen met NHR-ALL.
Met spectraal analyse werden ook de percentages delta, theta, alpha en overige golven zoals die bijdroegen aan de gemiddelde frequentie, berekend. De verschillen in de percentages deltagolven tussen twee onderzoekingen werden omgekeerd evenredig teruggevonden in de verschillen in percentages alpha en overige golven. De gemiddelde percentages thetagolven bleven gedurende de gehele studie vrijwel gelijk.
Het percentage deltagolven was het hoogst bij eerste diagnose (64.8%) en daalde significant tot 52.7% na inductiebehandeling. Aan het eind van de postirradiatie periode, bleek dit percentage weer significant gestegen tot 59.3%. Na de volgende 3 maanden was dit gedaald tot 57.7% en bleef hierna vrijwel gelijk. Bij de onderzoekingen in het eerste half jaar toonden de gemiddelde percentages alphagolven dezelfde fluctuaties als de deltagolven, zij het in tegengestelde richting. Na het eerste half jaar behandeling bleef het gemiddelde percentage alphagolven stijgen. Deze patronen waren hetzelfde bij kinderen met HR-ALL en NHR-ALL.

Er werd geen correlatie gevonden tussen de beoordelingen van de EEG's en de CT scans. Spectraal analyse kon geen dijdrage leveren aan de beoordelingen van de EEG's.

Bijna alle kinderen leden in meer of mindere mate aan het postradiatie syndroom. Een duidelijk PRS werd bij 83% van de evalueerbare kinderen vastgesteld. De symptomen waren ernstiger naarmate de kinderen ouder waren. Veertig procent van de EEG's was abnormaal.De gemiddelde frequentie was slechts 5.1 Hz. Er werd geen correlatie tussen de gemiddelde frequentie en de ernst van het PRS gezien. De kinderen die later een CZSL kregen toonden geen ernstiger verlopend PRS.

Bij 9 kinderen werd een CZS leukemie als eerste recidief vastgesteld. Bij hen werd geen afwijkend patroon in de CT scan of EEG beoordelingen noch in de uitkomsten van de spectraal analyse waargenomen. Met behulp van deze onderzoekingen konden de kinderen, die later een CZSL kregen, niet in een vroeg stadium geidentificeerd worden.

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E X T E N D E D

T A B L E S

R E F E R R I N G T O C H A P T E R S

III - VI

Table III.1. Patient characteristics at diagnosis.
General information *)

pat nr	sex	age yrs	Dx	FAB type	Immun class	Karyo type	Treat ment	RF
1	M	2.4	HR	ND	ND	ND	HR77	1.95
2	F	2.6	HR	ND	ND	ND	HR77	1.31
5	F	2.1	HR	ND	NONB	ND	HR77	1.04
8	M	5.6	HR	ND	NONB	ND	HR77	1.44
9	F	8.3	HR	ND	T	ND	HR77	1.36
16	F	0.8	HR	L2	NONB	ND	HR77	1.22
20	F	8.1	HR	L2	NONB	ND	HR77	1.38
21	M	4.8	HR	L2	T	ND	HR77	1.40
28	M	4.8	HR	L2	ND	ND	HR77	1.73
33	M	1.6	HR	L1	C	NL	HR77	1.55
34	M	5.1	HR	L1	T	NL	HR77	1.64
38	M	14.5	HR	L2	T	NL	HR77	1.26
39	M	9.8	HR	L2	T	NL	HR77	0.54
40	M	12.8	HR	L2	T	NL	HR77	1.26
41	M	4.0	HR	L1	T	PS	HR77	1.89
48	M	1.3	HR	L1	NULL	NL	HR77	1.35
55	M	2.9	HR	L2	T	NL	HR77	1.82
56	F	9.9	HR	L1	T	PS	HR77	1.00
58	F	12.9	HR	L2	C	NL	HR77	1.83
65	F	14.1	HR	L1	C	FAIL	HR77	0.98
69	M	2.3	HR	L1	C	>50	HR77	1.13
70	F	2.8	HR	L1	PREB	PS	HR77	1.30
72	F	8.1	HR	L2	T	PS	HR77	1.35
79	F	4.0	HR	L1	T	4750	HR77	1.30
80	M	11.4	HR	L1	T	HYPO	HR77	1.48
84	F	6.6	HR	L1	T	HYPO	HR77	1.36
3	M	3.3	NHR	AUL	ND	ND	IIIA	1.36
7	M	8.4	NHR	AUL	ND	ND	IIIA	1.05
4	F	3.3	NHR	L1	NONB	ND	IIIB	0.55
6	F	4.1	NHR	AUL	ND	ND	IIIB	1.42
10	F	3.0	NHR	ND	ND	ND	IIIB	1.52
23	M	0.8	NHR	L1	ND	ND	VA	1.42
25	M	14.8	NHR	L1	ND	ND	VA	0.40
26	F	5.2	NHR	L1	NONB	ND	VA	0.90
27	M	10.2	NHR	L2	T	ND	VA	0.78
30	M	2.9	NHR	L1	ND	ND	VA	1.00
42	M	1.7	NHR	L1	C	PS	VA	1.16
43	M	8.8	NHR	L1	FAIL	HYPO	VA	0.44
49	M	2.9	NHR	L1	C	>50	VA	0.60
50	M	10.2	NHR	L1	C	NL	VA	0.68
51	F	7.8	NHR	L1	C	PS	VA	0.68
53	F	10.1	NHR	L1	PREB	4750	VA	0.78
54	F	3.8	NHR	L1	C	>50	VA	0.84
57	M	10.3	NHR	L2	B	PS	VA	0.82
60	F	3.2	NHR	L1	C	PS	VA	0.84
62	F	14.0	NHR	L1	C	>50	VA	0.55
63	F	3.8	NHR	L2	C	>50	VA	0.86
68	M	3.1	NHR	L1	PREB	FAIL	VA	1.16
71	M	7.7	NHR	L1	PREB	PS	VA	1.00
75	M	2.8	NHR	L1	C	>50	VA	0.37

Table III.1. Patient characteristics at diagnosis.
General information (continued)

pat nr	sex	age yrs	Dx	FAB type	Immun class	Karyo type	Treat ment	RF
11	M	2.0	NHR	L2	NONB	ND	VB	1.02
12	F	7.0	NHR	L2	NONB	ND	VB	1.02
14	F	3.6	NHR	ND	NONB	ND	VB	0.90
15	M	3.4	NHR	L2	ND	ND	VB	1.47
17	F	6.4	NHR	AUL	ND	4750	VB	0.74
18	F	2.8	NHR	L2	NONB	ND	VB	0.90
19	F	10.5	NHR	L1	NONB	ND	VB	1.05
22	F	2.0	NHR	L1	ND	ND	VB	0.88
31	F	14.3	NHR	L2	FAIL	ND	VB	0.58
32	M	3.0	NHR	L1	NONB	ND	VB	0.54
35	M	4.5	NHR	L1	NONB	>50	VB	0.73
36	M	8.1	NHR	L1	C	NL	VB	0.50
37	F	13.1	NHR	L2	PREB	NL	VB	0.86
44	F	8.9	NHR	L1	T	NL	VB	0.99
45	M	4.0	NHR	L1	C	NL	VB	0.41
46	F	3.2	NHR	L1	FAIL	FAIL	VB	0.95
47	M	1.3	NHR	L1	PREB	NL	VB	0.78
52	M	4.4	NHR	L1	PREB	PS	VB	0.66
59	M	1.9	NHR	L1	PREB	PS	VB	1.48
61	M	2.9	NHR	L1	C	4750	VB	0.50
66	M	5.2	NHR	L1	C	PS	VB	0.95
73	M	3.5	NHR	L1	PREB	NL	VB	1.21
74	M	5.4	NHR	L1	C	NL	VB	1.10

*) Dx = Diagnosis: Type of ALL classification
FAB = French-American-British classification
AUL = acute undifferentiated leukemia
ND = not done, not sent to laboratory
FAIL = sent to laboratory, but failure to do tests
Immunological type: C = common ALL, PREB = pre-B cell ALL,
NONB = no B or T (simple) characteristics
NULL = null cell ALL,
B = B cell ALL, T = T cell ALL,
Karyotype: NL = normal, PS = pseudodiploid,
HYPO = hypodiploid
Hyperdiploid group divided in:
4750 = 47 - 50 chromosomes,
>50 = more than 50 chromosomes
RF = Risk factor according to BFM

Table III.2. Patient characteristics at diagnosis
Hematological values

pat nr	sex	age yrs	Peripheral blood Hb mmol/L	thromb 10^9/L	WBC 10^9/L	blast %	BSE mm1eh	Bone marrow cell[1] 10^9/L	blast %
1	M	2.4	3.6	9	191.0	79	3	750	90
2	F	2.6	3.0	12	52.9	90	108	400	97
5	F	2.1	4.7	34	50.0	87	87	485	92
8	M	5.6	5.5	20	71.8	85	25	930	98
9	F	8.3	8.6	42	130.0	90	8	990	90
16	F	0.8	5.2	40	50.0	50	00	00	90
20	F	8.1	5.0	0	155.0	93	50	680	96
21	M	4.8	7.8	12	107.0	75	20	1050	90
28	M	4.8	4.1	27	195.0	93	35	1000	97
33	M	1.6	3.5	30	178.0	98	40	00	98
34	M	5.1	2.7	18	113.6	88	15	00	97
38	M	14.5	7.6	2	169.2	89	4	650	96
39	M	9.8	8.0	176	9.2	5	5	385	80
40	M	12.8	7.5	8	150.3	91	8	700	95
41	M	4.0	3.4	34	199.5	97	80	1000	96
48	M	1.3	3.9	12	198.7	95	70	485	99
55	M	2.9	4.0	18	175.0	88	35	240	97
56	F	9.9	8.6	110	98.4	76	3	950	90
58	F	12.9	6.3	6	180.0	94	18	680	98
65	F	14.1	5.8	38	88.0	94	47	950	100
69	M	2.3	3.7	6	76.0	85	65	280	96
70	F	2.8	3.9	17	62.1	73	80	106	90
72	F	8.1	4.6	51	212.0	93	30	1000	96
79	F	4.0	6.9	68	171.0	93	5	750	98
80	M	11.4	7.8	10	150.0	88	10	240	90
84	F	6.6	4.3	5	186.3	92	18	325	99
3	M	3.3	6.5	36	25.1	47	17	325	94
7	M	8.4	3.8	158	0.8	16	62	80	90
4	F	3.3	5.2	268	6.6	9	87	200	85
6	F	4.1	4.3	2	2.6	31	45	380	98
10	F	3.0	2.5	17	15.2	72	122	000	94
23	M	0.8	3.4	13	38.8	87	55	400	98
25	M	14.8	2.9	200	2.4	4	50	120	98
26	F	5.2	4.5	34	29.2	52	85	765	98
27	M	10.2	5.3	22	13.2	56	23	0	97
30	M	2.9	2.2	168	4.7	17	125	180	99
42	M	1.7	2.5	34	24.1	75	130	190	96
43	M	8.8	7.3	213	5.1	3	87	375	80
49	M	2.9	1.7	28	2.8	9	126	100	98
50	M	10.2	4.5	218	2.7	13	40	75	91
51	F	7.8	3.0	5	1.6	8	65	160	98
53	F	10.1	5.0	32	5.4	19	79	140	97
54	F	3.8	2.2	2	4.1	3	20	175	99
57	M	10.3	5.5	7	11.8	18	86	370	97
60	F	3.2	5.2	22	6.2	10	35	00	90
62	F	14.0	8.3	119	3.5	12	15	300	93
63	F	3.8	3.0	5	3.2	17	75	375	99
68	M	3.1	3.0	17	47.0	83	130	250	95
71	M	7.7	4.7	23	12.2	16	91	560	96
75	M	2.8	5.6	144	4.5	1	21	103	93

Table III.2. Patient characteristics at diagnosis
Hematological values (continued).

pat nr	sex	age yrs	Peripheral blood Hb mmol/L	thromb 10^9/L	WBC 10^9/L	blast %	BSE mm1eh	Bone marrow cell[1] 10^9/L	blast %
11	M	2.0	4.1	4	24.4	84	65	590	92
12	F	7.0	3.5	32	3.7	17	118	550	94
14	F	3.6	3.7	58	5.6	5	55	00	96
15	M	3.4	2.5	12	15.2	69	25	440	98
17	F	6.4	5.3	145	4.9	75	10	180	92
18	F	2.8	2.4	38	24.1	77	48	196	97
19	F	10.5	6.5	41	23.1	87	35	00	95
22	F	2.0	5.9	30	22.3	66	40	575	96
31	F	14.3	3.4	65	3.5	24	60	210	94
32	M	3.0	3.5	33	6.4	8	58	195	83
35	M	4.5	4.3	20	7.9	43	99	295	98
36	M	8.1	2.7	64	1.3	17	100	4	70
37	F	13.1	7.2	124	5.8	5	72	750	95
44	F	8.9	5.6	4	21.5	45	35	810	97
45	M	4.0	5.3	126	2.2	5	130	305	93
46	F	3.2	5.3	7	3.0	50	85	60	92
47	M	1.3	5.0	63	5.8	39	88	330	86
52	M	4.4	3.6	324	3.0	7	122	200	83
59	M	1.9	3.4	14	29.4	89	37	285	92
61	M	2.9	2.2	4	4.3	7	81	245	95
66	M	5.2	6.0	526	26.2	48	59	400	89
73	M	3.5	4.8	12	41.0	72	50	380	97
74	M	5.4	4.1	44	22.6	72	96	1265	98

[1] 000 = hypercellular on slide
00 = normal cellularity on slide
0 = hypoplastic on slide

Table III.3. Patient characteristics at diagnosis.
Leukemia load.

pat nr	sex	age yrs	RF	WBC 10^9/L	blast %	liver cm	spleen cm	lnn [1]	medi > [1]
1	M	2.4	1.95	191.0	79	8	11	G	N
2	F	2.6	1.31	52.9	90	3	5	G	N
5	F	2.1	1.04	50.0	87	2	0	G	N
8	M	5.6	1.44	71.8	85	4	6	G	N
9	F	8.3	1.36	130.0	90	3	4	G	Y
16	F	0.8	1.22	50.0	50	3	4	N	N
20	F	8.1	1.38	155.0	93	2	6	G	N
21	M	4.8	1.40	107.0	75	5	3	G	N
28	M	4.8	1.73	195.0	93	8	5	G	Y
33	M	1.6	1.55	178.0	98	5	5	N	N
34	M	5.1	1.64	113.6	88	6	7	L	Y
38	M	14.5	1.26	169.2	89	1	4	L	Y
39	M	9.8	0.54	9.2	5	0	0	L	Y
40	M	12.8	1.26	150.3	91	2	3	G	N
41	M	4.0	1.89	199.5	97	4	15	G	Y
48	M	1.3	1.35	198.7	95	3	3	L	N
55	M	2.9	1.82	175.0	88	5	12	L	Y
56	F	9.9	1.00	98.4	76	0	1	G	Y
58	F	12.9	1.83	180.0	94	5	12	L	N
65	F	14.1	0.98	88.0	94	0	0	L	N
69	M	2.3	1.13	76.0	85	1	3	L	N
70	F	2.8	1.30	62.1	73	3	5	G	N
72	F	8.1	1.35	212.0	93	1	6	G	Y
79	F	4.0	1.30	171.0	93	3	2	L	N
80	M	11.4	1.48	150.0	88	5	4	G	N
84	F	6.6	1.36	186.3	92	2	5	G	Y
3	M	3.3	1.36	25.1	47	7	3	G	N
7	M	8.4	1.05	0.8	16	10	1	G	N
4	F	3.3	0.55	6.6	9	0	0	N	N
6	F	4.1	1.42	2.6	31	10	6	L	N
10	F	3.0	1.52	15.2	72	5	10	G	N
23	M	0.8	1.42	38.8	87	6	4	G	N
25	M	14.8	0.40	2.4	4	0	0	N	N
26	F	5.2	0.90	29.2	52	1	½	L	N
27	M	10.2	0.78	13.2	56	0	0	G	N
30	M	2.9	1.00	4.7	17	5	3	G	N
42	M	1.7	1.16	24.1	75	4	2	G	N
43	M	8.8	0.44	5.1	3	0	0	N	N
49	M	2.9	0.60	2.8	9	2	0	L	N
50	M	10.2	0.68	2.7	13	3	0	L	N
51	F	7.8	0.68	1.6	8	3	2	L	N
53	F	10.1	0.78	5.4	19	3	0	L	N
54	F	3.8	0.84	4.1	3	5	3	L	N
57	M	10.3	0.82	11.8	18	2	1	N	N
60	F	3.2	0.84	6.2	10	4	1	L	N
62	F	14.0	0.55	3.5	12	½	0	G	N
63	F	3.8	0.86	3.2	17	4	2	G	N
68	M	3.1	1.16	47.0	83	4	½	L	N
71	M	7.7	1.00	12.2	16	1	7	L	N
75	M	2.8	0.37	4.5	1	½	0	L	N

Table III.3. Patient characteristics at diagnosis.
Leukemia load (continued).

pat nr	sex	age yrs	RF	WBC 10^9/L	blast %	liver cm	spleen cm	lnn	medi >
11	M	2.0	1.02	24.4	84	2	1	G	N
12	F	7.0	1.02	3.7	17	5	4	G	N
14	F	3.6	0.90	5.6	5	3	6	L	N
15	M	3.4	1.47	15.2	69	7	6	G	N
17	F	6.4	0.74	4.9	75	½	0	L	N
18	F	2.8	0.90	24.1	77	1	0	N	N
19	F	10.5	1.05	23.1	87	2	2	L	N
22	F	2.0	0.88	22.3	66	1	0	G	N
31	F	14.3	0.58	3.5	24	0	0	N	N
32	M	3.0	0.54	6.4	8	0	0	L	N
35	M	4.5	0.73	7.9	43	½	0	G	N
36	M	8.1	0.50	1.3	17	½	0	N	N
37	F	13.1	0.86	5.8	5	4	3	L	N
44	F	8.9	0.99	21.5	45	2	2	G	N
45	M	4.0	0.41	2.2	5	0	0	N	N
46	F	3.2	0.95	3.0	50	2	5	G	N
47	M	1.3	0.78	5.8	39	2	0	L	N
52	M	4.4	0.66	3.0	7	2	2	G	N
59	M	1.9	1.48	29.4	89	6	6	G	N
61	M	2.9	0.50	4.3	7	0	0	N	N
66	M	5.2	0.95	26.2	48	2	½	G	N
73	M	3.5	1.21	41.0	72	2	5	G	N
74	M	5.4	1.10	22.6	72	4	½	L	N

[1] N = no, G = generalised, L = localised, Y = yes

Table III.4. Patients course of disease

pat nr	treat ment	RF	months from 1st CR till relapse in BM	CNS	Tes	months 1st CR		months survival
1	HR77	1.95				134+		136+
2	HR77	1.31				133+		134+
5	HR77	1.04				130+		131+
8	HR77	1.44				2+	1)	4
9	HR77	1.36	6			6		10
16	HR77	1.22	31	43		31		46
20	HR77	1.38	49	13		13		121+
21	HR77	1.40				120+		121+
28	HR77	1.73				115+		116+
33	HR77	1.55		25	36	25		53
34	HR77	1.64			22	22		112+
38	HR77	1.26	2			2		5
39	HR77	0.54				103+		104+
40	HR77	1.26	9	12		9		21
41	HR77	1.89	6			6		17
48	HR77	1.35	31	22	33	22		34
55	HR77	1.82	0			0		14
56	HR77	1.00				86+		87+
58	HR77	1.83				1+	1)	2
65	HR77	0.98				77+		78+
69	HR77	1.13				74+		75+
70	HR77	1.30				74+		75+
72	HR77	1.35	4			4		19
79	HR77	1.3	12			12		19
80	HR77	1.48		24	16	16		32
84	HR77	1.36	29	4		4	2)	34
3	IIIA	1.36				131+		132+
7	IIIA	1.05	38		73	38		82
4	IIIB	0.55	99	99	99	99		131+
6	IIIB	1.42				130+		131+
10	IIIB	1.52				75+	3)	129+
23	VA	1.42				3+	4)	4
25	VA	0.40				116+		118+
26	VA	0.90				9+	5)	10
27	VA	0.78	14			14		25
30	VA	1.00		13		13		58
42	VA	1.16	38			22+	3)	72
43	VA	0.44				96+		97+
49	VA	0.60		16		16		91+
50	VA	0.68	42	9	33	9		44
51	VA	0.68	33			33		90+
53	VA	0.78				88+		89+
54	VA	0.84		22	57(eye)	22		76
57	VA	0.82	0	0		0		8
60	VA	0.84		32		32		84+
62	VA	0.55				81+		82+
63	VA	0.86				80+		80+
68	VA	1.16				74+		76+
71	VA	1.00				73+		74+
75	VA	0.37				69+		70+

