

# **CLINICAL AND DIAGNOSTIC FEATURES IN LISSENCEPHALY TYPE I**

(Klinische en diagnostische kenmerken van lissencephaly type I)

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## The End

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*It is time for me to go, mother; I am going. When in the paling darkness of the lonely dawn you stretch out your arms for your baby in the bed, I shall say, "Baby is not there!" - mother I am going. I shall become a delicate draught of air and caress you; and I shall be ripples in the water when you bathe, and kiss you and kiss you again. In the gusty night when the rain patters on the leaves you will hear my whisper in your bed, and my laughter will flash with the lightning through the open window into your room. If you lie awake, thinking of your baby till late into the night, I shall sing to you from the stars, "Sleep mother, sleep." On the straying moonbeams I shall steal over your bed, and lie upon your bosom while you sleep. I shall become a dream, and through the little opening of your eyelids I shall slip into the depths of your sleep; and when you wake up and look round startled, like a twinkling firefly I shall flit out into the darkness. When, on the great festival of puja, the neighbours' children come and play about the house, I shall melt into the music of the flute and throb in your heart all day. Dear auntie will come with puja-presents and will ask, "Where is your baby, sister?" Mother you will tell her softly, "He is in the pupils of my eyes, he is in my body and in my soul."*

Rabindranath Tagore [113]

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*Naskah promosi ini dipersembahkan kepada yang percinta Frank  
(Ibu Sri Wahyu)*

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# GENERAL INTRODUCTION

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The incentive to start this study in 1986 were two patients with lissencephaly, observed during my training as a neurologist. Such an exceptional occasion prompted an attempt to collect a large group of patients with lissencephaly type I, a rare congenital disorder, in order to increase our knowledge about epidemiology, clinical signs, neurophysiological and neuro-imaging characteristics, and genetic aspects. Thanks to the cooperation of many colleagues in departments of childneurology in the Netherlands, it became possible to collect the patients described in this thesis.

In Chapter 1 a survey of the present knowledge concerning lissencephaly is given. The differences between lissencephaly type I and type II are explained. This thesis concerns the type I only. Chapter 2 deals about the epidemiology of lissencephaly and is probably the first study about the prevalence at birth and the survival rate of lissencephaly type I. The clinical details of the patients studied are presented in Chapter 3.

The diagnostic methods in lissencephaly type I are explored in Chapter 4 (neurophysiology) and in Chapter 5 (neuroimaging). A special type of lissencephaly type I, the Miller-Dieker syndrome, has recently become related to a deletion of the short arm of chromosome 17. In Chapter 6 the details of cytogenetical and DNA-studies are described. Chapter 7 reports three patients with the Smith-Magenis syndrome, which is also characterized by a deletion of a part of the short arm of chromosome 17.



## Chapter 1

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# A SURVEY OF LISSENCEPHALY

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## DEFINITIONS

The word 'lissencephaly' is a description derived from normal embryologic development, where 'lissos' means smooth and 'encephalon' means brain. In small lower animals the lissencephalic, smooth brain without sulci, is the normal state.[89] Gyrencephaly, the presence of sulci, is characteristic for larger animals, including humans. It is peculiar to name a serious developmental disorder of the human brain after the normal state of lower animals. Some authors use the term lissencephaly for both agyria (meaning no gyri), pachygyria (meaning few gyri) as well as for polymicrogyria (meaning very small gyri). Agyria and pachygyria differ in degree only. Polymicrogyria, in which an increased number of small sulci is present, has to be distinguished from them, but combinations occur, as was reported in one of the first patients described [74] and in later reports.[91]

## DEVELOPMENT OF THE BRAIN

Normal ontogenesis of the nervous system is a complex process that can be divided in phases: neurulation; cellular proliferation and neuronal migration; maturation of cellular components, synaptic development and myelination. Neurulation refers to the formation of the neural tube, which takes place in the third and fourth week of gestation.[122]

Neuronal migration is occurring in different manners in different pathways: to the neocortex; to the cerebellum; to the corpus pontobulbare to form pontine and medullary nuclei; and to the corpus gangliothalamicum to form the thalamus and basal ganglia.[105] Migration of neocortical neurons proceeds from the germinal matrix in the ventricular zone, where proliferation takes place, to the cortical plate. This process begins at the 8th week and is for the greatest part completed after 16 weeks. According to autoradiographic studies this