Table III.4. Patients course of disease
(continued)

pat nr	treat ment	RF	months from 1st CR till relapse in BM	CNS	Tes	months 1st CR		months survival
11	VB	1.02				126+		127+
12	VB	1.02				123+		125+
14	VB	0.90				123+		124+
15	VB	1.47				21+	1)	22
17	VB	0.74				17+	5)	18
18	VB	0.90				121+		121+
19	VB	1.05	6			6		9
22	VB	0.88	53	16		16		54
31	VB	0.58	0	3		0		9
32	VB	0.54				111+		113+
35	VB	0.73				111+		111+
36	VB	0.50	6			6		17
37	VB	0.86				104+		105+
44	VB	0.99				96+		97+
45	VB	0.41				96+		97+
46	VB	0.95				96+		97+
47	VB	0.78				95+		96+
52	VB	0.66				89+		90+
59	VB	1.48				83+		84+
61	VB	0.50				81+		82+
66	VB	0.95				76+		77+
73	VB	1.21				71+		72+
74	VB	1.10	29		29	29		64

cut off date: july 1st 1989
1) died of bacterial infection
2) other CNS prophylaxis after cerebrovascular accident
3) second malignancy
4) died of Pneumocystis Carinii pneumonitis
5) died of varicella

Table IV.1. Measurements (mm) of frontal horn span on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		43			40	41	42		40	40	40
002		34			32	32	33		31	32	31
005	29			28	32	29	30		30	26	27
008	33	34		35							
009	25	25		24							
016	23			25	20	22	14				
020	23	35		35	35	35					
021	33	39		39	37	37	38		37	37	37
028	36	37		34	34	36	38		35	36	33
033	28	29		27	30		31				
034	40	44		42	40	43					
038	33	36									
039	32	34		35	33	35	35		36	30	35
040	34			38	38						
041	32	35		31	33						
048	24	31		23	29	33					
055	34	36									
056	35	37		38	37	36	37		37	35	37
058	28										
065	33	35		36	38	37	36		37	36	
069	29	36		34	36	35	35		34		
070	25	28		28	29	26	28		29		
072	32	33		35							
079		36		30	30	33					
080	31	36		36	36	38					
084	31	32									
003	29	34		29	32	31	32	29	26		
007		37		34	35	37	38	35	35		
004	31			33	30	33	31	30	30		
006	28	28		28	29	29	28	28	29		
010		39		35	33	34	33	38	36		
023	35	35									
025	24	29		27	28	30	29	30	28		
026	26	28		34	28						
027	30	29		28	32	34					
030	33	34		32	33	34					
042	29	32		29	30	31	31	30	31		
043	30	32		31	31	32	31	27	28		
049	35	37		37	31	32					
050	40	42		40	39						
051	27	28		29	28	27	29	28			
053	37	39		39	37	36	38	36	36		
054	34	38		33	34						
057	36	36									
060		31		32	28	28	29	29			
062	33	30		32	32	32	32	32	31		
063	36	38		38	37	37	37	35	36		
068	36	38		37	33	34					
071	29			31	31	30	31	30	29		
075	30	32		31	29	32	31	30	32		

Table IV.1. Measurements (mm) of frontal horn span on CT scan.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	33	36		37	33	34	34	32	32		
012	29	33		34	35	32	34	34	34		
014	31	32		33	36	34	34	32	31		
015	36	39		38	38	37					
017	30	32		37	33	34					
018	27	24		26	25	27	26	27	25		
019	34	35		40	43						
022	30	30		33	30	34					
031	35	35									
032	27	27		26	25	25	27	25	26		
035	31	31		35	31	29	31	30	28		
036	35	38		35	38						
037	29	28		29	32	32	32	31			
044	26	30		31	32	32	29	32	30		
045	35	37		39	37	39	41	36	34		
046	36	38		33	35	33	35	33	34		
047	30	28		28	24	30	27		26		
052	36	39		35	37	35	36	36	33		
059	30	34		28	30	30	31	31			
061	31	32		31	29	30	30	31	30		
066	40	40		40	40	40	42	41	42		
073	30	31		32	30	31	32	31	29		
074	34	38		37	36	39	38				

Table IV.2. Measurements (mm) of frontal horn width on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		13			10	10	10		6	6	8
002		7			5	5	6		4	5	5
005	4			4	3	4	6		5	4	2
008	3	4		6							
009	5	8		8							
016	3			3	3	2	2				
020	2	5		5	5	5					
021	4	6		7	6	7	9		7	5	6
028	3	5		5	5	4	6		4	5	3
033	3	5		3	4		5				
034	10	13		10	9	14					
038	5	8									
039	5	6		8	6	6	6		6	6	6
040	3			8	7						
041	2	5		5	5						
048	2	4		4	3	1					
055	2	7									
056	5	6		8	8	7	7		8	8	8
058	2										
065	6	7		8	8	9	10		10	10	
069	3	5		5	6	4	3		4		
070	1	3		4	4	3	3		2		
072	2	6		5							
079	2	4		5	3	3					
080	2	6		4	5	4					
084	0	5									
003	5	8		5	6	6	5	5	4		
007		6		4	8	8	5	6	5		
004	5			7	5	5	6	5	5		
006	1	2		1	0	0	0	0	1		
010		8		9	5	5	4	6	8		
023	5	7									
025	4	4		3	3	2	3	3	4		
026	1	3		5	5						
027	2	4		4	3	4					
030	5	6		5	4	4					
042	4	4		4	3	3	3	1	2		
043	4	5		6	5	5	4	5	4		
049	4	6		5	4	4					
050	1	3		5	1						
051	3	4		6	4	2	2	2			
053	6	8		7	5	5	8	3	6		
054	8	9		8	7						
057	3	4									
060		3		4	2	2	1	2			
062	2	3		3	3	2	3	2	2		
063	2	7		5	5	5	6	4	4		
068	8	10		10	8	8					
071	3			6	4	5	5	3	3		
075	3	5		4	4	5	5	4	4		

Table IV.2. Measurements (mm) of frontal horn width on CT scan.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	3	7		7	5	3	4	4	3		
012	4	5		5	5	4	5	5	5		
014	3	4		5	5	5	5	4	3		
015	3	8		7	5	4					
017	3	6		8	8	6					
018	2	5		4	3	4	4	4	3		
019	4	9		10	10						
022	4	5		7	4	5					
031	3	6									
032	3	4		5	4	5	5	4	3		
035	3	3		5	3	4	4	4	4		
036	5	8		7	8						
037	5	5		5	6	6	7	4			
044	2	4		4	5	5	3	3	2		
045	6	8		9	9	9	10	6	5		
046	8	12		9	8	7	8	7	7		
047	4	6		5	5	3	3		2		
052	5	8		6	5	5	5	4	4		
059	1	3		5	3	2	2	1			
061	4	7		5	4	4	4	3	2		
066	6	8		5	5	6	7	6	6		
073	1	3		4	4	3	2	2	1		
074	7	11		11	10	12	10				

Table IV.3. Measurements (mm) of bicaudate distance on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		19			15	14	15		12	10	13
002		12			8	12	13		8	10	12
005	6			9	7	9	10		8	8	6
008	9	12		15							
009	13	14		15							
016	8			8	9	10	8				
020	7	14		10	11	10					
021	10	13		15	14	13	15		14	13	13
028	8	11		12	12	13	11		10	10	8
033	8	10		8	9		13				
034	8	15		13	11	13					
038	7	10									
039	8	11		16	14	13	11		11	12	11
040	8			15	15						
041	10	12		13	11						
048	10	14		14	10	11					
055		14									
056	10	11		13	13	15	14		14	15	16
058	6										
065	9	13		13	14	15	16		15	15	
069	11	15		13	13	14	12		12		
070	4	9		10	9	7	7		7		
072	9	14		11							
079	10	12		14	13	12					
080	10	14		14	15	18					
084	5	11									
003	8	15		10	12	11	10	8	8		
007		15		12	13	16	13	14	11		
004	5			7	4	5	5	6	5		
006	5	7		2	6	4	3	6	4		
010		15		17	12	11	10	10	11		
023	13	16									
025	5	6		6	5	6	6	5	5		
026	7	11		15	15						
027	11	13		10	10	10					
030	9	10		7	7	8					
042	13	13		11	9	10	10	9	9		
043	6	9		12	9	9	7	8	8		
049	10	10		12	8	8					
050	14	17		20	15						
051	6	7		9	8	8	7	6			
053	8	10		9	8	8	10	7	7		
054	10	14		13	10						
057	9	10									
060	8	8		9	5	6	5	6			
062	8	7		7	6	7	8	8	7		
063	8	12		13	12	9	11	9	10		
068	10	11		14	10	10					
071	5			12	7	7	6	6	6		
075	8	12		11	10	10	10	8	9		

Table IV.3. Measurements (mm) of bicaudate distance on CT scan.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	7	14		13	9	8	9	8	7		
012	9	8		9	8	8	8	7	7		
014	6	7		7	6	8	8	7	7		
015	11	18		12	11	9					
017	11	14		16	18	13					
018	5	8		8	6	6	8	9	7		
019	8	16		14	18						
022	5	6		9	6	6					
031	8	8									
032	5	9		7	8	8	9	7	8		
035	12	13		17	14	13	10	13	12		
036	5	10		9	10						
037	7	9		12	10	11	12	10			
044	4	5		7	8	6	6	6	5		
045	12	13		15	14	16	18	11	9		
046	8	15		9	8	8	9	9	7		
047	8	11		9	8	7	6	9	5		
052	8	12		12	8	8	9	6	6		
059	8	10		13	10	9	8	7			
061	8	14		12	9	9	9	7	7		
066	10	14		14	12	13	12	12	12		
073	5	8		7	10	10	7	9	6		
074	8	13		13	13	13	12				

Table IV.4. Measurements (mm) of third ventricle on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		7			6	5	4		5	5	4
002		6			4	5	4		4	4	2
005	3			5	4	4	4		5	3	3
008	3	5		6							
009	3	4		4							
016	3	4		3	4	3	4				
020	2	4		5	2	5					
021	5	7		7	7	7	8		7	5	6
028	4	5		6	5	6	6		6	4	3
033	4	5		4	5		5				
034	2	5		6	5	5					
038	3	5									
039	2	5		6	5	4	5		4	4	3
040	4			8	6						
041	3	5		4	5						
048	4	8		6	6	5					
055	5	9									
056	3	6		8	7	7	7		8	8	8
058	1										
065	4	5		7	6	7	7		8	6	
069	3	4		7	7	7	5		5		
070	2	5		4	4	4	3		3		
072	4	5		4							
079	3	6		4	4	4					
080	4	5		6	6	6					
084	2	4									
003	4	5		5	5	4	4	3	4		
007		6		6	6	7	7	5	6		
004	3			4	3	3	3	3	3		
006	2	3		1	1	1	0	1	0		
010		8		8	5	5	3	4	4		
023	4	6									
025	2	3		4	3	3	3	3	2		
026	3	5		9	6						
027	4	5		5	4	5					
030	4	5		5	4	3					
042	5	5		5	4	4	3	3	3		
043	1	4		4	3	3	2	3	3		
049	4	6		6	4	4					
050	3	5		9	6						
051	5	5		7	4	5	5	4			
053	3	5		5	5	5	4	4	4		
054	5	5		5	4						
057	2	5									
060	2	4		5	3	2	2	2			
062	2	4		4	4	2	3	3	3		
063	3	8		8	9	7	6	4	4		
068	3	5		5	4	3					
071	2			4	3	2	2	2	2		
075	3	3		5	4	4	4	3	3		

Table IV.4. Measurements (mm) of third ventricle on CT scan. (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	3	4		6	4	3	3	3	2		
012	4	4		6	5	5	5	4	5		
014	1	2		5	3	3	3	2	2		
015	3	7		5	5	5					
017	3	5		7	6	6					
018	3	4		5	4	4	4	3	3		
019	3	5		9	11						
022	3	4		5	3	3					
031	3	4									
032	3	5		5	3	3	4	3	2		
035	5	6		8	7	6	6	5	4		
036	1	6		3	5						
037	4	4		5	5	5	5	4			
044	2	4		4	4	4	4	3	3		
045	5	7		8	6	7	8	5	4		
046	5	9		6	5	5	5	4	4		
047	5	5		5	4	3	2	1	2		
052	4	7		6	5	5	4	3	4		
059	4	6		5	5	6	4	4			
061	5	7		6	5	5	5	4	3		
066	4	5		5	4	4	4	4	4		
073	2	4		5	4	4	4	3	3		
074	2	4		5	4	5	4				

Table IV.5. Measurements (mm) of plexus chorioideus distance on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		49			50	52	44		48	49	40
002		47			50	52	50		48	52	40
005	49			46	47	45	49		46	46	48
008	42	46		49							
009	40	40		44							
016	37	41		37	45	42	42				
020	36	40		36	50	39					
021	49	49		50	54	50	54		54	52	49
028	50	54		55	55	60	61		56	51	55
033	42	45		47	45		53				
034	45	48		53	44	49					
038	41	55									
039	43	45		51	50	47	44		45	49	46
040	45			45	49						
041	48	45		51	51						
048	45	50			42						
055	52	51									
056	47			44	53	43	50		51	52	52
058	47										
065	44	48		42	48	36	36		35	38	
069	61	53		57	55	53	55		52		
070	33	33		37	37	38	40		44		
072	32	36		39							
079		51		50	48	54					
080	50	55		52	53	56					
084	40	52									
003	40	48		49	45		48	45			
007		50		45	48	51	53	50	46		
004	43			51	47	46	45		45		
006	40	44		45	47	46	46	49	46		
010		50		51	52	50	48	51	48		
023	45	46									
025	48	48		50	47		49	53	51		
026	40	49		53	45						
027	44	50		50	50	49					
030	51	52		50	55	52					
042	51	45		51	48	47	46	46	48		
043		46		48	48	48	38	43	41		
049	41	42		47	41	48					
050	55	59		61	58						
051	56	48		48	51	48	48	48			
053	44	49		45	45	52	52	44	52		
054	46	52		53							
057	40	42									
060	35	48		52	44	42	38	38			
062	50	46		47	50	48	48	48	48		
063		57		56	53	55	58	56	56		
068	47	50		48	50	52					
071	45			52	48	48	52	46	44		
075	38	46		42	44	41	39	38	45		

Table IV.5. Measurements (mm) of plexus chorioideus distance on CT scan. (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	47	52		50	50	53	53	51	50		
012	48	46		47	50	47	50	47	50		
014	44	41		49	45	47	45	46	47		
015	47	47		55	51	52					
017	40	39		40	40	42					
018	46	41		40	39	40	39	36	42		
019		50		59	56						
022		49		46	40	50					
031	50	51									
032	44	47		49	56	50	48		45		
035	50	48		50	49	50	50	50	47		
036	42	47		44	43						
037				38	42		44	45			
044	41	38		46	38	48	40	44	41		
045	46	50		54	52	48	49	45	45		
046	42	45		44	44	39	47	48	38		
047	40	49		43	44		40		36		
052	53	58		57	58	55	58	56	58		
059	53	52		51	51	53	56	54			
061	43	55		51	52	54	40	43	40		
066	47	55		51	53	58	60	60	58		
073	43	49		46	52	46	48	42	40		
074	44	47		51	48	48	52				

Table IV.6. Measurements (mm) of cella media width on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		40			43	36	40		39	42	36
002		32			28	32	33		29	26	33
005	22			25	20	16	27		18		28
008	24	31		33							
009	27	30		35							
016	23					21	25				
020	22	30		30	27	23					
021	35	35		35	35	39	42		39	35	36
028	29	30		30	32	30	30		33	29	30
033		28		24			34				
034	25	34		35	33	34					
038		25									
039	26	32			32	33	31		29	29	33
040	25			35	34						
041	34	35		26	28						
048		27		32		20					
055	33	35									
056	28	30		27	33	25	33		32	33	33
058	23										
065	37	30		32	33	35	36		36	36	
069	30	30		30	35	34	30		30		
070	25	25		21	28	18	20		20		
072	19	21		25							
079	25	30		23	30	24					
080	25	34		34	35	35					
084	17	28									
003	28	34		29	30	29	30	32	26		
007		33		30	30	35	36	35	36		
004	23			25	28	31	22	26	27		
006		32			27		21		20		
010		34		35	33	35	35	38	34		
023	28	32									
025	22	21		21			20		21		
026	17	17		30	23						
027	15	28		27	26	26					
030	34	33		32	22	30					
042	27	26		31	27	24	26		20		
043	27	26		29	28	27	23	29	28		
049	32	40		38	33	32					
050		36		41	30						
051	25	25		30	31	23					
053	34	37		35	35	31	29	33	34		
054	31	35		32							
057	25	31									
060	15	17		33	15						
062	26	28		26	20	21		27	22		
063	17	32		38	35	38	32	32	30		
068	33	33		35	33	35					
071	25			30	31	27	31	27	27		
075	21	25		21	32	28	25	20	16		

Table IV.6. Measurements (mm) of cella media width on CT scan.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	16	35		30	30	29	33	31	23		
012	28	26			29	30	32		32		
014	24	24		29	27	29	26	25	28		
015	29	36		35	29	26					
017	28			34	34	33					
018	28			32		26	28	24	32		
019		33		35	43						
022		32		30	30	30					
031	30	29									
032		23		24	21	26	24				
035	31	30		35	31	29	35	29	31		
036	28	34		31	37						
037	31	28		27	33	28		28			
044		25		29	27	26	28	27	25		
045	32	39		41	32		40	33			
046	32	35		33	28	32	33	27	30		
047	24	27		23	24		27	24	23		
052	24	33		28	28	28	36	30	28		
059	33	33		31	28	23	29				
061	34	37		32	25	31	27	28	23		
066	35	41		40	38	38	39	37	38		
073				31	27	29	26	29	20		
074	32	35		34	34	37	35				

Table IV.7. Measurements (mm) of inner tabula distance at level of caudate nucleus on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		110			107	109	110		107	120	113
002		101			99	103	104		103	104	106
005	99			102	100	103	104		104	105	106
008	107	108		109							
009	90	87		89							
016	95			98	98	104	103				
020	104	107		99	104	101					
021	105	106		106	107	105	107		105	106	106
028	113	114		116	115	115	113		116	116	114
033	107	104		101	103		108				
034	113	116		112	113	114					
038	118	118									
039	109	105		108	110	113	105		111	110	115
040	118			116	119						
041	111	105		113	110						
048	109	105		113	106	107					
055	113	115									
056	116	113		115	116	115	117		116	113	117
058	102										
065	102	105		103	103	103	105		103	107	
069	108	112		108	107	103	110		110		
070	91	97		93	98	96	97		95		
072	106	111		104							
079	111	108		115	111	115					
080	119	120		125	121	122					
084	107	113									
003	101	104		110	104	105	104	105	105		
007		116		114	115	117	112	118	114		
004	106			106	105	105	106	107	108		
006	104	103		102	103	104	101	105	104		
010		109		108	106	107	107	107	105		
023	102	102									
025	107	103		104	103	104	103	103	104		
026	108	105		104	108						
027	105	109		107	106	110					
030	104	104		103	103	105					
042	119	116		117	116	120	120	114	117		
043	98	98		100	99	103	102	98	101		
049	116	115		116	113	108					
050	118	119		119	115						
051	102	104		104	105	101	103	99			
053	117	119		115	111	108	118	108	113		
054	105	107		108	106						
057	112	112									
060	107	103		99	102	102	96	103			
062	119	110		108	110	110	114	118	111		
063	121	118		117	115	116	119	119	119		
068	114	111		117	114	116					
071	104			107	102	98	102	99	99		
075	103	111		110	102	110	109	106	110		

Table IV.7. Measurements (mm) of inner tabula distance at level of caudate nucleus on CT scan (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	109	109		110	108	109	110	113	110		
012	102	102		101	98	100	100	103	99		
014	101	100		100	101	105	102	103	105		
015	110	114		110	110	110					
017	103	101		101	103	101					
018	89	96		90	91	93	97	105	101		
019	115	114		113	114						
022	97	94		96	95	97					
031	111	112									
032	104	105		103	106	106	108	108	109		
035	112	111		111	112	110	109	111	115		
036	110	106		109	109						
037	106	108		105	106	111	110	103			
044	105	100		105	105	106	98	104	98		
045	123	123		124	124	126	128	120	120		
046	109	109		108	108	109	109	105	110		
047	99	99		100	102	101	102	104	98		
052	124	124		119	122	119	123	117	121		
059	104	104		108	101	101	105	106			
061	107	108		102	108	102	105	105	103		
066	114	123		125	123	123	123	124	124		
073	107	110		110	105	108	111	108	103		
074	115	113		107	108	112	110				

Table IV.8. Measurements (mm) of inner tabula distance at level of frontals horn on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		105			104	105	108		104	116	109
002		92			90	96	96		92	95	100
005	94			96	94	97	97		95	99	99
008	101	98		102							
009	85	86		85							
016	84			88	93	95	97				
020	103	104		102	101	101					
021	106	105		107	107	106	108		107	105	107
028	111	109		110	112	113	109		110	109	109
033	99	97		94	96		103				
034	107	108		104	105	109					
038	109	109									
039	106	101		107	108	110	103		107	108	111
040	109			110	112						
041	106	103		109	106						
048	100	99		108	101	98					
055	105	102									
056	109	110		108	112	109	112		107	109	111
058	101										
065	100	103		99	99	100	100		102	103	
069	101	102		98	99	98	104		102		
070	88	89		88	95	91	94		90		
072	101	105		102							
079	105	102		110	103	107					
080	111	120		122	120	120					
084	95	100									
003	95	99		95	97	100	96	102	100		
007		109		108	110	115	108	114	109		
004	98			96	95	96	98	102	101		
006	95	98		93	95	95	95	99	99		
010		103		103	100	100	100	103	100		
023	97	98									
025	102	102		101	102	101	102	101	102		
026	97	97		94	101						
027	96	100		99	97	100					
030	101	98		98	97	101					
042	111	108		111	109	113	113	109	112		
043	93	93		94	94	97	95	92	94		
049	110	110		109	108	106					
050	116	115		115	110						
051	93	95		98	99	93	95	91			
053	111	116		112	109	109	114	105	113		
054	101	102		103	99						
057	110	111									
060	102	94		95	95	91	91	96			
062	111	108		106	107	107	109	114	106		
063	114	110		111	109	110	113	109	112		
068	110	108		110	107	110					
071	98			102	97	95	98	98	94		
075	97	101		99	95	100	102	98	102		

Table IV.8. Measurements (mm) of inner tabula distance at level of frontal horns on CT scan (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	100	99		100	99	99	103	106	101		
012	100	99		95	97	95	100	100	100		
014	102	100		100	100	102	102	102	103		
015	105	107		105	104	102					
017	95	95		96	96	95					
018	87	93		90	90	91	93	99	99		
019	106	109		103	106						
022	88	85		86	85	88					
031	110	110									
032	101	96		100	103	104	104	103	103		
035	103	101		100	101	105	105	106	111		
036	106	106		105	106						
037	102	104		100	100	104	104	98			
044	104	100		105	104	104	99	104	98		
045	116	115		117	117	120	120	114	111		
046	105	105		105	105	104	105	98	105		
047	94	97		95	98	97	97		95		
052	118	118		115	114	116	115	109	112		
059	97	94		100	95	93	96	97			
061	100	103		97	99	99	99	101	97		
066	113	121		112	119	118	122	125	122		
073	98	103		102	98	101	99	98	95		
074	113	113		106	106	110	109				

Table IV.9. Measurements (mm) of outer tabula distance at level of frontal horns on CT scan.

pt	weeknumber										
nr	0	6	9	18	32	60	116	144	172	200	228
001		118			117	116	117		115	129	119
002		103			103	109	108		105	106	111
005	107			110	106	110	108		107	108	110
008	116	117		116							
009	100	100		100							
016	99			101	104	104	108				
020	117	119		108	115	114					
021	119	118		119	121	119	120		120	120	121
028	123	123		124	125	126	125		125	124	123
033	109	107		106	106		113				
034	120	119		119	118	120					
038	125	125									
039	120	118		121	123	124	119		123	123	127
040	130			130	132						
041	119	116		120	119						
048	112	111		120	113	113					
055	119	115									
056	130	130		130	134	130	131		127	131	127
058	115										
065	119	119		119	119	121	123		121	121	
069	111	111		110	111	110	114		113		
070	98	99		98	103	101	103		100		
072	116	116		115							
079	115	112		122	113	120					
080	132	136		139	136	141					
084	110	110									
003	110	112		109	113	113	111	117	113		
007		135		125	124	126	123	126	124		
004	109			110	110	110	111	113	112		
006	110	111		107	107	108	108	112	111		
010		115		117	113	113	112	113	111		
023	107	108									
025	118	116		116	116	115	116	116	116		
026	111	112		111	114						
027	112	113		115	115	115					
030	115	112		111	113	113					
042	124	121		125	125	125	121	119	123		
043	109	107		110	108	112	109	107	109		
049	120	123		123	123	119					
050	130	127		129	130						
051	109	110		112	114	106	111	111			
053	127	129		127	127	125	129	126	130		
054	114	117		116	117						
057	122	125									
060	107	104		107	106	102	101	107			
062	132	127		126	128	127	130	135	130		
063	126	124		124	120	121	125	123	124		
068	124	121		123	121	126					
071	110			113	108	106	111	110	106		
075	108	112		111	106	111	113	108	112		

Table IV.9. Measurements (mm) of outer tabula distance at level of frontal horns on CT scan (continued)

pt	weeknumber										
nr	0	6	9	18	32	60	116	144	172	200	228
011	111	113		116	112	113	116	116	113		
012	111	111		108	108	110	111	113	111		
014	115	113		113	112	116	115	113	116		
015	118	120		119	117	116					
017	108	106		105	107	105					
018	99	105		101	102	102	104	108	112		
019	122	125		120	123						
022	99	97		98	97	100					
031	124	124									
032	112	108		111	115	114	116	115	115		
035	116	116		116	116	119	116	118	120		
036	120	119		118	117						
037	117	119		117	115	119	124	116			
044	114	110		113	113	113	109	113	109		
045	129	129		131	129	134	130	124	123		
046	119	118		119	119	119	118	114	119		
047	104	106		106	108	108	108		104		
052	129	130		128	131	130	129	126	128		
059	108	105		113	102	104	108	114			
061	111	114		108	110	109	109	112	109		
066	125	131		126	132	129	133	136	132		
073	111	113		112	109	112	116	112	107		
074	125	123		119	119	123	125				

Table IV.10. Measurements (mm) of maximal inner tabula distance on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		120			121	122	124		123	139	126
002		119			119	120	122		122	123	123
005	115			116	116	116	117		117	118	121
008	121	121		122							
009	105	105		105							
016	114	114		116	115	121	118				
020	125	125		120	119	120					
021	125	125		126	129	126	125		128	128	125
028	129	133		132	132	131	134		134	133	131
033	120	119		118	119		124				
034	121	121		122	122	122					
038	126	128									
039	122	119		122	123	125	119		127	123	129
040	132			133	132						
041	121	122		126	126						
048	125	123		125	125	127					
055	129	125									
056	125	129		127	127	128	130		129	127	131
058	115										
065	115	115		121	121	119	116		119	119	
069	122	123		124	121	120	125		123		
070	112	114		110	117	116	116		114		
072	116	121		116							
079	124	123		128	127	131					
080	135	132		139	133	138					
084	119	121									
003	118	116		116	116	117	118	118	118		
007		134		136	135	136	136	135	135		
004	123			123	125	124	124	124	124		
006	119	120		119	119	119	119	119	119		
010		116		118	117	119	118	119	115		
023	109	107									
025	124	125		125	124	124	124	124	124		
026	125	125		125	124						
027	116	121		119	119	120					
030	120	120		120	120	119					
042	123	120		124	124	126	126	119	126		
043	114	113		116	113	117	113	112	115		
049	132	132		132	132	125					
050	130	132		131	134						
051	122	122		123	123	117	122	117			
053	128	129		129	128	126	129	123	128		
054	119	120		118	116						
057	122	127									
060	123	123		123	120	120	117	124			
062	132	127		127	127	127	124	131	128		
063	135	131		134	130	131	135	131	131		
068	126	125		130	126	130					
071	122			125	120	117	124	125	118		
075	119	125		121	119	123	122	123	125		

Table IV.10. Measurements (mm) of maximal inner tabula distance on CT scan (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	116	116		115	116	118	118	119	118		
012	118	117		118	118	120	119	119	120		
014	116	115		118	116	116	117	118	118		
015	124	124		124	125	125					
017	117	116		116	115	116					
018	112	114		113	114	113	115	118	118		
019	125	126		125	126						
022	120	119		119	120	119					
031	122	121									
032	119	117		117	119	118	119	119	120		
035	121	124		124	124	124	124	124	128		
036	120	119		118	120						
037	120	118		118	120	125	122	126			
044	118	115		116	118	119	116	121	113		
045	126	126		132	130	132	133	126	126		
046	118	118		122	122	122	119	118	121		
047	115	115		115	115	116	118	119	113		
052	140	140		136	141	139	139	135	140		
059	126	125		125	119	122	127	129			
061	123	123		119	121	121	123	124	119		
066	127	136		132	137	135	136	138	138		
073	123	130		127	122	126	128	124	123		
074	129	125		120	120	127	125				

Table IV.11. Measurements (mm) of maximal outer tabula distance on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		130			133	133	135		134	150	136
002		130			130	130	132		133	132	132
005	124			126	126	126	127		126	127	131
008	135	135		135							
009	115	115		117							
016	122	124		125	125	131	129				
020	135	135		132	131	134					
021	137	136		138	139	139	137		139	142	139
028	142	144		144	145	145	145		145	145	145
033	129	127		127	129		134				
034	135	135		135	136	136					
038	140	140									
039	136	134		136	137	138	134		141	135	143
040	148			148	149						
041	135	134		139	137						
048	135	133		136	136	140					
055	140	135									
056	140	142		143	144	140	143		144	145	145
058	128										
065	131	130		132	133	134	135		133	135	
069	134	133		134	132	129	137		134		
070	123	124		121	126	125	126		123		
072	130	132		130							
079	135	136		138	139	144					
080	147	148		152	148	155					
084	130	131									
003	128	130		130	130	130	131	131	131		
007		147		148	147	149	148	148	148		
004	132			134	135	135	135	136	135		
006	130	130		131	130	130	130	129	131		
010		128		128	129	129	130	129	124		
023	119	117									
025	136	137		136	135	136	136	136	136		
026	135	135		135	136						
027	128	131		130	130	131					
030	134	133		132	134	134					
042	134	132		134	134	138	135	130	137		
043	128	128		129	127	132	127	123	130		
049	143	144		143	143	137					
050	145	146		147	146						
051	132	133		134	136	129	134	130			
053	141	142		143	143	142	144	140	145		
054	130	132		133	132						
057	135	138									
060	132	133		132	130	130	128	135			
062	150	140		144	143	143	144	149	146		
063	148	146		146	143	142	148	147	145		
068	140	139		140	139	142					
071	134			135	131	130	136	137	130		
075	130	133		130	129	134	134	133	136		

Table IV.11. Measurements (mm) of maximal outer tabula distance on CT scan (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	126	126		126	127	129	128	130	129		
012	130	129		129	130	130	130	130	129		
014	127	126		128	126	127	127	128	128		
015	135	135		134	135	136					
017	126	126		126	126	127					
018	122	123		125	124	125	125	129	130		
019	138	138		137	140						
022	130	128		129	129	129					
031	134	134									
032	129	128		127	130	130	130	130	132		
035	133	136		135	135	134	136	136	138		
036	132	131		131	135						
037	134	132		133	135	137	137	138			
044	131	126		129	130	131	126	129	125		
045	141	140		144	142	145	145	139	139		
046	132	132		134	132	135	131	130	134		
047	125	125		125	125	126	127	128	122		
052	150	151		148	155	151	151	148	152		
059	136	135		135	130	132	136	140			
061	134	134		131	132	132	133	134	131		
066	140	145		144	148	148	148	151	150		
073	134	139		136	129	137	140	137	136		
074	140	137		133	133	140	140				

Table IV.12. Calculated Huckmannumbers (mm) on CT scan.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		62			55	55	57		52	50	53
002		46			40	44	46		39	42	43
005	35			37	38	38	40		38	34	33
008	42	46		50							
009	38	39		39							
016	31			33	29	32	22				
020	30	49		45	46	45					
021	43	52		54	51	50	53		51	50	50
028	44	48		46	46	49	49		45	46	41
033	36	39		35	39		44				
034	48	59		55	51	56					
038	40	46									
039	40	45		51	47	48	46		47	42	46
040	42			53	53						
041	42	47		44	44						
048	34	45		37	39	44					
055	34	50									
056	45	48		51	50	51	51		51	50	53
058	34										
065	42	48		49	52	52	52		52	51	
069	40	51		47	49	49	47		46		
070	29	37		38	38	33	35		36		
072	41	47		46							
079		48		44	43	45					
080	41	50		50	51	52					
084	36	43									
003	37	49		39	44	42	42	37	34		
007		52		46	48	53	51	49	46		
004	36			40	34	38	36	36	35		
006	33	35		30	35	33	31	34	33		
010		54		52	45	45	43	48	47		
023	48	51									
025	29	35		33	33	36	35	35	33		
026	33	39		49	43						
027	41	42		38	42	44					
030	42	44		39	40	42					
042	42	45		40	39	41	41	39	40		
043	36	41		43	40	41	38	35	36		
049	45	47		49	39	40					
050	54	59		60	54						
051	33	35		38	36	35	36	34			
053	45	49		48	45	44	48	43	43		
054	44	52		46	44						
057	45	46									
060		39		41	33	34	34	35			
062	41	37		39	38	39	40	40	38		
063	44	50		51	49	46	48	44	46		
068	46	49		51	43	44					
071	34			43	38	37	37	36	35		
075	38	44		42	39	42	41	38	41		

Table IV.12. Calculated Huckmannumbers (mm) on CT scan.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	40	50		50	42	42	43	40	39		
012	38	41		43	43	40	42	41	41		
014	37	39		40	42	42	42	39	38		
015	47	57		50	49	46					
017	41	46		53	51	47					
018	32	32		34	31	33	34	36	32		
019	42	51		54	61						
022	35	36		42	36	40					
031	43	43									
032	32	36		33	33	33	36	32	34		
035	43	44		52	45	42	41	43	40		
036	40	48		44	48						
037	36	37		41	42	43	44	41			
044	30	35		38	40	38	35	38	35		
045	47	50		54	51	55	59	47	43		
046	44	53		42	43	41	44	42	41		
047	38	39		37	32	37	33		31		
052	44	51		47	45	43	45	42	39		
059	38	44		41	40	39	39	38			
061	39	46		43	38	39	39	38	37		
066	50	54		54	52	53	54	53	54		
073	35	39		39	40	41	39	40	35		
074	42	51		50	49	52	50				

Table IV.13. Interpretation of Huckmannumbers according to Meese

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	2	2		2	2	2
002		2			0	0	2		0	0	0
005	0			0	0	0	0		0	0	0
008	0	2		2							
009	0	0		0							
016	0	0		0	0	0	0				
020	0	2		1	2	1					
021	0	2		2	2	2	2		2	2	2
028	0	2		2	2	2	2		1	2	0
033	2	2		1	0		0				
034	2	2		2	2	2					
038	0	2									
039	0	1		2	2	2	2		2	0	2
040	0			2	2						
041	0	2		0	0						
048	0	2		2	2	0					
055	0	2									
056	1	2		2	2	2	2		2	2	2
058	0										
065	0	2		2	2	2	2		2	2	
069	0	2		2	2	2	2		2		
070	0	0		0	0	0	0		0		
072	0	2		2							
079		2		0	0	1					
080	0	2		2	2	2					
084	0	0									
003	0	2		0	0	0	0	0	0		
007		2		2	2	2	2	2	2		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		2		2	1	1	0	2	2		
023	2	2									
025	0	0		0	0	0	0	0	0		
026	0	0		2	0						
027	0	0		0	0	0					
030	0	0		0	0	0					
042	2	2		0	0	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	1	2		2	0	0					
050	2	2		2	2						
051	0	0		0	0	0	0	0			
053	1	2		2	1	0	2	0	0		
054	0	2		2	0						
057	1	2									
060	0	0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	2		2	2	2	2	0	2		
068	2	2		2	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.13. Interpretation of Huckmannumbers according to Meese
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	2		2	0	0	0	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	2	2		2	2	2					
017	0	2		2	2	2					
018	0	0		0	0	0	0	0	0		
019	0	2		2	2						
022	0	0		0	0	0					
031	0	0									
032	0	0		0	0	0	0	0	0		
035	0	0		2	1	0	0	0	0		
036	0	2		0	2						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	2	2		2	2	2	2	2	0		
046	0	2		0	0	0	0	0	0		
047	2	2		2	0	0	0	0	0		
052	0	2		2	1	0	1	0	0		
059	1	0		0	0	0	0	0			
061	0	2		0	0	0	0	0	0		
066	2	2		2	2	2	2	2	2		
073	0	0		0	0	0	0	0	0		
074	0	2		2	2	2	2				

0 = normal 1 = borderline abnormal 2 = abnormal
blank = no data available

Table IV.14. Interpretation of ventricular width according to Meese.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	2	2		2	2	2
002		0			0	0	1		0	0	1
005	0			0	0	0	0		0	0	0
008	0	0		0							
009	0	0		0							
016	0	0		0	0	0	0				
020	0	0		0	0	0					
021	2	2		2	2	2	2		2	0	2
028	0	0		0	0	0	0		0	0	0
033	0	0		0	0		2				
034	0	2		2	0	1					
038	0	0									
039	0	0			0	0	0		0	0	0
040	0			2	0						
041	1	2		0	0						
048	0	0		0	0	0					
055	0	2									
056	0	0		2	1	1	1		2	0	2
058	0										
065	2	0		1	0	2	2		2	2	
069	0	0		1	2	2	0		0		
070	0	0		0	0	0	0		0		
072	0	0		0							
079	0	0		0	0	0					
080	0	0		0	0	0					
084	0	0									
003	0	2		0	0	0	0	0	0		
007		0		0	0	1	1	0	0		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		2		2	2	2	2	2	2		
023	0	2									
025	0	0		0	0	0	0	0	0		
026	0	0		2	0						
027	0	0		0	0	0					
030	2	1		0	0	0					
042	0	0		0	0	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	0	2		2	0	0					
050	0	0		2	0						
051	0	0		0	0	0	0	0			
053	0	2		0	0	0	0	0	0		
054	0	2		0	0						
057	0	0									
060	0	0		1	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	2		2	2	2	0	0	0		
068	0	0		1	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.14. Interpretation of ventricular width according to Meese.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	2		0	0	0	2	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	0	2		2	0	0					
017	0	0		2	2	2					
018	0	0		0	0	0	0	0	0		
019	0	0		2	2						
022	0	1		0	0	0					
031	0	0									
032	0	0		0	0	0	0	0	0		
035	0	0		2	0	0	0	0	0		
036	0	2		0	2						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	0	2		2	0	1	2	0	0		
046	0	2		0	0	0	2	0	0		
047	1	0		0	0	0	0	0	0		
052	0	1		0	0	0	0	0	0		
059	0	0		0	0	0	0	0			
061	2	2		0	0	0	0	0	0		
066	1	2		2	2	2	2	0	2		
073	0	0		0	0	0	0	0	0		
074	0	2		2	2	2	1				

Table IV.15. Interpretation of frontal horn span according to Enzmann

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	2	2		2	2	2
002		0			0	0	0		0	0	0
005	0			0	0	0	0		0	0	0
008	0	0		1							
009	0	0		0							
016	0	0		0	0	0	0				
020	0	1		1	1	1					
021	0	2		2	2	2	2		2	2	2
028	2	2		0	0	2	2		1	2	0
033	0	0		0	0		0				
034	2	2		2	2	2					
038	0	2									
039	0	0		1	0	1	1		2	0	1
040	0			2	2						
041	0	1		0	0						
048	0	0		0	0	0					
055	0	2									
056	1	2		2	2	2	2		2	1	2
058	0										
065	0	1		2	2	2	2		2	2	
069	0	2		0	2	1	1		0		
070	0	0		0	0	0	0		0		
072	0	0		1							
079		2		0	0	0					
080	0	2		2	2	2					
084	0	0									
003	0	0		0	0	0	0	0	0		
007		2		0	1	2	2	1	1		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		2		1	0	0	0	2	2		
023	1	1									
025	0	0		0	0	0	0	0	0		
026	0	0		0	0						
027	0	0		0	0	0					
030	0	0		0	0	0					
042	0	0		0	0	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	1	2		2	0	0					
050	2	2		2	2						
051	0	0		0	0	0	0	0			
053	2	2		2	2	2	2	2	2		
054	0	2		0	0						
057	2	2									
060		0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	2	2		2	2	2	2	1	2		
068	2	2		2	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.15. Interpretation of frontal horn span according to Enzmann (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	2		2	0	0	0	0	0		
012	0	0		0	1	0	0	0	0		
014	0	0		0	2	0	0	0	0		
015	2	2		2	2	2					
017	0	0		2	0	0					
018	0	0		0	0	0	0	0	0		
019	0	1		2	2						
022	0	0		0	0	0					
031	1	1									
032	0	0		0	0	0	0	0	0		
035	0	0		1	0	0	0	0	0		
036	1	2		1	2						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	1	2		2	2	2	2	2	0		
046	2	2		0	1	0	1	0	0		
047	0	0		0	0	0	0	0	0		
052	2	2		1	2	1	2	2	0		
059	0	0		0	0	0	0	0			
061	0	0		0	0	0	0	0	0		
066	2	2		2	2	2	2	2	2		
073	0	0		0	0	0	0	0	0		
074	0	2		2	2	2	2				

Table IV.16. Interpretation of frontal horn width according to Enzmann

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	2	2		1	1	2
002		2			0	0	1		0	0	0
005	0			0	0	0	1		0	0	0
008	0	0		1							
009	0	2		2							
016	0	0		0	0	0	0				
020	0	0		0	0	0					
021	0	1		2	1	2	2		2	0	1
028	0	0		0	0	0	1		0	0	0
033	0	0		0	0		0				
034	2	2		2	2	2					
038	0	2									
039	0	1		2	1	1	1		1	1	1
040	0			2	2						
041	0	0		0	0						
048	0	0		0	0	0					
055	0	2									
056	0	1		2	2	2	2		2	2	2
058	0										
065	1	2		2	2	2	2		2	2	
069	0	0		0	1	0	0		0		
070	0	0		0	0	0	0		0		
072	0	1		0							
079	0	0		0	0	0					
080	0	1		0	0	0					
084	0	0									
003	0	2		0	1	1	0	0	0		
007		1		0	2	2	0	1	0		
004	0			2	0	0	1	0	0		
006	0	0		0	0	0	0	0	0		
010		2		2	0	0	0	1	2		
023	0	2									
025	0	0		0	0	0	0	0	0		
026	0	0		0	0						
027	0	0		0	0	0					
030	0	1		0	0	0					
042	0	0		0	0	0	0	0	0		
043	0	0		1	0	0	0	0	0		
049	0	1		0	0	0					
050	0	0		0	0						
051	0	0		1	0	0	0	0			
053	1	2		2	0	0	2	0	1		
054	2	2		2	2						
057	0	0									
060		0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	2		0	0	0	1	0	0		
068	2	2		2	2	2					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.16. Interpretation of frontal horn width according to Enzmann (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	2		2	0	0	0	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	0	2		2	0	0					
017	0	1		2	2	1					
018	0	0		0	0	0	0	0	0		
019	0	2		2	2						
022	0	0		2	0	0					
031	0	1									
032	0	0		0	0	0	0	0	0		
035	0	0		0	0	0	0	0	0		
036	0	2		2	2						
037	0	0		0	1	1	2	0			
044	0	0		0	0	0	0	0	0		
045	1	2		2	2	2	2	1	0		
046	2	2		2	2	2	2	2	2		
047	0	1		0	0	0	0	0	0		
052	0	2		1	0	0	0	0	0		
059	0	0		0	0	0	0	0			
061	0	2		0	0	0	0	0	0		
066	1	2		0	0	1	2	1	1		
073	0	0		0	0	0	0	0	0		
074	2	2		2	2	2	2				

Table IV.17. Interpretation of intercaudate distance according to Enzmann

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	1	2		0	0	0
002		0			0	0	0		0	0	0
005	0			0	0	0	0		0	0	0
008	0	0		2							
009	0	1		2							
016	0	0		0	0	0	0				
020	0	1		0	0	0					
021	0	0		2	1	0	2		1	0	0
028	0	0		0	0	0	0		0	0	0
033	0	0		0	0		0				
034	0	2		0	0	0					
038	0	0									
039	0	0		2	1	0	0		0	0	0
040	0			2	2						
041	0	0		0	0						
048	0	1		1	0	0					
055		1									
056	0	0		0	0	2	1		1	2	2
058	0										
065	0	0		0	1	2	2		2	2	
069	0	2		0	0	1	0		0		
070	0	0		0	0	0	0		0		
072	0	1		0							
079	0	0		1	0	0					
080	0	1		1	2	1					
084	0	0									
003	0	2		0	0	0	0	0	0		
007		2		0	0	2	0	1	0		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		2		2	0	0	0	0	0		
023	0	2									
025	0	0		0	0	0	0	0	0		
026	0	0		2	2						
027	0			0	0	0					
030	0	0		0	0	0					
042	0	0		0	0	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	0	0		0	0	0					
050	1	2		2	2						
051	0	0		0	0	0	0	0			
053	0	0		0	0	0	0	0	0		
054	0	1		0	0						
057	0	0									
060	0	0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	0		0	0	0	0	0	0		
068	0	0		1	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.17. Interpretation of intercaudate distance according to Enzmann (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	1		0	0	0	0	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	0	2		0	0	0					
017	0	1		2	2	0					
018	0	0		0	0	0	0	0	0		
019	0	2		1	2						
022	0	0		0	0	0					
031	0	0									
032	0	0		0	0	0	0	0	0		
035	0	0		2	1	0	0	0	0		
036	0	0		0	0						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	0	0		2	2	2	2	0	0		
046	0	2		0	0	0	0	0	0		
047	0	0		0	0	0	0	0	0		
052	0	0		0	0	0	0	0	0		
059	0	0		0	0	0	0	0			
061	0	1		0	0	0	0	0	0		
066	0	1		1	0	0	0	0	0		
073	0	0		0	0	0	0	0	0		
074	0	0		0	0	0	0				

Table IV.18. Interpretation of ventricular width according to Enzmann

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	2	2		1	1	2
002		0			0	0	0		0	0	0
005	0			0	0	0	0		0	0	0
008	0	0		1							
009	0	2		2							
016	0	0		0	0	0	0				
020	0	1		0	0	0					
021	0	1		2	1	2	2		2	0	1
028	0	0		0	0	0	1		0	0	0
033	0	0		0	0		0				
034	2	2		2	2	2					
038	0	2									
039	0	0		2	1	1	1		1	0	1
040	0			2	2						
041	0	0		0	0						
048	0	0		0	0	0					
055	0	2									
056	0	1		2	2	2	2		2	2	2
058	0										
065	0	1		2	2	2	2		2	2	
069	0	2		0	1	1	0		0		
070	0	0		0	0	0	0		0		
072	0	1		0							
079	0	0		0	0	0					
080	0	2		1	2	2					
084	0	0									
003	0	2		0	0	0	0	0	0		
007		2		0	1	2	0	1	0		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		2		2	0	0	0	1	2		
023	0	2									
025	0	0		0	0	0	0	0	0		
026	0	0		0	0						
027	0	0		0	0	0					
030	0	0		0	0	0					
042	0	0		0	0	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	0	1		0	0	0					
050	1	2		2	2						
051	0	0		0	0	0	0	0			
053	1	2		2	0	0	2	0	1		
054	0	2		0	0						
057	0	0									
060	0	0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	2		0	0	0	1	0	0		
068	2	2		2	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.18. Interpretation of ventricular width according to Enzmann
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	2		2	0	0	0	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	0	2		2	0	0					
017	0	1		2	2	0					
018	0	0		0	0	0	0	0	0		
019	0	2		2	2						
022	0	0		0	0	0					
031	0	1									
032	0	0		0	0	0	0	0	0		
035	0	0		2	0	0	0	0	0		
036	0	2		1	2						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	1	2		2	2	2	2	1	0		
046	2	2		0	1	0	1	0	0		
047	0	0		0	0	0	0	0	0		
052	0	2		1	0	0	0	0	0		
059	0	0		0	0	0	0	0			
061	0	1		0	0	0	0	0	0		
066	1	2		1	0	1	2	1	1		
073	0	0		0	0	0	0	0	0		
074	0	2		2	2	2	2				

Table IV.19. Interpretation of measurements of sulci

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		2			2	2	2		2	2	2
002		2			1	0	0		0	0	0
005	2			2	2	2	2		2	2	0
008	0	2		2							
009	0	2		2							
016	1	1			1	0	0				
020	0	1		1	0	1					
021	0	2		2	2	2	2		2	1	0
028	0	2		2	2	2	2		2	1	0
033	0	2		2	0		2				
034	0	2		2	2	1					
038	1	2									
039	0	1		2	2	2	2		2	1	0
040	0			2	2						
041	0	1		0	0						
048	0	1		0	0	0					
055	0	2									
056	0	2		2	2	2	2		2	1	2
058	0										
065	0	1		2	2	2	2		2	2	
069	0	2		2	2	0	0		0		
070	0	2		2	2	2	0		0		
072	0	2		2							
079	0	2		1	1	2					
080	0	2		2	2	2					
084	0	2									
003	0	2		0	0	0	0	0	0		
007		1		0	1	0	1	1	1		
004	0			2	2	2	1	0	0		
006	0	0		0	0	0	0	0	0		
010		2		2	2	2	2	2	2		
023	1	2									
025	0	0		0	0	0	0	0	0		
026	0	2		2	2						
027	0	2		2	2	2					
030	2	2		2	2	2					
042	0	2		1	1	0	0	0	0		
043	0	2		2	2	2	1	0	0		
049	2	2		2	0	0					
050	0	2		2	2						
051	1	2		2	2	1	1	0			
053	1	2		2	2	1	0	0	0		
054	0	2		0							
057	0	1									
060	0	1		2	1	0	0	0			
062	0	1		2	2	2	2	2	2		
063	0	1		2	2	2	2	1	0		
068	0	2		2	2	2					
071	0			2	2	2	2	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.19. Interpretation of measurements of sulci
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	2		2	2	2	2	0	2		
012	0	2		2	2	2	2	1	2		
014	0	2		2	2	2	2	0	1		
015	0	2		2	2	2					
017	0	2		2	2	2					
018	2	2		2	2	2	2	2	0		
019	0	2		2	2						
022	0	2		2	2	2					
031	1	2									
032	0	0		2	2	2	2	0	0		
035	0	2		2	2	2	2	2	0		
036	0	2		1	0						
037	0	0		2	2	2	2	2			
044	0	2		2	2	2	2	0	0		
045	0	2		2	2	1	2	0	0		
046	2	2		1	1	1	1	0	1		
047	0	0		0	0	0	0	0	0		
052	0	2		2	0	0	0	0	0		
059	0	2		2	0	0	0	0			
061	0	2		2	0	1	0	0	0		
066	0	2		2	2	1	1	0	1		
073	0	2		2	2	2	2	2	0		
074	0	2		2	2	2	2				

Table IV.20. Number of hypodense areas on CT scan

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		0			2	2	2		1	0	1
002		1			1	0	1		0	6	4
005	0			0	0	0	0		0	0	0
008	0	0		0							
009	0	0		0							
016	0	0		0	0	0	0				
020	0	0		0	0	0					
021	0	0		0	0	0	0		0	0	0
028	0	0		0	0	1	1		3	6	6
033	0	0		0	0		0				
034	0	0		0	2	2					
038	0	0									
039	0	0		0	0	0	0		0	0	0
040	0			0	0						
041	0	0		0	0						
048	0	0		8	8	8					
055	0	0									
056	0	0		0	0	0	0		0	0	0
058	0										
065	0	0		0	0	0	0		0	0	
069	0	0		0	0	0	2		2		
070	0	0		0	6	0	0		4		
072	0	0		0							
079	0	0		0	6	6					
080	0	0		0	0	0					
084	0	0									
003	0	0		0	0	0	0	0	0		
007		0		6	6	4	0	0	0		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		0		1	4	4	2	0	0		
023	0	0									
025	0	0		0	0	0	0	0	0		
026	0	0		0	0						
027	0	0		0	0	0					
030	0	0		0	0	0					
042	0	0		4	2	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	0	0		0	6	6					
050	0	0		0	0						
051	0	0		0	0	0	0	0			
053	0	0		0	0	0	0	0	0		
054	0	0		0	0						
057	0	0									
060	0	0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	0		0	0	0	0	0	0		
068	0	0		0	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.20. Number of hypodense areas on CT scan
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	0		0	0	0	0	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	0	0		0	0	0					
017	0	0		0	0	0					
018	0	0		0	0	0	0	0	0		
019	0	1		3	3						
022	0	0		0	0	0					
031	0	0									
032	0	0		0	0	0	0	0	0		
035	0	0		0	4	0	0	0	0		
036	0	0		0	0						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	0	0		6	6	0	0	0	0		
046	0	0		4	4	2	2	2	0		
047	0	0		0	0	0	0	2	4		
052	0	0		0	0	0	0	0	0		
059	0	0		0	0	0	0	0			
061	0	0		0	0	0	0	0	0		
066	0	0		0	0	0	0	2	2		
073	0	0		0	0	0	0	0	0		
074	0	0		0	0	0	0				

Table IV.21. Number of areas with calcifications on CT scan

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
001		0			0	0	6		1	1	2
002		0			0	0	0		0	0	0
005	0			0	0	0	0		0	0	0
008	0	0		0							
009	0	0		0							
016	0	0		0	0	0	0				
020	0	0		0	0	0					
021	0	0		0	0	0	0		0	0	0
028	0	0		0	0	0	0		0	0	0
033	0	0		0	0		5				
034	0	0		0	0	0					
038	0	0									
039	0	0		0	0	0	0		0	0	0
040	0			0	0						
041	0	0		0	0						
048	0	0		0	1	3					
055	0	0									
056	0	0		0	0	0	0		0	0	0
058	0										
065	0	0		0	0	0	0		0	0	
069	0	0		0	0	0	0		0		
070	0	0		0	0	0	0		0		
072	0	0		0							
079	0	0		0	0	0					
080	0	0		0	0	0					
084	0	0									
003	0	0		0	0	0	0	0	0		
007		0		0	0	0	0	0	0		
004	0			0	0	0	0	0	0		
006	0	0		0	0	0	0	0	0		
010		0		0	0	0	6	6	6		
023	0	0									
025	0	0		0	0	0	0	0	0		
026	0	0		0	0						
027	0	0		0	0	0					
030	0	0		0	0	0					
042	0	0		0	0	0	0	0	0		
043	0	0		0	0	0	0	0	0		
049	0	0		0	0	0					
050	0	0		0	0						
051	0	0		0	0	0	0	0			
053	0	0		0	0	0	0	0	0		
054	0	0		0	0						
057	0	0									
060	0	0		0	0	0	0	0			
062	0	0		0	0	0	0	0	0		
063	0	0		0	0	0	0	0	0		
068	0	0		0	0	0					
071	0			0	0	0	0	0	0		
075	0	0		0	0	0	0	0	0		

Table IV.21. Number of areas with calcifications on CT scan
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
011	0	0		0	0	0	0	0	0		
012	0	0		0	0	0	0	0	0		
014	0	0		0	0	0	0	0	0		
015	0	0		0	0	0					
017	0	0		0	0	0					
018	0	0		0	0	0	0	0	0		
019	0	0		0	0						
022	0	0		0	0	0					
031	0	0									
032	0	0		0	0	0	0	0	0		
035	0	0		0	0	0	0	0	0		
036	0	0		0	0						
037	0	0		0	0	0	0	0			
044	0	0		0	0	0	0	0	0		
045	0	0		0	0	0	0	0	0		
046	0	0		0	0	0	0	0	0		
047	0	0		0	0	0	0	0	0		
052	0	0		0	0	0	0	0	0		
059	0	0		0	0	0	0	0			
061	0	0		0	0	0	0	0	0		
066	0	0		0	0	0	0	0	0		
073	0	0		0	0	0	0	0	0		
074	0	0		0	0	0	0				

Table IV.22. Changes in measures at different times compared with former evaluation (Huckmannumber). Percentages in all children with HR-ALL

week	n	<	=	>	range (mm) from	to	mean delta
0 - 6	19			100	+ 1	+19	+ 7.6
6 - 18	17	53	12	35	- 8	+ 6	- 1.0
18 - 32	17	35	24	41	- 4	+ 4	- 0.2
32 - 60	16	19	25	56	- 5	+ 5	+ 1.1
60 - 116	11	27	27	45	-10	+ 3	- 0.3
116 - 172	10	60	20	20	- 7	+ 1	- 1.9
172 - 200	8	75		26	- 5	+ 3	- 1.3
200 - 228	7	29	14	57	- 5	+ 4	+ 0.7
172 - 228	7	57		43	- 5	+ 4	- 0.6

Table IV.23. Changes in measures at different times compared with former evaluation (Huckmannumber). Percentages in children with HR-ALL aged 0 - 2 years.

week	n	<	=	>	range (mm) from	to	mean delta
0 - 6	2			100	+ 3	+11	+ 7.0
6 - 18	2	100			- 8	- 4	- 6.0
18 - 32	3	33		67	- 4	+ 4	+ 0.7
32 - 60	2			100	+ 3	+ 5	+ 4.0
60 - 116	1	100			-10		-10.0

Table IV.24. Changes in measures at different times compared with former evaluation (Huckmannumber). Percentages in children with HR-ALL aged 2 years and over.

week	n	<	=	>	range (mm) from	to	mean delta
0 - 6	17			100	+ 1	+19	+ 7.6
6 - 18	15	47	13	40	- 4	+ 6	- 0.3
18 - 32	14	36	29	36	- 4	+ 3	- 0.4
32 - 60	14	21	29	50	- 5	+ 5	+ 0.7
60 - 116	10	20	30	50	- 2	+ 3	+ 0.7
116 - 172	10	60	20	20	- 7	+ 1	- 1.9
172 - 200	8	75		26	- 5	+ 3	- 1.3
200 - 228	7	29	14	57	- 5	+ 4	+ 0.7
172 - 228	7	57		43	- 5	+ 4	- 0.6

Table IV.25. Changes in measures at different times compared with former evaluation (Huckmannumber). Percentages in all children with NHR-ALL

week	n	<	=	>	range (mm) from	to	mean delta
0 - 6	42	2	5	93	- 4	+12	+ 4.3
6 - 18	42	48	7	45	-11	+10	- 0.5
18 - 32	44	66	7	27	-10	+ 7	- 1.9
32 - 60	39	36	10	54	- 4	+ 5	+ 0.5
60 - 116	32	38	22	41	- 4	+ 4	+ 0.0
116 - 144	30	67	10	23	-12	+ 5	- 1.5
144 - 172	26	69	8	23	- 5	+ 3	- 1.2
116 - 172	27	81	11	8	-16	+ 4	- 2.6

Table IV.26. Changes in measures at different times compared with former evaluation (Huckmannumber). Percentages in children with NHR-ALL aged 0 - 2 years.

week	n	<	=	>	range (mm) from	to	mean delta
0 - 6	4			100	+ 1	+ 6	+ 3.3
6 - 18	3	100			- 5	- 2	- 3.3
18 - 32	3	100			- 5	- 1	- 2.3
32 - 60	3	33		67	- 1	+ 5	+ 2.0
60 - 116	3	33	67		- 4	0	- 1.3
116 - 144	2	100			- 2	- 1	- 1.5
144 - 172	1			100		+ 1	+ 1.0
116 - 172	2	100			- 2	- 1	- 1.5

Table IV.27. Changes in measures at different times compared with former evaluation (Huckmannumber). Percentages in children with NHR-ALL aged 2 years and over.

week	n	<	=	>	range (mm) from	to	mean delta
0 - 6	38	3	5	92	- 4	+12	+ 4.5
6 - 18	39	44	8	49	-11	+10	- 0.3
18 - 32	41	63	7	29	-10	+ 7	- 1.9
32 - 60	36	36	11	53	- 4	+ 5	+ 0.3
60 - 116	29	38	17	45	- 3	+ 4	+ 0.2
116 - 144	28	64	11	25	-12	+ 5	- 1.5
144 - 172	25	72	8	20	- 5	+ 3	- 1.2
116 - 172	25	80	12	8	-16	+ 4	- 2.7

Table IV.28. Changes in measures at different times compared with those at diagnosis (Huckmannumber). Percentages in all children with HR-ALL

week	n	<	=	>	range (mm) from	to	mean cumdelta
0 - 6	19			100	+ 1	+19	+ 7.6
0 - 18	19	5		95	- 1	+15	+ 6.2
0 - 32	16	6		94	- 2	+16	+ 6.3
0 - 60	13			100	+ 1	+15	+ 7.5
0 - 116	10	10		90	- 9	+10	+ 5.4
0 - 172	8			100	+ 1	+10	+ 6.0
0 - 200	6	17		83	- 1	+ 9	+ 4.0
0 - 228	5	40		60	- 3	+ 8	+ 3.2

Table IV.29. Changes in measures at different times compared with those at diagnosis (Huckmannumber). Percentages in children with HR-ALL aged 0 - 2 years.

week	n	<	=	>	range (mm) from	to	mean cumdelta
0 - 6	2			100	+ 3	+11	+ 7.0
0 - 18	3	33		67	- 1	+ 3	+ 1.3
0 - 32	3	33		67	- 2	+ 5	+ 2.0
0 - 60	2			100	+ 1	+10	+ 5.5
0 - 116	2	50		50	- 9	+ 8	- 0.5

Table IV.30. Changes in measures at different times compared with those at diagnosis (Huckmannumber). Percentages in children with HR-ALL aged 2 years and over.

week	n	<	=	>	range (mm) from	to	mean cumdelta
0 - 6	17			100	+ 1	+19	+ 7.6
0 - 18	16			100	+ 1	+15	+ 7.0
0 - 32	13			100	+ 2	+16	+ 7.3
0 - 60	11			100	+ 3	+15	+ 7.8
0 - 116	8			100	+ 5	+10	+ 6.9
0 - 172	8			100	+ 1	+10	+ 6.0
0 - 200	6	17		83	- 1	+ 9	+ 4.0
0 - 228	5	40		60	- 3	+ 8	+ 3.2

Table IV.31. Changes in measures at different times compared with those at diagnosis (Huckmannumber). Percentages in all children with NHR-ALL

week	n	<	=	>	range (mm) from	to	mean cumdelta
0 - 6	42	2	5	93	- 4	+12	+ 4.3
0 - 18	41	17		83	- 3	+16	+ 4.3
0 - 32	41	24	7	69	- 6	+19	+ 2.6
0 - 60	36	28	8	64	- 5	+10	+ 2.2
0 - 116	29	17	10	72	- 5	+12	+ 2.7
0 - 144	27	26	33	41	- 3	+ 8	+ 1.0
0 - 172	25	48	16	36	- 7	+ 5	- 0.4

Table IV.32. Changes in measures at different times compared with those at diagnosis (Huckmannumber). Percentages in children with NHR-ALL aged 0 - 2 years.

week	n	<	=	>	range (mm) from	to	mean cumdelta
0 - 6	4			100	+ 1	+ 6	+ 3.3
0 - 18	3	67		33	- 2	+ 3	+ 0.0
0 - 32	3	67		33	- 6	+ 2	- 2.3
0 - 60	3	67		33	- 1	+ 1	- 0.3
0 - 116	3	67		33	- 5	+ 1	- 1.7
0 - 144	2	50	50		- 3	0	- 1.5
0 - 172	2	100			- 7	- 2	- 4.5

Table IV.33. Changes in measures at different times compared with those at diagnosis (Huckmannumber). Percentages in children with NHR-ALL aged 2 years and over.

week	n	<	=	>	range (mm) from	to	mean cumdelta
0 - 6	38	3	5	92	- 4	+12	+ 4.5
0 - 18	38	13		87	- 3	+16	+ 4.6
0 - 32	38	21	8	71	- 6	+19	+ 2.9
0 - 60	33	24	9	67	- 5	+10	+ 2.5
0 - 116	26	12	12	76	- 2	+12	+ 3.2
0 - 144	25	24	32	44	- 2	+ 8	+ 1.2
0 - 172	23	43	17	39	- 5	+ 5	- 0.1

Table IV.34. Codes of Huckmannumbers at different times
Children with HR-ALL age 0 - 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	3	2	67			1	33
6	3	1	33			2	67
18	3	1	33	1	33	1	33
32	3	2	67			1	33
60	2	2	100				
116	2	2	100				

Table IV.35. Codes of Huckmannumbers at different times
Children with HR-ALL age >= 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	20	18	90	1	5	1	5
6	20	3	15	1	5	15	80
18	17	5	29	1	6	11	65
32	16	5	31			11	69
60	14	3	21	2	14	9	64
116	10	2	20			8	80
144							
172	10	3	30	1	10	6	60
200	8	3	37			5	63
228	7	3	43			4	57

Table IV.36. Codes of Huckmannumbers at different times
Children with NHR-ALL age 0 - 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	4			1	25	3	75
6	4	1	25			3	75
18	3	2	67			1	33
32	3	3	100				
60	3	3	100				
116	3	3	100				
144	3	3	100				
172	2	2	100				

Table IV.37. Codes of Huckmannumbers at different times
Children with NHR-ALL age >= 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	41	33	80	3	5	5	12
6	41	20	49			21	51
18	41	23	56			18	44
32	41	27	66	4	10	10	24
60	36	28	78	1	3	7	19
116	29	22	76	1	3	6	21
144	28	24	86			4	14
172	25	21	84			4	16

Table IV.38. Differences in codes at different times
compared with codes at former evaluation (Huckmannumber).
Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	20			30	10	60
6 - 18	18	11	11	72	6	
18 - 32	17		6	88	6	
32 - 60	16	6	6	81	6	
60 - 116	11			91		9
116 - 172	10	10	10	80		
172 - 200	8	13		75	13	
200 - 228	7	14		71		14
172 - 228	7		14	86		

Table IV.39. Differences in codes at different times
compared with codes at former evaluation (Huckmannumber).
Percentages in children with HR-ALL age < 2 years

week	n	-2	-1	=	+1	+2
0 - 6	3			67		33
6 - 18	3		33	67		
18 - 32	3		33	67		
32 - 60	2	50		50		
60 - 116	1			100		

Table IV.40. Differences in codes at different times compared with codes at former evaluation (Huckmannumber). Percentages in children with HR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	17			24	12	65
6 - 18	15	13	7	73	7	
18 - 32	14			93	7	
32 - 60	14		7	86	7	
60 - 116	10			90		10
116 - 172	10	10	10	80		
172 - 200	8	13		75	13	
200 - 228	7	14		71		14
172 - 228	7		14	86		

Table IV.41. Differences in codes at different times compared with codes at former evaluation (Huckmannumber). Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43		2	65	7	26
6 - 18	42	12		83		5
18 - 32	44	14	9	75		2
32 - 60	39		8	92		
60 - 116	32		3	91	3	3
116 - 144	31	6	3	87		3
144 - 172	27	4		93		4
116 - 172	27	7	4	85		4

Table IV.42. Differences in codes at different times compared with codes at former evaluation (Huckmannumber). Percentages in children with NHR-ALL age < 2 years

week	n	-2	-1	=	+1	+2
0 - 6	4		25	75		
6 - 18	3	33		67		
18 - 32	3	33		67		
32 - 60	3			100		
60 - 116	3			100		
116 - 144	3			100		
144 - 172	2			100		
116 - 172	2			100		

Table IV.43. Differences in codes at different times compared with codes at former evaluation (Huckmannumber). Percentages in children with NHR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	39			64	8	28
6 - 18	39	10		85		5
18 - 32	41	12	10	76		2
32 - 60	36		8	92		
60 - 116	29		3	90	3	3
116 - 144	28	7	4	86		4
144 - 172	25	4		92		4
116 - 172	25	8	4	84		4

Table IV.44. Differences in codes at different times compared with codes at diagnosis (Huckman acc. to Meese). Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	20			30	10	60
0 - 18	19		5	32	11	53
0 - 32	16		6	31	6	56
0 - 60	13			38	15	46
0 - 116	10	10		30	10	50
0 - 172	8			25	25	50
0 - 200	6			33	17	50
0 - 228	5			40	20	40

Table IV.45. Differences in codes at different times compared with codes at diagnosis (Huckman acc. to Meese). Percentages in children with HR-ALL age 0 - 2 years

week	n	-2	-1	=	+1	+2
0 - 6	3			67		33
0 - 18	3		33	33		33
0 - 32	3	33		33		33
0 - 60	2			100		
0 - 116	2	50		50		

Table IV.46. Differences in codes at different times compared with codes at diagnosis (Huckman acc. to Meese). Percentages in children with HR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	17			24	12	65
0 - 18	16			31	13	56
0 - 32	13			31	8	62
0 - 60	11			27	18	55
0 - 116	8			25	13	63
0 - 172	8			25	25	50
0 - 200	6			33	17	50
0 - 228	5			40	20	40

Table IV.47. Differences in codes at different times compared with codes at diagnosis (Huckman acc. to Meese). Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43		2	65	7	26
0 - 18	42	2	2	69	5	21
0 - 32	42	7	5	71	5	12
0 - 60	37	8	8	76		8
0 - 116	30	7	3	77	7	7
0 - 144	29	7	7	86		
0 - 172	25	12	4	80		4

Table IV.48. Differences in codes at different times compared with codes at diagnosis (Huckman acc. to Meese). Percentages in children with NHR-ALL age 0 - 2 years

week	n	-2	-1	=	+1	+2
0 - 6	4		25	75		
0 - 18	3	33	33	33		
0 - 32	3	67	33			
0 - 60	3	67	33			
0 - 116	3	67	33			
0 - 144	3	67	33			
0 - 172	2	100				

Table IV.49. Differences in codes at different times compared with codes at diagnosis (Huckman acc. to Meese). Percentages in children with NHR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	39			64	8	28
0 - 18	39			72	5	23
0 - 32	39	3	3	77	5	13
0 - 60	34	3	6	82		9
0 - 116	27			85	7	7
0 - 144	26		4	96		
0 - 172	23	4	4	87		4

Table IV.50. Codes according to Meese at different times Children with HR-ALL age 0 - 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	3	3	100				
6	3	3	100				
18	3	3	100				
32	3	3	100				
60	2	2	100				
116	2	1	50			1	50

Table IV.51. Codes according to Meese at different times Children with HR-ALL age >= 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	21	18	86	1	5	2	9
6	21	16	76			5	24
18	16	10	63	2	13	4	25
32	16	12	75	1	6	3	19
60	14	8	57	2	14	4	29
116	10	5	50	2	20	3	30
144							
172	10	6	60			4	40
200	8	6	75			2	25
228	7	3	43	1	14	3	43

Table IV.52. Codes according to Meese at different times
Children with NHR-ALL age 0 - 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	4	3	75	1	25		
6	4	3	75			1	25
18	3	3	100				
32	3	3	100				
60	3	3	100				
116	3	3	100				
144	3	3	100				
172	2	2	100				

Table IV.53. Codes according to Meese at different times
Children with NHR-ALL age >= 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	41	38	93	1	2	2	5
6	41	24	59	3	7	14	34
18	41	27	66	2	5	12	29
32	41	34	83			7	17
60	36	29	81	2	6	5	14
116	29	22	76	2	7	5	17
144	28	27	96			1	4
172	25	23	92			2	8

Table IV.54. Differences in codes at different times
compared with codes at former evaluation (Meese).
Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	21	5		81	5	10
6 - 18	17	6		76	12	6
18 - 32	16	13	13	69	6	
32 - 60	16			88	6	6
60 - 116	11	9		82	9	
116 - 172	10		10	80	10	
172 - 200	8	25		75		
200 - 228	7			57	14	29
172 - 228	7			86	14	

Table IV.55. Differences in codes at different times
compared with codes at former evaluation (Meese).
Percentages in children with HR-ALL age < 2 years

week	n	-2	-1	=	+1	+2
0 - 6	3			100		
6 - 18	3			100		
18 - 32	3			100		
32 - 60	2			100		
60 - 116	1			100		

Table IV.56. Differences in codes at different times
compared with codes at former evaluation (Meese).
Percentages in children with HR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	18	6		78	6	11
6 - 18	14	7		71	14	7
18 - 32	13	15	15	62	8	
32 - 60	14			86	7	7
60 - 116	10	10		80	10	
116 - 172	10		10	80	10	
172 - 200	8	25		75		
200 - 228	7			57	14	29
172 - 228	7			86	14	

Table IV.57. Differences in codes at different times
compared with codes at former evaluation (Meese).
Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43		5	60	7	28
6 - 18	42	17	7	60	5	12
18 - 32	44	14	5	80		2
32 - 60	39			95	5	
60 - 116	32	3	3	84	3	6
116 - 144	31	13	3	84		
144 - 172	27			96		4
116 - 172	27	11	4	85		

Table IV.58. Differences in codes at different times compared with codes at former evaluation (Meese).
Percentages in children with NHR-ALL age < 2 years

week	n	-2	-1	=	+1	+2
0 - 6	4		25	50		25
6 - 18	3			100		
18 - 32	3			100		
32 - 60	3			100		
60 - 116	3			100		
116 - 144	3			100		
144 - 172	2			100		
116 - 172	2			100		

Table IV.59. Differences in codes at different times compared with codes at former evaluation (Meese).
Percentages in children with NHR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	39		3	62	8	28
6 - 18	39	18	8	56	5	13
18 - 32	41	15	5	78		2
32 - 60	36			94	6	
60 - 116	29	3	3	83	3	7
116 - 144	28	14	4	82		
144 - 172	25			96		4
116 - 172	25	12	4	84		

Table IV.60. Differences in codes at different times compared with codes at diagnosis (Meese).
Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	21	5		81	5	10
0 - 18	19		11	68	5	16
0 - 32	17	6	6	76	6	6
0 - 60	14			79	14	7
0 - 116	10			80	10	10
0 - 172	8			88		13
0 - 200	6	17		83		
0 - 228	5			80	20	

Table IV.61. Differences in codes at different times compared with codes at diagnosis (Meese).
Percentages in children with HR-ALL age 0 - 2 years

week	n	-2	-1	=	+1	+2
0 - 6	3			100		
0 - 18	3			100		
0 - 32	3			100		
0 - 60	2			100		
0 - 116	2			50		50

Table IV.62. Differences in codes at different times compared with codes at diagnosis (Meese).
Percentages in children with HR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	18	6		78	6	11
0 - 18	16		13	63	6	19
0 - 32	14	7	7	71	7	7
0 - 60	12			75	17	8
0 - 116	8			88	13	
0 - 172	8			88		13
0 - 200	6	17		83		
0 - 228	5			80		20

Table IV.63. Differences in codes at different times compared with codes at diagnosis (Meese).
Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43		5	60	7	28
0 - 18	42	5	2	62	7	24
0 - 32	42	5	2	79	2	12
0 - 60	37	5	3	78	5	8
0 - 116	30	3	3	77	7	10
0 - 144	29	3	7	90		
0 - 172	25	4	4	88	4	

Table IV.64. Differences in codes at different times compared with codes at diagnosis (Meese).
Percentages in children with NHR-ALL age 0 - 2 years

week	n	-2	-1	=	+1	+2
0 - 6	4		25	50		25
0 - 18	3		33	67		
0 - 32	3		33	67		
0 - 60	3		33	67		
0 - 116	3		33	67		
0 - 144	3		33	67		
0 - 172	2		50	50		

Table IV.65. Differences in codes at different times compared with codes at diagnosis (Meese).
Percentages in children with NHR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	39		3	62	8	28
0 - 18	39	5		62	8	26
0 - 32	39	5		79	3	13
0 - 60	34	6		79	6	9
0 - 116	27	4		78	7	11
0 - 144	26	4	4	92		
0 - 172	23	4		91	4	

Table IV.66. Differences in codes at different times compared with codes at former evaluation (Enzmann).
Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	21			52	24	24
6 - 18	18	6	17	50	22	6
18 - 32	17		12	76	12	
32 - 60	16			94	6	
60 - 116	11		9	82	9	
116 - 172	10		20	80		
172 - 200	8	12	13	75		
200 - 228	7			57	43	
172 - 228	7		14	71	14	

Table IV.67. Differences in codes at different times compared with codes at former evaluation (Enzmann).
Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43			58	19	23
6 - 18	42	12	12	71	2	2
18 - 32	44	14	5	75	7	
32 - 60	39	3	3	90	5	
60 - 116	32	3		84	9	3
116 - 144	31	3	13	77	6	
144 - 172	27		7	85	7	
116 - 172	27	4	15	78		4

Table IV.68. Differences in codes at different times compared with codes at diagnosis (Enzmann).
Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	21			52	24	24
0 - 18	20			60	10	30
0 - 32	17			59	18	24
0 - 60	14			57	14	29
0 - 116	10			50	20	30
0 - 144						
0 - 172	8			50	13	38
0 - 200	6			67		33
0 - 228	5			40	40	20

Table IV.69. Differences in codes at different times compared with codes at diagnosis (Enzmann).
Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43			58	19	23
0 - 18	42	2		71	12	14
0 - 32	42	2	7	76	5	10
0 - 60	37	5	3	86	3	3
0 - 116	30		3	80	13	3
0 - 144	29	3	3	93		
0 - 172	25	4	4	92		

Table IV.70. Comparison of the coded evaluations of CT scans
Huckman compared with Meese.
Percentages of codes for children with HR-ALL

		Concordant			Huckm < Meese			Huckm > Meese		
week	n	00	11	22	01	02	12	10	20	21
0	23	74			4	9		4	9	
6	23	17		22				4	57	
18	19	32		21				11	26	11
32	19	37		16					42	5
60	16	31		25				13	19	13
116	12	25		25		8			25	17
144										
172	10	30		40				10	20	
200	8	38		25					38	
228	7	29		43	14				14	

Table IV.71. Comparison of the coded evaluations of CT scans
Huckman compared with Meese.
Percentages of codes for children with NHR-ALL

		Concordant			Huckm < Meese			Huckm > Meese		
week	n	00	11	22	01	02	12	10	20	21
0	45	69				4		9	13	4
6	45	42		33	4				18	2
18	44	55		27	2				14	2
32	44	68		14			2	7	9	
60	39	80		10			3		3	5
116	32	69		6		9		3	6	6
144	31	87		3					10	
172	27	85		7					7	

Table IV.72. Comparison of the coded evaluations of CT scans
Huckman compared with Enzmann.
Percentages of codes for children with HR-ALL

		Concordant			Huckm < Enzm			Huckm > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	23	87		4				4	4	
6	23	13		26		4		4	30	22
18	20	25		30		5		10	20	10
32	19	37		32					16	16
60	16	31		38				13	6	13
116	12	33		33					17	17
144										
172	10	30		30				10	10	20
200	8	38		25					25	13
228	7	43		29						29

Table IV.73. Comparison of the coded evaluations of CT scans
Huckman compared with Enzmann.
Percentages of codes for children with NHR-ALL

		Concordant			Huckm < Enzm			Huckm > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	45	71	2	2		2		7	9	7
6	45	44		40	2				7	7
18	44	55		25	2				14	5
32	44	66		14	2			9	7	2
60	39	80		8				3	8	3
116	32	75		13	3			3	3	3
144	31	87								13
172	27	82		4	4				7	4

Table IV.74. Comparison of the coded evaluations of CT scans
Meese compared with Enzmann.
Percentages of codes for children with HR-ALL

		Concordant			Meese < Enzm			Meese > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	24	83				4		4	8	
6	23	44		13	17	17			4	4
18	19	53		21	11	5	5	5		
32	19	53		5	5	21	5			11
60	16	50		19	6	6	13			6
116	12	33		25	17		8	8	8	
144										
172	10	50		30	10					10
200	8	63		13		13				13
228	7	29		29	14			14		14

Table IV.75. Comparison of the coded evaluations of CT scans
Meese compared with Enzmann.
Percentages of codes for children with NHR-ALL

		Concordant			Meese < Enzm			Meese > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	45	80	2		7	4		2	4	
6	45	47		29	4	9	2	4		4
18	44	59		18	5	5	2	2	7	2
32	44	75		9	5	5			7	
60	39	82		3			5		8	3
116	32	72		6	3	3	3	3	6	3
144	31	87			10					3
172	27	89		4	4					4

Table IV.76. Codes of sulci at different times
Children with HR-ALL age 0 - 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	3	2	67	1	33		
6	3			2	67	1	33
18	2	1	50			1	50
32	3	2	67	1	33		
60	2	2	100				
116	2	1	50			1	50

Table IV.77. Codes of sulci at different times
Children with HR-ALL age >= 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	21	19	90	1	5	1	5
6	20			4	20	16	80
18	17	1	6	2	12	14	82
32	16	2	13	2	13	12	75
60	14	2	14	2	14	10	71
116	10	3	30			7	70
144							
172	10	3	30			7	70
200	8	1	13	4	50	3	38
228	7	5	71			2	29

Table IV.78. Codes of sulci at different times
Children with NHR-ALL age 0 - 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	4	3	75	1	25		
6	4	1	25			3	75
18	3	1	33	1	33	1	33
32	3	2	67	1	33		
60	3	3	100				
116	3	3	100				
144	3	3	100				
172	2	2	100				

Table IV.79. Codes of sulci at different times
Children with NHR-ALL age >= 2 years

	code	0		1		2	
week	n	n	%	n	%	n	%
0	41	34	83	3	7	4	10
6	41	5	12	5	12	31	76
18	41	6	15	2	5	33	80
32	40	8	20	3	8	29	73
60	36	8	22	6	17	22	61
116	29	8	28	6	21	15	52
144	28	19	68	3	11	6	21
172	25	17	68	4	16	4	16

Table IV.80. Differences in codes at different times
compared with codes at former evaluation (sulci).
Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	21			5	29	67
6 - 18	17		18	71	12	
18 - 32	16	6	6	88		
32 - 60	16	6	19	63	13	
60 - 116	11	9		91		
116 - 172	10			100		
172 - 200	8		50	50		
200 - 228	7	14	43	29	14	
172 - 228	7	57		43		

Table IV.81. Differences in codes at different times
compared with codes at former evaluation (sulci).
Percentages in children with HR-ALL age < 2 years

week	n	-2	-1	=	+1	+2
0 - 6	3			33	33	33
6 - 18	2		50	50		
18 - 32	2	50		50		
32 - 60	2		50	50		
60 - 116	1			100		

Table IV.82. Differences in codes at different times compared with codes at former evaluation (sulci). Percentages in children with HR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	18				28	72
6 - 18	15		13	73	13	
18 - 32	14		7	93		
32 - 60	14	7	14	64	14	
60 - 116	10	10		90		
116 - 172	10			100		
172 - 200	8		50	50		
200 - 228	7	14	43	29	14	
172 - 228	7	57		43		

Table IV.83. Differences in codes at different times compared with codes at former evaluation (sulci). Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43			23	19	58
6 - 18	42	5	10	74	7	5
18 - 32	43	9	5	84	2	
32 - 60	39		18	79	3	
60 - 116	32		12	81	6	
116 - 144	31	19	23	58		
144 - 172	27	11	4	67	15	4
116 - 172	27	30	11	59		

Table IV.84. Differences in codes at different times compared with codes at former evaluation (sulci). Percentages in children with NHR-ALL age < 2 years

week	n	-2	-1	=	+1	+2
0 - 6	4			25	25	50
6 - 18	3		33	67		
18 - 32	3	33		67		
32 - 60	3		33	67		
60 - 116	3			100		
116 - 144	3			100		
144 - 172	2			100		
116 - 172	2			100		

Table IV.85. Differences in codes at different times compared with codes at former evaluation (sulci). Percentages in children with NHR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	39			23	18	59
6 - 18	39	5	8	74	8	5
18 - 32	40	7	5	85	3	
32 - 60	36		17	81	3	
60 - 116	29		14	79	7	
116 - 144	28	21	25	54		
144 - 172	25	12	4	64	16	4
116 - 172	25	32	12	56		

Table IV.86. Differences in codes at different times compared with codes at diagnosis (sulci). Percentages in children with HR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	21			5	29	67
0 - 18	19			16	11	74
0 - 32	17			35	6	59
0 - 60	14		7	21	14	57
0 - 116	10		10	30		60
0 - 172	8			38		63
0 - 200	6			17	67	17
0 - 228	5	20		60		20

Table IV.87. Differences in codes at different times compared with codes at diagnosis (sulci). Percentages in children with HR-ALL age 0 - 2 years

week	n	-2	-1	=	+1	+2
0 - 6	3			33	33	33
0 - 18	2			50		50
0 - 32	3			100		
0 - 60	2		50	50		
0 - 116	2					50

Table IV.88. Differences in codes at different times compared with codes at diagnosis (sulci).
Percentages in children with HR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	18				28	72
0 - 18	17			12	12	76
0 - 32	14			21	7	71
0 - 60	12			17	17	67
0 - 116	8			38		63
0 - 172	8			38		63
0 - 200	6			17	67	17
0 - 228	5	20		60		20

Table IV.89. Differences in codes at different times compared with codes at diagnosis (sulci).
Percentages in children with NHR-ALL

week	n	-2	-1	=	+1	+2
0 - 6	43			23	19	58
0 - 18	42		2	21	10	67
0 - 32	41	2	2	27	10	59
0 - 60	37	3	3	35	8	51
0 - 116	30		7	40	10	43
0 - 144	29	3	7	69	7	14
0 - 172	25	4	8	68	8	12

Table IV.90. Differences in codes at different times compared with codes at diagnosis (sulci).
Percentages in children with NHR-ALL age 0 - 2 years

week	n	-2	-1	=	+1	+2
0 - 6	4			25	25	50
0 - 18	3			33	33	33
0 - 32	3			67	33	
0 - 60	3			100		
0 - 116	3			100		
0 - 144	3			100		
0 - 172	2			100		

Table IV.91. Differences in codes at different times compared with codes at diagnosis (sulci).
Percentages in children with NHR-ALL age >= 2 years

week	n	-2	-1	=	+1	+2
0 - 6	39			23	18	59
0 - 18	39		3	21	8	69
0 - 32	38	3	3	24	8	63
0 - 60	34	3	3	29	9	56
0 - 116	27		7	33	11	48
0 - 144	26	4	8	65	8	15
0 - 172	23	4	9	65	9	13

Table IV.92. Comparison of the coded evaluations of CT scans Sulci combined with Huckman.
Percentages of codes for children with HR-ALL

		Concordant			Sulci < Huckm			Sulci > Huckm		
week	n	00	11	22	01	02	12	10	20	21
0	23	74			4	9		9	4	
6	23		4	61			17	4	13	
18	19	5	5	58		5		5	16	5
32	19	11		53		11		16	11	
60	16	19	6	44		6	6		13	6
116	12	17		50		17			17	
144										
172	10	20		50		10			10	10
200	8	13		25			38	13	13	
228	7	43		29		29				

Table IV.93. Comparison of the coded evaluations of CT scans Sulci combined with Huckman.
Percentages of codes for children with NHR-ALL

		Concordant			Sulci < Huckm			Sulci > Huckm		
week	n	00	11	22	01	02	12	10	20	21
0	45	62	2		4	16	2	4	7	2
6	45	11		44		2	7	4	31	
18	44	9		36		7		7	41	
32	43	19		19	2	2	2	7	42	7
60	39	26		10		3	5	10	44	3
116	32	28		9	3	3	6	13	38	
144	31	65		3		7	3	7	16	
172	27	67		4		4	7	7	11	

Table IV.94. Comparison of the coded evaluations of CT scans
Sulci combined with Meese.
Percentages of codes for children with HR-ALL

		Concordant			Sulci < Meese			Sulci > Meese		
week	n	00	11	22	01	02	12	10	20	21
0	24	75			4	8		8	4	
6	23			17			4	22	57	
18	18	11		22				11	44	11
32	19	21		16				16	42	5
60	16	19	6	19		6		6	38	6
116	12	25		33	8				25	8
144										
172	10	30		40					30	
200	8	13		25				50	13	
228	7	43		29	14	14				

Table IV.95. Comparison of the coded evaluations of CT scans
Sulci combined with Meese.
Percentages of codes for children with NHR-ALL

		Concordant			Sulci < Meese			Sulci > Meese		
week	n	00	11	22	01	02	12	10	20	21
0	45	76		2	4	2		9	7	
6	45	13		31			2	9	38	7
18	44	16		27				7	46	5
32	43	21		14		2		9	54	
60	39	26	3	11	3		3	10	46	
116	32	34	3	9			6	9	34	3
144	31	71		3				10	16	
172	27	70		4			4	11	11	

Table IV.96. Comparison of the coded evaluations of CT scans
Sulci combined with Enzmann.
Percentages of codes for children with HR-ALL

		Concordant			Sulci < Enzm			Sulci > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	24	83				4		8	4	
6	23		9	30				17	30	13
18	19	11		37				11	32	11
32	19	21		32				16	16	16
60	16	19		31	6		6	6	25	6
116	12	33		33					17	17
144										
172	10	30		30					20	20
200	8	13		13			13	38	13	13
228	7	43		29	29					

Table IV.97. Comparison of the coded evaluations of CT scans
Sulci combined with Enzmann.
Percentages of codes for children with NHR-ALL

		Concordant			Sulci < Enzm			Sulci > Enzm		
week	n	00	11	22	01	02	12	10	20	21
0	45	73	2	2	7	2		7	7	
6	45	13		36			4	7	31	9
18	44	16	2	25				5	48	5
32	43	21	5	12		2		5	56	
60	39	26	3	3		3	3	10	54	
116	32	31	3	6		3	3	13	38	3
144	31	65	3		7			7	16	3
172	27	67	4	4	4			11	11	

Table V.1. Visual interpretation of EEG.
Codes for general impression.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	3	1	2	1	1	1	1		1	1	1
2	1	1	1	1	1	1	1		1	1	1
5	1			1	1	1	1		3	2	2
8	1	1	2	4							
9	1	1	1	1	1						
16	1	1	1	1	1	1	1				
20	1	1	1	1	1	1					
21	2	1	1	1	1	3	1		1	1	1
28	1	1	1	3	3	3	1		1	2	3
33	1		1	1	1	1	1				
34	4			5	2	5					
38	3	1	3								
39	1	1	3	4	3	3	3		3	3	3
40	2	2	3	4	1						
41	1	1	1	1	1						
48	3	1	1	1	1	1					
55	3	2									
56	1	3	1	1	1	1	1		1	1	1
58	2										
65	3	3	3	3	3	3	3		1	1	
69	3	1	1	4	1	1	1		1		
70	1	1	2	4	4	2	1		3		
72	2	3	1	1							
79	1	1	2	2	1	2					
80	4	3	3	1	1	2					
84	1	5									
3	1	1		1	2	1	3	3	1		
7	1	1		3	1	1	1	1			
4	1	1		1	1	1	1	1	2		
6	1	1		1	1	1	1	1	1		
10		3	3	3	2		2	2	2		
23	2	1	1								
25	3	1	1	2	1	3	2	1	1		
26	1	1	1	3	1						
27				5	4	1					
30	1	1	1	1	1	1					
42	1	1	1	1	2	1	1	1	1		
43	1	3	1	1	1	1	1	3	3		
49	3	1	2	1	1	3					
50	1	1	3	3	3						
51	1	3	1	3	2	3	3	2			
53	2	1	1	2	1	3	1	1	1		
54	1	1	1	1	2	1					
57	1	4									
60	1	1	1	1	1	1	1	1			
62	1	2	2	4	3	4	3	3	1		
63	1	1	1	2	1	1	1	2	3		
68	3	2	4	4	3	1					
71	3	3	1	3	3	3	3	3	3		
75	1	1	1	1	1	1	1	1	1		

Table V.1. Visual interpretation of EEG.
Codes for general impression (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	1	1	1	1	1	1	1	1	1		
12	1	1	1	3	1	1	1	1	1		
14	1	1	1	2	1	3	3	1	1		
15	1	1	1	1	1	1					
17	1	3	3								
18	1	1	1	1	1	1	1	1	1		
19	1	4	4	5	3						
22	4	1	3	3	1	1					
31	3										
32	1	1		3	2	1	1	1	1		
35	1	1	1	1	1	1	1	1	1		
36	3	3		1	3						
37	1	1	1	3	3	1	1	1			
44	4	3	1	1	2	3	3	3	3		
45	5	1	3	1	1	3	4	3	3		
46	4	4	1	3	1	1	3	1	1		
47	1	1	1	1	1	1	1	2	2		
52	3	2	3	4	3	1	1	1	1		
59	1	1	1	1	1	1	1	1	1		
61	3	2	1	1	1	1	1	1	1		
66	4	3	2	1	1	1	3	3	3		
73	3	2	1	1	3	1	1	1	1		
74	4	3	3	3	1	1	3				

Table V.2. Visual interpretation of EEG.
Codes for focal abnormalities.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	0	0	0	0	0	0	0		0	0	0
2	0	0	0	0	0	0	0		0	0	0
5	0			0	1	0	0		0	0	0
8	0	0	0	0							
9	0	0	0	0	0						
16	0	0	0	0	0	0	0				
20	0	0	0	0	0	0					
21	1	1	1	2	0	0	0		0	0	0
28	0	0	0	1	0	0	0		0	1	1
33	0		0	0	0	0	0				
34	1			2	0	0					
38	0	0	0								
39	0	0	0	0	0	0	0		0	0	0
40	1	0	0	0	0						
41	0	0	1	0	0						
48	0	0	1	0	0	0					
55	2	0									
56	0	0	0	0	0	0	0		0	0	0
58	0										
65	1	1	0	1	0	0	0		0	0	
69	1	0	0	1	0	0	0		0		
70	0	0	1	1	1	2	0		0		
72	0	1	1	0							
79	1	1	1	1	0	0					
80	2	0	1	0	0	0					
84	0	2									
3	0	0		0	0	0	0	0	0		
7	0	0		0	0	0	1	1			
4	0	0		0	0	0	0	0	1		
6	0	0		0	1	1	0	0	0		
10		0	0	0	0		0	0	0		
23	0	0	0								
25	0	0	0	0	0	0	0	0	0		
26	1	0	0	0	0						
27				2	0	0					
30	0	0	0	0	0	0					
42	0	1	0	1	2	1	0	0	0		
43	0	0	1	0	0	0	0	0	0		
49	0	0	0	0	0	0					
50	0	0	0	0	0						
51	0	0	0	1	0	0	1	0			
53	0	0	0	0	0	0	0	0	0		
54	0	0	0	0	0	0					
57	2	1									
60	0	0	0	0	0	0	0	0			
62	0	0	0	2	1	1	1	1	0		
63	0	0	0	0	0	0	0	0	0		
68	0	0	0	0	1	0					
71	0	0	0	0	0	1	1	0	0		
75	0	0	0	0	0	0	0	0	0		

Table V.2. Visual interpretation of EEG.
Codes for focal abnormalities (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	0	0	0	0	0	0	0	0	0		
12	0	0	0	1	0	0	0	0	0		
14	0	0	0	0	0	0	0	0	0		
15	0	0	0	0	0	0					
17	0	0	0								
18	0	0	0	0	0	1	0	0	0		
19	1	1	2	2	1						
22	0	2	2	2	0	1					
31	0										
32	0	0		0	1	0	0	0	0		
35	0	0	0	0	0	0	0	0	0		
36	0	1		1	1						
37	0	0	0	0	0	0	0	0			
44	0	0	1	0	0	0	0	1	1		
45	2	0	0	0	1	1	1	1	1		
46	2	2	1	1	0	0	1	1	0		
47	0	0	0	0	0	0	0	0	0		
52	0	0	0	0	0	0	0	0	0		
59	0	0	0	0	0	0	0	0	0		
61	1	0	0	0	0	0	0	0	0		
66	0	0	0	0	0	1	0	0	0		
73	1	1	0	0	1	1	0	0	0		
74	0	0	0	0	0	0	0				

Table V.3. Mean frequency derived from spectral analysis.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	2.85	3.79	5.15	5.14	6.73	4.92	5.21		4.68	4.94	4.54
2	4.52	7.38	3.77	3.58	5.51	5.79	4.56		5.22	3.96	4.74
5	3.32			4.69	5.43		4.56		4.11	4.02	4.17
8	2.89	7.00	5.72	5.06							
9	3.81		4.82	6.54	4.37						
16	2.94		7.05	3.09	2.39	3.72	5.87				
20	5.47	8.22	6.07	6.18	5.73	7.36					
21	4.76	5.25	3.69	3.82	4.86	4.64	6.89		4.49	4.10	6.97
28	5.61	6.27	5.73	10.88	9.92	7.95	6.57		5.35	4.32	4.56
33	6.62			4.86	4.40	5.36	4.96				
34	2.94			2.59	4.28	4.33					
38	5.20	5.65	6.66								
39	7.01	4.91	5.86	4.96	6.11	3.74	5.70		5.51	3.86	4.98
40	5.41	6.01	7.79	13.54	7.63						
41	3.21	8.18	5.24	6.55	3.68						
48	3.80	6.82	3.22	4.32	4.70	6.31					
55	2.69	3.96									
56	4.71	4.68	4.09	5.04	4.59	5.27	4.63		7.34	4.85	6.39
58	3.24										
65	4.72	7.98	8.59	7.03	8.80	6.93	5.80		5.99	5.26	
69	3.50	5.25	5.82	2.54	5.75	5.75	5.41		3.74		
70	3.02	3.89	5.10	2.87	4.10	4.33	3.66		3.54		
72	3.78	4.99	4.01	4.84							
79	3.68	4.64	4.75	4.42	5.05	4.25					
80	3.97	4.60	5.16	6.56	5.91	5.53					
84	3.31										
3	3.53	7.42		4.26	4.97	5.12	5.22	4.76	4.47		
7	3.33	5.95		4.35	6.12	5.38	5.13	5.33			
4	3.86	4.71		6.14	4.68	5.71		7.07	5.54		
6	3.39	4.63		4.69	4.41	5.22	4.59	4.41	4.59		
10		4.72	4.98		4.12	5.80	3.52	4.14	3.92		
23	3.52	3.67									
25	8.37	9.38	7.82	9.89	6.08	5.53	8.02	7.35	8.67		
26	4.68	5.03	5.54	6.43	6.97						
27				5.24	7.04	5.45					
30	6.44	9.08	5.22	3.85	3.80	3.64					
42	4.27	7.67	4.44	5.88	4.65	4.06	4.78	4.74	4.59		
43	5.71	6.49	6.91	4.63	4.95	5.43	5.23	6.34	5.46		
49	2.57	4.23	4.23	3.50	4.54	5.08					
50	4.28	9.08	9.60	6.82	5.35						
51	4.55	4.11	4.77	2.86	3.77	5.57	3.73	3.73			
53	3.70	6.46	7.04	6.34	6.45	7.06	5.59	8.34	6.88		
54	4.72	6.18	4.63	4.57	2.67	6.67					
57	3.96	4.20									
60	4.84	4.72	4.16	5.27	4.81	5.10	5.86	4.00			
62	4.47	4.53	5.55	4.28	4.86	5.46	5.99	6.25	5.64		
63	5.69	8.63	4.17	4.30	4.74	7.29	5.11	6.74	4.39		
68	2.49	4.44	5.33	4.41	4.31	4.96					
71	3.18	3.70	3.99	3.96	4.23	4.61	4.72	4.16	4.18		
75	8.68	6.64	7.28	4.31	4.54	4.85	6.00	5.08	6.14		

Table V.3. Mean frequency derived from spectral analysis.
(continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	4.78	9.87	7.67	5.35	5.18	10.60	5.11	6.53	6.30		
12	5.84	6.47	6.46	4.96	7.29	6.03	8.86	4.73	8.23		
14	4.56	4.22	4.43	4.73	3.96	5.16	4.64	5.03	4.36		
15	4.01	5.89	3.71	3.80	5.14	6.53					
17	4.32	4.09	6.43								
18	4.84		4.76	4.24	5.59	5.25	5.66	4.78	4.96		
19	4.51	4.25	3.36	2.74	3.67						
22	3.73	4.12	4.51	4.73	3.56	3.25					
31	6.89										
32	4.22	6.89		4.29	3.83	4.45	4.21		4.41		
35	5.37	7.66	7.22	5.36	5.17	6.43	6.68	4.45	4.90		
36	4.13	6.39		5.48	7.84						
37	6.55	6.92	5.45	6.56	6.05	4.56	5.57	5.70			
44	5.03	7.40	5.86	6.35	5.21	5.19	6.23	4.83	4.48		
45	4.26	11.88	6.26	5.02	6.07	5.79	3.58	4.65	6.67		
46	3.28	3.98	4.54	5.84	3.71	3.63	3.79	4.55	3.84		
47	3.31	5.94	3.95	4.21	3.72	3.64	4.18	6.66	4.56		
52	3.65	5.51	6.86	5.42	4.01	5.47	7.16	8.14	5.77		
59	3.88	4.17	4.76	5.63	5.98	5.52	5.54	5.39	5.49		
61	2.31	3.36	3.14	3.49	3.46	4.53	3.97	5.51	3.96		
66	2.93	4.26	5.06	3.28	4.09	3.80	4.19	4.15	3.70		
73	2.92	4.51	4.24	6.06	4.73	4.36	4.99	4.85	5.05		
74	5.33	10.00	5.32	4.99	7.37	7.22	8.23				

Table V.4. Percentage of deltafrequency derived from spectral analysis

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	79.5	46.5	61.9	64.3	56.3	60.9	64.5		61.8	61.3	63.7
2	64.9	44.1	69.4	68.8	56.4	56.1	65.0		57.7	66.0	59.2
5	64.7			49.2	52.9		61.5		58.2	66.0	60.5
8	79.7	47.9	47.6	66.0							
9	66.6		57.8	49.4	64.1						
16	82.0		52.1	82.2	86.1	77.7	52.5				
20	42.6	37.7	46.7	51.8	46.8	29.0					
21	58.1	54.9	70.1	66.1	61.2	63.6	27.8		62.1	63.8	30.7
28	56.7	52.7	53.8	28.0	33.5	42.7	50.6		54.0	64.9	60.0
33	57.3			51.5	54.5	62.7	62.0				
34	85.6			89.0	62.2	52.6					
38	49.0	51.3	43.9								
39	34.1	56.8	53.5	57.0	54.1	71.6	49.0		59.5	65.2	59.6
40	57.0	50.7	39.8	16.0	40.1						
41	73.3	45.9	50.3	57.4	67.8						
48	76.3	53.2	70.3	57.5	62.2	60.4					
55	77.4	66.8									
56	63.3	59.6	61.8	52.8	61.6	55.6	57.7		20.2	57.1	49.9
58	76.6										
65	59.1	24.7	39.3	45.0	12.6	47.8	54.4		54.8	55.3	
69	72.9	58.0	55.5	87.5	60.0	56.1	54.7		63.0		
70	74.0	68.0	63.2	83.2	70.9	70.3	72.1		73.7		
72	65.3	58.8	66.7	62.1							
79	69.2	60.8	59.4	63.8	56.3	65.1					
80	65.3	55.6	56.1	45.0	52.0	57.7					
84	75.8										
3	73.4	43.9		50.8	44.3	53.0	51.6	48.8	61.9		
7	69.9	53.5		69.1	48.5	58.5	55.6	51.2			
4	55.4	52.4		53.5	63.8	57.5		46.1	58.3		
6	64.8	62.2		63.2	66.1	59.2	63.2	66.6	61.2		
10		70.5	62.9		68.0	55.2	76.1	62.6	65.2		
23	75.2	74.2									
25	41.8	38.1	45.9	34.8	55.1	58.1	37.1	44.8	21.8		
26	59.6	59.7	50.2	50.7	43.6						
27				64.0	46.0	58.6					
30	55.6	39.2	59.8	66.4	69.5	73.2					
42	61.6	46.6	61.3	49.5	59.5	65.8	59.1	58.9	57.2		
43	58.3	48.4	50.5	62.8	63.5	48.5	53.6	48.6	49.6		
49	78.8	64.6	57.7	66.9	51.0	57.6					
50	68.9	38.9	36.4	54.5	57.5						
51	62.1	59.1	60.2	77.4	72.5	54.2	71.6	69.1			
53	68.6	35.5	43.3	38.7	39.5	34.5	47.4	39.6	37.1		
54	66.1	59.2	67.9	70.0	85.5	57.6					
57	61.8	65.0									
60	59.9	49.9	58.1	57.2	58.2	61.7	52.2	67.5			
62	54.9	55.3	50.8	55.0	63.4	46.6	53.6	35.1	52.8		
63	51.1	37.3	50.2	58.7	52.5	45.1	53.0	49.0	62.0		
68	81.6	64.5	50.1	61.0	60.8	53.8					
71	72.2	67.3	66.8	66.7	63.4	60.5	57.4	66.0	63.4		
75	40.0	50.3	49.9	60.1	59.0	64.0	55.0	55.3	51.2		

Table V.4. Percentage of deltafrequency derived from spectral analysis (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	66.2	38.1	45.0	44.6	61.2	34.5	58.4	51.6	51.4		
12	56.5	49.6	52.4	60.3	50.2	55.4	41.8	59.0	43.0		
14	67.9	64.9	58.8	61.2	67.6	57.9	63.5	61.2	62.6		
15	73.1	55.9	65.7	72.4	60.6	53.9					
17	60.5	66.6	48.6								
18	62.1		57.0	67.1	55.7	61.2	53.0	59.3	58.8		
19	55.0	47.2	75.0	84.7	55.8						
22	69.8	56.4	47.3	56.1	72.0	70.9					
31	30.0										
32	68.9	45.3		54.0	63.4	60.3	56.2		56.9		
35	58.5	44.9	44.1	49.4	51.9	50.3	51.4	63.8	55.1		
36	70.2	56.5		59.3	41.8						
37	36.0	30.9	61.7	46.5	60.6	69.6	62.0	56.5			
44	55.7	45.6	45.4	50.1	51.5	55.3	49.0	58.1	62.3		
45	72.7	28.3	53.6	65.9	57.1	61.0	74.9	64.6	56.0		
46	60.8	61.1	49.1	52.5	62.6	67.6	66.5	62.2	69.3		
47	79.0	58.5	71.8	69.4	69.4	73.7	70.3	53.3	66.6		
52	70.9	58.6	49.0	57.6	66.4	55.0	46.4	44.6	59.5		
59	69.0	61.3	57.1	54.7	47.9	55.4	51.0	58.2	57.3		
61	88.2	70.1	76.0	72.6	71.4	67.3	70.5	59.5	67.5		
66	75.4	53.6	50.7	72.2	57.3	58.1	58.9	64.6	63.5		
73	79.6	62.2	62.3	53.3	57.2	67.7	60.0	60.5	58.6		
74	65.6	39.4	62.6	66.7	51.2	55.8	43.9				

Table V.5. Percentage of thetafrequency derived from spectral analysis

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	16.4	50.8	18.0	16.8	14.1	22.2	15.2		20.3	20.6	20.7
2	20.6	20.8	18.6	22.4	22.0	18.8	17.4		19.6	20.5	21.1
5	31.0			38.0	28.3		22.9		30.3	21.8	27.6
8	15.3	23.4	35.6	16.0							
9	22.8		26.2	23.4	22.0						
16	11.0		17.2	10.3	10.7	10.6	20.8				
20	38.4	24.7	28.7	21.9	30.9	13.7					
21	22.3	25.0	17.9	23.6	18.7	16.4	21.5		17.6	20.4	15.1
28	21.0	22.1	23.7	19.3	19.9	20.7	18.8		22.8	19.0	22.3
33	16.1			35.4	32.0	15.5	18.9				
34	8.3			7.0	25.0	36.9					
38	28.4	22.7	22.2								
39	36.7	24.1	20.8	25.4	19.1	17.3	22.6		17.1	22.3	21.0
40	19.4	18.5	20.6	9.3	22.5						
41	21.9	17.2	31.1	10.4	22.9						
48	12.0	16.4	25.7	31.3	22.1	11.8					
55	20.5	22.4									
56	17.6	22.3	24.2	29.2	19.4	20.1	22.5		19.9	18.7	19.5
58	13.6										
65	22.5	12.7	17.9	21.8	8.9	19.4	20.1		19.3	21.2	
69	19.1	22.1	20.4	8.6	15.6	20.8	23.5		28.1		
70	21.5	20.9	18.0	12.7	15.2	14.7	16.9		15.9		
72	24.1	22.4	20.5	20.8							
79	19.8	22.4	23.8	20.5	26.0	20.4					
80	20.3	28.5	23.5	25.5	22.8	18.1					
84	13.7										
3	18.1	24.8		39.8	42.4	29.5	30.9	37.8	24.5		
7	22.7	21.8		15.8	25.3	18.6	20.6	22.3			
4	37.6	32.3		20.9	19.3	18.9		21.4	20.3		
6	30.2	19.9		19.4	18.8	20.6	19.7	16.7	21.4		
10		12.3	18.5		18.9	19.7	15.8	23.6	23.1		
23	16.1	15.7									
25	17.0	16.4	16.3	15.2	15.9	17.6	16.8	19.6	14.3		
26	26.4	22.2	31.3	23.5	28.1						
27				16.4	22.9	19.6					
30	16.3	16.5	20.3	21.7	19.8	15.4					
42	24.5	20.9	24.2	29.1	26.3	21.5	24.1	25.1	26.6		
43	16.9	23.3	17.6	21.1	16.5	30.1	25.5	23.4	27.8		
49	18.3	20.8	30.0	26.3	37.3	23.8					
50	16.9	17.7	17.1	14.9	22.3						
51	23.3	30.5	24.2	19.4	16.2	24.5	16.9	20.5			
53	19.6	26.1	18.1	29.5	20.4	19.2	19.2	15.9	18.2		
54	17.0	13.5	15.0	12.7	8.9	11.6					
57	25.0	21.3									
60	22.0	34.4	29.3	24.1	24.1	18.6	23.0	19.2			
62	28.5	28.1	24.9	34.9	16.8	28.6	19.9	27.9	21.7		
63	28.1	23.5	40.5	29.8	32.8	23.2	28.7	22.0	23.2		
68	16.7	21.6	28.7	24.3	24.7	28.0					
71	22.6	22.5	20.8	21.7	22.6	23.4	19.3	19.6	23.0		
75	22.8	22.7	19.3	28.2	27.6	18.8	21.4	26.0	23.5		

Table V.5. Percentage of thetafrequency derived from spectral analysis (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	16.7	15.4	20.4	39.6	19.0	14.5	21.5	20.5	22.4		
12	20.0	22.6	19.8	23.2	17.2	18.6	14.9	23.0	18.2		
14	16.3	22.1	27.0	23.7	20.5	23.5	19.5	20.7	24.0		
15	14.6	22.0	25.1	16.3	20.8	18.0					
17	26.3	21.1	24.4								
18	18.0		25.3	18.3	21.8	17.1	21.8	22.9	21.6		
19	30.3	45.6	17.6	10.3	40.3						
22	20.9	33.8	42.6	30.8	19.4	22.5					
31	38.5										
32	18.1	23.3		35.6	26.3	24.6	32.3		30.1		
35	21.2	21.1	23.8	35.5	33.0	19.8	18.1	20.4	25.6		
36	18.5	16.1		18.7	21.8						
37	30.8	37.0	14.8	25.0	12.1	13.0	15.0	18.1			
44	24.6	20.0	27.9	22.3	28.0	24.4	21.8	22.2	20.9		
45	12.1	12.3	18.4	13.6	15.9	13.7	15.8	15.5	13.0		
46	36.4	29.4	39.1	24.4	29.1	23.4	23.1	23.0	19.6		
47	11.6	17.1	14.6	16.9	20.4	15.0	15.2	17.9	17.2		
52	18.8	20.8	23.2	21.6	21.4	23.5	22.3	16.0	17.2		
59	20.2	26.2	27.0	22.5	30.0	21.0	23.5	19.0	20.1		
61	9.4	22.0	16.5	19.9	20.4	17.3	17.6	19.9	20.9		
66	20.3	36.0	34.1	20.9	32.5	34.3	29.6	22.6	27.7		
73	14.6	23.8	24.8	22.9	28.6	18.5	21.9	23.0	24.2		
74	13.0	11.9	15.4	14.5	15.3	12.7	17.4				

Table V.6. Percentage of alphafrequency derived from spectral analysis.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	1.8	1.9	7.5	5.3	7.9	6.8	6.7		9.1	7.6	7.3
2	5.7	14.3	6.9	5.5	8.8	11.1	9.0		11.9	9.4	12.5
5	2.6			6.3	6.4		7.2		7.2	5.6	5.8
8	2.5	8.0	5.4	4.4							
9	5.5		7.5	9.2	5.9						
16	2.7		7.5	2.2	2.0	3.8	13.4				
20	9.4	11.4	9.9	9.9	9.7	53.2					
21	12.8	10.0	8.0	7.2	11.4	12.6	46.5		15.4	12.5	50.8
28	8.2	7.5	9.1	11.9	10.4	10.9	13.3		13.4	9.0	11.4
33	5.3			6.3	8.3	7.5	8.9				
34	1.9			1.2	5.0	5.9					
38	16.6	15.2	17.6								
39	13.3	10.9	11.3	8.4	9.9	5.3	19.4		10.0	8.8	8.7
40	11.9	17.7	15.5	9.1	13.4						
41	2.5	8.7	8.3	6.3	5.1						
48	3.6	8.0	2.2	3.5	6.0	6.5					
55	1.4	4.8									
56	10.1	10.3	9.6	10.8	11.9	14.7	14.5		56.4	18.5	14.5
58	6.3										
65	10.0	53.7	12.7	12.9	71.6	11.8	11.0		10.2	12.6	
69	3.4	7.6	7.9	1.5	8.1	8.0	10.0		6.0		
70	2.6	5.1	6.4	1.4	6.0	5.9	5.9		5.7		
72	6.8	8.9	7.2	7.1							
79	6.5	8.6	8.2	7.5	7.9	7.4					
80	10.9	9.7	10.2	13.2	10.3	11.7					
84	5.6										
3	3.1	7.6		4.4	5.2	6.7	6.2	5.9	5.4		
7	4.2	9.5		5.9	12.1	10.9	15.8	18.9			
4	4.0	8.6		8.6	6.8	8.6		11.0	7.3		
6	2.8	9.2		7.8	6.7	8.4	8.7	7.8	9.3		
10		4.5	6.7		6.0	10.7	3.0	8.1	6.8		
23	2.7	3.4									
25	13.7	11.7	13.5	12.6	12.9	11.2	25.4	14.7	50.1		
26	5.8	7.6	7.9	6.9	8.7						
27				5.5	10.0	8.0					
30	7.1	11.9	7.8	7.7	5.1	5.6					
42	8.6	7.4	7.1	7.7	6.3	7.2	8.6	8.0	10.5		
43	9.3	10.5	11.0	7.4	8.5	12.1	11.4	11.9	12.7		
49	1.7	7.7	8.3	2.9	7.4	8.4					
50	4.3	9.5	9.2	6.8	7.2						
51	5.2	4.5	5.6	1.8	4.3	7.6	5.4	5.1			
53	8.0	30.6	22.4	22.5	31.4	36.6	27.7	20.0	34.6		
54	4.9	8.1	5.7	6.0	2.3	8.6					
57	10.2	6.5									
60	9.1	11.1	8.8	6.9	9.5	7.6	11.9	7.6			
62	12.5	12.7	14.7	6.6	9.9	18.3	12.4	31.3	15.0		
63	7.0	8.6	5.9	5.5	7.9	8.4	8.1	9.4	7.6		
68	1.1	5.5	12.1	8.4	9.0	11.1					
71	4.4	5.6	6.1	5.7	7.1	7.5	18.3	7.4	7.2		
75	6.7	7.3	7.2	5.0	5.8	5.8	7.7	9.2	9.3		

Table V.6. Percentage of alphafrequency derived from spectral analysis (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	5.8	8.6	10.3	5.7	7.0	10.2	9.3	9.8	9.7		
12	8.4	9.8	9.3	5.4	8.9	10.3	10.3	10.2	11.0		
14	5.5	5.6	8.0	5.7	6.2	7.4	7.5	7.1	6.7		
15	3.9	5.7	6.0	4.5	6.1	8.8					
17	6.6	4.9	9.0								
18	10.3		10.1	7.1	9.6	9.8	13.0	9.5	10.5		
19	9.1	4.6	3.2	1.7	2.5						
22	4.0	5.4	3.8	3.9	3.3	3.3					
31	21.6										
32	5.2	13.0		6.3	6.6	8.1	8.1		7.9		
35	7.5	10.1	11.4	5.9	6.5	12.8	11.9	8.4	11.9		
36	3.4	7.9		7.2	10.3						
37	21.7	18.4	8.9	10.8	8.6	6.2	6.9	11.6			
44	10.1	10.8	14.7	10.8	10.9	9.9	15.0	11.6	10.1		
45	4.6	7.8	9.7	7.1	9.4	8.6	4.0	11.1	10.3		
46	1.9	3.7	5.6	7.7	4.3	4.6	5.3	6.3	4.9		
47	3.3	7.1	5.0	5.8	5.6	5.5	6.3	9.1	6.7		
52	5.3	6.6	7.5	7.2	6.2	9.1	9.9	12.1	7.9		
59	4.9	7.4	8.0	9.8	9.2	12.2	15.6	10.9	9.8		
61	1.2	3.7	3.6	3.5	4.2	5.3	4.6	6.3	5.6		
66	2.9	5.7	6.4	3.6	6.1	4.7	6.5	6.3	6.0		
73	2.8	5.7	6.5	7.1	5.7	5.0	7.6	6.1	6.5		
74	5.7	8.7	8.1	6.1	9.0	7.7	11.8				

Table V.7. Percentage of restfrequency derived from spectral analysis.

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
1	2.3	0.8	12.6	13.6	21.7	10.1	13.6		8.8	10.5	8.3
2	8.8	20.8	5.1	3.3	12.8	14.0	8.6		10.8	4.1	7.2
5	1.7			6.5	12.4		8.4		4.3	6.6	6.1
8	2.5	20.7	11.4	13.6							
9	5.1		8.5	18.0	8.0						
16	4.3		23.2	5.3	1.2	7.9	13.3				
20	9.6	26.2	14.7	16.4	12.6	4.1					
21	6.8	10.1	4.0	3.1	8.7	7.4	4.2		4.9	3.3	3.4
28	14.1	17.7	13.4	40.8	36.2	25.7	17.3		9.8	7.1	6.3
33	21.3			6.8	5.2	14.3	10.2				
34	4.2			2.8	7.8	4.6					
38	6.0	10.8	16.3								
39	15.9	8.2	14.4	9.2	16.9	5.8	9.0		13.4	3.6	10.8
40	11.7.	13.1	24.1	65.6	24.0						
41	2.3	28.2	10.3	25.9	4.2						
48	8.1	22.4	1.8	7.7	9.7	21.3					
55	0.7	6.0									
56	9.0	7.8	4.3	7.2	7.1	9.6	5.3		3.5	5.7	16.1
58	3.5										
65	8.4	8.9	30.1	20.2	6.9	21.0	14.5		15.7	10.9	
69	4.6	12.3	16.2	2.4	16.3	15.1	11.8		2.8		
70	1.9	6.0	12.4	2.7	7.9	9.1	5.0		4.7		
72	3.8	9.9	5.6	10.0							
79	4.5	8.2	8.6	8.2	9.8	7.1					
80	3.5	6.2	10.2	16.3	14.9	12.5					
84	4.9										
3	5.4	23.7		5.0	8.1	10.8	11.3	7.5	8.2		
7	3.2	15.2		9.2	14.1	12.0	8.0	7.6			
4	3.0	6.7		17.0	10.1	15.0		21.5	14.1		
6	2.2	8.7		9.6	8.4	11.8	8.4	8.9	8.1		
10		12.7	11.9		7.1	14.4	5.1	5.7	4.9		
23	6.0	6.7									
25	27.5	33.8	24.3	37.4	16.1	13.1	20.7	20.9	13.8		
26	8.2	10.5	10.6	18.9	19.6						
27				14.1	21.1	13.8					
30	21.0	32.4	12.1	4.2	5.6	5.8					
42	5.3	25.1	7.4	13.7	7.9	5.5	8.2	8.0	5.7		
43	15.5	17.8	20.9	8.7	11.5	9.3	9.5	16.1	9.9		
49	1.2	6.9	4.0	3.9	4.3	10.2					
50	9.9	33.9	37.3	23.8	13.0						
51	9.4	5.9	10.0	1.4	7.0	13.7	6.1	5.3			
53	3.8	7.8	16.2	9.3	8.7	9.7	5.7	24.5	10.1		
54	12.0	19.2	11.4	11.3	3.3	22.8					
57	3.0	7.2									
60	9.0	4.6	3.8	11.8	8.2	12.1	12.9	5.7			
62	4.1	3.9	9.6	3.5	9.9	6.5	5.7	5.7	10.6		
63	13.8	30.6	3.4	6.0	6.8	23.3	10.1	19.6	7.2		
68	0.6	8.4	9.1	6.3	5.5	7.1					
71	0.8	4.6	6.3	5.9	6.9	8.6	5.0	7.0	6.4		
75	30.5	19.7	23.6	6.7	7.6	11.4	15.9	9.5	16.0		

Table V.7. Percentage of restfrequency derived from spectral analysis (continued)

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200	228
11	11.3	37.9	24.3	10.1	12.8	40.8	10.8	18.1	16.5		
12	15.1	18.0	18.5	11.1	23.7	15.7	33.0	7.8	27.8		
14	10.3	7.4	6.2	9.4	5.7	11.2	9.5	11.0	6.7		
15	8.4	16.4	3.2	6.8	12.5	19.3					
17	6.6	7.4	18.0								
18	9.6		7.6	7.5	12.9	11.9	12.2	8.3	9.1		
19	5.6	2.6	4.2	3.3	1.4						
22	5.3	4.4	6.3	9.2	5.3	3.3					
31	9.9										
32	7.8	18.4		4.1	3.7	7.0	3.4		5.1		
35	12.8	23.9	20.7	9.2	8.6	17.1	18.6	7.1	7.4		
36	7.9	19.5		14.8	26.1						
37	11.5	13.7	14.6	17.7	18.7	11.2	16.1	13.8			
44	9.6	23.6	12.0	16.7	9.6	10.4	14.2	8.1	6.7		
45	10.6	51.6	18.3	13.4	17.6	16.7	5.3	8.8	20.7		
46	0.8	5.8	6.2	15.4	4.0	4.4	5.1	8.5	6.2		
47	6.1	17.3	8.6	7.9	4.6	5.8	8.2	19.7	9.5		
52	5.0	14.0	20.3	13.6	6.0	12.4	21.4	27.2	15.4		
59	5.8	5.1	7.9	13.0	12.9	11.4	9.8	11.9	12.8		
61	1.2	4.2	3.9	4.0	4.0	10.1	7.3	14.2	6.0		
66	1.4	4.7	8.8	3.3	4.1	2.9	5.1	6.6	2.8		
73	3.0	8.3	6.4	16.7	8.5	8.8	10.5	10.4	10.8		
74	15.7	40.0	13.9	12.7	24.5	23.8	26.9				

Table V.8. Spectral analysis EEG
means , VA group

wknr	n	freq	delta	theta	alpha	rest
0	18	4.784	62.117	21.000	6.794	10.089
6	18	6.013	52.950	22.094	9.456	15.500
9	16	5.668	53.694	23.600	9.581	13.125
18	17	5.091	58.494	23.106	7.406	10.994
32	17	4.927	58.853	22.541	9.018	9.588
60	15	5.384	55.987	21.553	10.933	11.527
116	10	5.503	54.000	21.480	13.690	9.980
144	10	5.673	53.390	21.920	12.460	12.230
172	8	5.744	49.388	22.288	18.375	9.963

Table V.9. Spectral analysis EEG
means , VB group

wknr	n	freq	delta	theta	alpha	rest
0	23	4.376	64.852	20.487	6.770	7.883
6	21	6.085	52.143	23.790	7.676	16.390
9	20	5.200	56.660	24.090	7.755	11.495
18	21	4.882	60.505	22.690	6.329	10.471
32	21	5.030	58.705	23.514	6.962	10.819
60	19	5.337	59.521	19.758	7.868	12.853
116	17	5.446	57.512	20.665	9.035	12.788
144	15	5.330	58.467	20.313	9.093	12.100
172	15	5.112	59.227	21.513	8.367	10.900

Table V.10. Spectral analysis EEG
Means, age 0 - 2 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	7	4.049	71.486	15.929	4.443	8.129
6	5	5.654	58.760	19.260	6.660	15.320
9	5	4.684	62.520	21.740	5.960	9.780
18	6	4.665	60.800	24.250	5.883	9.067
32	6	4.307	63.267	23.583	6.233	6.917
60	6	4.768	65.950	15.900	7.117	11.033
116	5	5.066	58.980	20.500	10.560	9.940
144	3	5.597	56.800	20.667	9.333	13.200
172	3	4.880	60.367	21.300	9.000	9.333

Table V.11. Spectral analysis EEG
Means, age 2 - 4 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	24	4.057	67.996	20.458	4.283	7.258
6	23	5.560	55.183	23.965	7.217	13.635
9	20	4.842	58.390	24.870	7.255	9.485
18	23	4.433	62.235	24.252	5.517	7.996
32	24	4.578	61.700	23.204	6.467	8.629
60	23	5.338	59.278	20.122	7.643	12.957
116	17	4.793	60.812	21.965	7.712	9.500
144	12	5.253	56.967	23.333	8.025	11.667
172	17	4.625	61.065	23.035	7.535	8.365
200	3	4.307	64.433	20.967	7.533	7.067
228	3	4.483	61.133	23.133	8.533	7.200

Table V.12. Spectral analysis EEG
Means, age 4 - 6 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	13	4.054	68.469	19.277	5.308	6.946
6	12	6.692	50.742	21.192	8.208	19.858
9	11	5.581	53.764	25.300	8.182	12.755
18	13	5.270	61.231	18.908	6.392	13.469
32	12	5.490	56.217	23.125	7.700	12.958
60	10	5.510	56.340	21.900	8.810	12.950
116	8	5.986	52.138	20.400	14.075	13.400
144	5	5.160	60.840	18.240	9.140	11.720
172	7	5.067	58.771	20.757	10.600	9.871
200	2	4.210	64.350	19.700	10.750	5.200
228	2	5.765	45.350	18.700	31.100	4.850

Table V.13. Spectral analysis EEG
Means, age 6 - 10 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	14	4.584	60.936	23.443	7.307	8.314
6	12	5.617	54.958	22.617	8.750	13.675
9	11	5.388	55.491	23.191	9.200	12.109
18	12	5.013	59.900	21.908	7.467	10.717
32	11	5.474	56.182	21.727	9.045	13.045
60	9	5.398	54.289	21.189	14.611	9.911
116	8	5.529	54.463	20.513	13.763	11.263
144	6	4.853	58.667	21.833	10.850	8.650
172	6	5.867	49.667	21.150	17.900	11.283
200	2	4.355	61.150	20.500	13.650	4.650
228	2	5.685	54.750	20.250	11.600	13.450

Table V.14. Spectral analysis EEG
Means, age older than 10 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	13	5.021	55.692	23.908	12.062	8.338
6	11	6.278	44.836	24.964	17.300	12.900
9	10	6.702	49.220	19.300	12.790	18.690
18	10	6.900	48.420	20.280	10.170	21.120
32	10	6.184	48.260	20.490	17.780	13.470
60	7	5.789	53.271	19.357	14.829	12.543
116	5	6.194	50.900	18.200	16.680	12.540
144	4	6.910	44.000	20.375	19.400	16.225
172	4	6.795	41.625	18.375	27.475	12.550
200	1	5.260	55.300	21.200	12.600	10.900

Table V.15. Spectral analysis EEG
Means, age 0 - 4 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	31	4.055	68.784	19.435	4.319	7.455
6	28	5.577	55.821	23.125	7.118	13.936
9	25	4.810	59.216	24.244	6.996	9.544
18	29	4.481	61.938	24.252	5.593	8.217
32	30	4.523	62.013	23.280	6.420	8.287
60	29	5.220	60.659	19.248	7.534	12.559
116	22	4.855	60.395	21.632	8.359	9.600
144	15	5.322	56.933	22.800	8.287	11.973
172	20	4.664	60.960	22.775	7.755	8.510
200	3	4.307	64.433	20.967	7.533	7.067
228	3	4.483	61.133	23.133	8.533	7.200

Table V.16. Spectral analysis EEG
Means, age 4 - 10 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	27	4.329	64.563	21.437	6.344	7.656
6	24	6.155	52.850	21.904	8.479	16.767
9	22	5.485	54.627	24.245	8.691	12.432
18	25	5.146	60.592	20.348	6.908	12.148
32	23	5.482	56.200	22.457	8.343	13.000
60	19	5.457	55.368	21.563	11.558	11.511
116	16	5.758	53.300	20.456	13.919	12.331
144	11	4.993	59.655	20.200	10.073	10.045
172	13	5.436	54.569	20.938	13.969	10.523
200	4	4.283	62.750	20.100	12.200	4.925
228	4	5.725	50.050	19.475	21.350	9.150

Table V.17. Spectral analysis EEG
Means, age 2 - 6 years

wk nr	n	freq Hz	delta	theta	alpha	rest
				percentage		
0	37	4.056	68.162	20.043	4.643	7.149
6	35	5.948	53.660	23.014	7.557	15.769
9	31	5.104	56.748	25.023	7.584	10.645
18	36	4.735	61.872	22.322	5.833	9.972
32	36	4.882	59.872	23.178	6.878	10.072
60	33	5.390	58.388	20.661	7.997	12.955
116	25	5.175	58.036	21.464	9.748	10.748
144	17	5.226	58.106	21.835	8.353	11.682
172	24	4.754	60.396	22.371	8.429	8.804
200	5	4.268	64.400	20.460	8.820	6.320
228	5	4.996	54.820	21.360	17.560	6.260

Table V.18. Follow up of children with first relapse in the CNS.
Percentage of deltafrequency derived from spectral analysis

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200
20	42.6	37.7	46.7	51.8	46.8	29.0				
33	57.3			51.5	54.5	62.7	62.0			
48	76.3	53.2	70.3	57.5	62.2	60.4				
30	55.6	39.2	59.8	66.4	69.5	73.2				
49	78.8	64.6	57.7	66.9	51.0	57.6				
50	68.9	38.9	36.4	54.5	57.5					
54	66.1	59.2	67.9	70.0	85.5	57.6				
60	59.9	49.9	58.1	57.2	58.2	61.7	52.2	67.5		
22	69.8	56.4	47.3	56.1	72.0	70.9				

Table V.19. Follow up of children with first relapse in the CNS.
Percentage of thetafrequency derived from spectral analysis

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200
20	38.4	24.7	28.7	21.9	30.9	13.7				
33	16.1			35.4	32.0	15.5	18.9			
48	12.0	16.4	25.7	31.3	22.1	11.8				
30	16.3	16.5	20.3	21.7	19.8	15.4				
49	18.3	20.8	30.0	26.3	37.3	23.8				
50	16.9	17.7	17.1	14.9	22.3					
54	17.0	13.5	15.0	12.7	8.9	11.0				
60	22.0	34.4	29.3	24.1	24.1	18.6	23.0	19.2		
22	20.9	33.8	42.6	30.8	19.4	22.5				

Table V.20. Follow up of children with first relapse in the CNS. Percentage of alphafrequency derived from spectral analysis

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200
20	9.4	11.4	9.9	9.9	9.7	53.2				
33	5.3			6.3	8.3	7.5	8.9			
48	3.6	8.0	2.2	3.5	6.0	6.5				
30	7.1	11.9	7.8	7.7	5.1	5.6				
49	1.7	7.7	8.3	2.9	7.4	8.4				
50	4.3	9.5	9.2	6.8	7.2					
54	4.9	8.1	5.7	6.0	2.3	8.6				
60	9.1	11.1	8.8	6.9	9.5	7.6	11.9	7.6		
22	4.0	5.4	3.8	3.9	3.3	3.3				

Table V.21. Follow up of children with first relapse in the CNS. Percentage of restfrequency derived from spectral analysis

pt nr	weeknumber 0	6	9	18	32	60	116	144	172	200
20	9.6	26.2	14.7	16.4	12.6	4.1				
33	21.3			6.8	5.2	14.3	10.2			
48	8.1	22.4	1.8	7.7	9.7	21.3				
30	21.0	32.4	12.1	4.2	5.6	5.8				
49	1.2	6.9	4.0	3.9	4.3	10.2				
50	9.9	33.9	37.3	23.8	13.0					
54	12.0	19.2	11.4	11.3	3.3	22.8				
60	9.0	4.6	3.8	11.8	8.2	12.1	12.9	5.7		
22	5.3	4.4	6.3	9.2	5.3	3.3				

Table VI.1. Postirradiation syndrome.
Codes for symptoms, signs and overall severity; days duration.

pat nr	S	L	So	H	A	I	N	V	An	F	D	C	P	W	dur	G*)
1	0	0	2	0	0	0	0	0	2	2	0	0	0	0	14	2
2	2	2	2	2	0	0	0	1	1	2	0	0	0	0	9	2
5	0	0	1	0	0	0	0	0	2	0	0	0	2	0	8	1
8	2	4	5	2	2	0	2	4	5	2	4	0	4	4	41	5
9	1	2	4	0	0	0	0	1	2	0	9	1	2	1	37	3
16	0	0	2	0	0	0	0	0	0	2	0	0	0	0	10	1
20	2	0	2	0	0	0	0	0	3	2	0	0	0	2	15	2
21	2	2	0	0	0	0	0	0	2	2	0	0	0	2	13	2
28	0	0	1	0	0	1	0	0	2	0	0	0	0	0	4	1
33	0	2	0	0	2	0	0	0	0	0	0	0	0	2	5	1
34	2	2	2	2	1	2	0	2	4	2	0	0	0	2	23	4
38	2	2	0	0	0	0	0	2	2	2	0	0	0	0	+5	2
39	2	4	4	2	2	0	2	4	4	2	2	0	2	2	27	4
40	2	2	2	0	0	0	4	4	4	2	2	0	0	2	27	5
41	0	0	0	0	0	1	0	0	2	0	0	0	1	0	10	1
48	2	2	4	0	0	0	0	2	4	2	2	0	1	0	32	4
55	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
56	2	4	5	2	2	1	2	2	3	2	3	2	2	2	19	4
58	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
65	2	2	5	0	3	0	4	4	4	2	2	2	0	0	15	4
69	2	2	5	0	0	1	0	2	2	0	1	2	1	0	27	4
70	0	1	5	0	0	2	2	0	4	4	0	4	2	1	30	4
72	2	4	5	0	0	2	2	1	4	0	2	2	1	0	25	3
79	2	2	4	2	1	2	2	1	2	2	2	2	1	0	33	3
80	1	2	3	0	1	2	0	0	2	2	1	2	0	1	34	2
84	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
3	0	0	0	0	0	0	1	1	1	0	9	9	2	1		0
7	2	2	0	0	0	0	0	0	3	2	2	0	2	2	25	3
4	2	2	2	0	0	0	0	0	2	0	9	2	9	9	24	3
6	2	0	2	0	0	0	0	2	2	0	0	0	9	9	11	2
10	1	1	0	0	0	0	0	0	2	0	0	0	1	2	22	1
23	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
25	0	0	0	0	0	0	2	2	2	0	0	2	0	0		2
26	0	1	0	0	0	0	0	2	0	2	2	0	1	0	13	2
27	0	2	2	0	2	0	2	3	1	2	0	0	0	1	30	3
30	0	0	0	0	0	0	0	2	3	0	0	0	0	0	31	1
42	0	0	4	0	2	0	0	0	2	2	0	0	0	0	31	2
43	2	2	4	0	0	1	0	0	2	3	2	2	2	0	31	3
49	2	2	4	0	0	2	0	0	2	2	1	2	0	0	22	3
50	2	2	4	2	0	0	0	0	2	2	2	2	2	2	15	3
51	4	4	5	0	4	4	4	2	5	2	4	2	2	3	36	5
53	4	2	4	0	1	0	1	1	4	3	2	2	1	2	12	3
54	0	0	3	0	2	4	0	0	3	0	2	1	0	1	24	3
57	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
60	2	2	2	0	0	0	0	2	2	2	2	0	0	1	14	3
62	2	4	4	0	0	0	3	4	4	2	2	2	2	2	25	5
63	2	1	1	0	0	0	0	0	2	0	0	0	1	0		7
68	2	2	2	0	2	2	0	0	1	2	2	2	1	2	20	7
71	2	2	4	0	1	1	0	0	2	2	1	1	2	2	18	3
75	0	1	2	0	0	0	0	1	2	0	2	2	1	0	23	2

Table VI.1. Postirradiation syndrome.
Codes for symptoms, signs and overall severity; days duration.
(continued)

pat nr	S	L	So	H	A	I	N	V	An	F	D	C	P	W	dur	G*)
11	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
12	0	0	2	0	0	0	0	0	0	2	0	0	0	0	6	1
14	0	0	5	2	0	0	0	0	0	2	0	0	2	0	9	3
15	0	0	0	0	0	0	0	0	4	0	0	0	0	0	17	2
17	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
18	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
19	2	2	4	0	0	0	2	2	2	2	0	0	0	2	14	3
22	2	2	1	0	0	0	0	2	3	2	2	0	2	2	17	3
31	9	9	9	9	9	9	9	9	9	9	9	9	9	9		7
32	0	2	0	0	0	0	0	0	1	2	2	0	0	0	10	2
35	0	1	2	0	0	0	1	2	2	2	0	0	0	0	13	3
36	0	0	2	0	0	0	0	0	4	0	2	2	2	2	27	3
37	2	4	0	0	0	0	0	2	4	4	0	2	0	2	19	4
44	2	3	2	0	0	0	2	4	5	2	2	2	2	2	25	5
45	2	4	5	0	0	0	1	2	5	2	2	2	0	0	15	4
46	3	3	4	2	2	1	0	0	2	0	2	2	0	1	25	4
47	0	0	2	0	0	1	0	0	2	2	2	0	1	1	22	2
52	2	3	0	0	0	0	0	2	4	0	4	0	2	4	6	2
59	1	0	2	0	1	2	0	0	4	2	1	1	1	0	24	2
61	2	2	2	0	2	0	2	2	2	2	2	2	2	2	24	3
66	0	1	0	0	0	0	0	0	1	0	1	0	0	0	4	1
73	2	2	2	0	0	0	1	1	2	2	0	2	0	0	22	2
74	2	2	2	0	2	2	2	4	5	0	1	0	2	2	32	4

*) S = slowness, L = lethargy, So = somnolence, H = headache,
A = ataxia, I = irritability, N = nausea, V = vomiting, An = anorexia,
F = fever of unknown origin, D = dull eyes, C = acrocyanosis,
P = paleness, W = worn out, dur = duration in days, G = overall grade.

Codes:
- 0 no signs or symptoms
- 1 very slight signs or symptoms
- 2 slight signs or symptoms
- 3 moderate signs or symptoms
- 4 severe signs or symptoms, just manageable at home
- 5 very severe signs or symptoms, hospitalization necessary
- 6 life threatening signs or symptoms
- 7 for grade only: not interpretable because of intercurrent infections, early relapse or insufficient data.
- 9 for signs or symptoms: not interpretable because of intercurrent infections, early relapse or insufficient data.

Naschrift

Zonder de hulp van velen was dit proefschrift nooit tot stand gekomen.
Hierbij wil ik hen allen bedanken.
Onverlet ieders inzet en de waardering die ik daarvoor voel, wil ik toch enkelen in het bijzonder dank zeggen.

Mijn promotor Prof. Dr. M. de Vlieger wil ik bedanken voor zijn enthousiasme, steun en zorg welke hij steeds bij de verzameling van de gegevens en bij de interim evaluaties aan de dag legde. Voor zijn opbouwende kritiek en steun bij de uitwerking tot dit proefschrift ben ik hem zeer erkentelijk.
Mijn copromotor Dr. G.E. van Zanen wil ik bedanken voor de gelegenheid die hij mij heeft gegeven om aan dit onderzoek te kunnen werken. Voor zijn constructieve adviezen, die mede de vorm van dit proefschrift bepaald hebben, ben ik hem zeer erkentelijk.
De overige leden van de promotiecommissie, Prof. K. Hoornstra, Prof. Dr. H.A.C. Kamphuisen en Prof. Dr. H.J. Neyens dank ik voor het beoordelen van het manuscript en hun kritische opmerkingen.

Dr. K.J. van Dongen dank ik voor de begeleiding die hij mij bij de beoordelingen en metingen van de CT scans bood. Zijn bereidheid om steeds van advies te dienen heb ik zeer gewaardeerd.
Drs. H.L.J. Tanghe dank ik voor zijn medewerking om dit onderzoek te kunnen afronden. Joke bedank ik voor haar niet aflatende bereidwilligheid om steeds weer CT scans op te zoeken.
De dames en heren van de afdeling Neuroradiologie die gedurende alle jaren bereid waren om tijd in te ruimen voor "mijn" patienten ben ik zeer veel dank verschuldigd. Met veel geduld bereidden zij de kinderen voor op de CT scans en besteedden zo mogelijk nog meer aandacht dan normaal aan de positionering van de patienten om optimaal vergelijkbare CT scans te verkrijgen.
Marianne wil ik bedanken voor haar steun bij het plannen van de onderzoekingen en voor het maken van de afspraken.

Joke bedank ik voor haar zorgvuldige werk en geduldige omgang met de kinderen bij het afleiden van de EEG's en voor de steun bij het coderen van de interpretaties van de uitslagen. Haar hulp bij de begeleiding van de diverse keuzepraktikanten is van onmisbare waarde geweest.

Zonder de hulp van Cees Jongkind waren de data nooit in bewerkbare vorm gekomen. Voor het wegwijs maken in de computer dank ik hem zeer.

De firma Lederle dank ik voor het ter beschikking stellen van een tekstverwerker hetgeen het schrijven een stuk gemakkelijker gemaakt heeft.

John, Joop en Hillie van de AVD dank ik voor het vele werk aan de figuren en tabellen en hun inzet om de deadline te halen.

Toos, Inge, Friederieke en Willem dank ik voor hun bereidwilligheid om mij van diverse taken te ontlasten om de voltooing van dit proefschrift mogelijk te maken.

Mijn paranymphen Friederieke en Inge dank ik voor hun nimmer aflatende steun tijdens de bewerking van dit proefschrift en voor hun enthousiasme om de aan het paranymphschap verbonden taken, in het bijzonder die in de laatste hectische maanden, op zich te nemen.

Last but not least dank ik alle kinderen en hun ouders die bij de uitvoering van dit onderzoek betrokken waren.

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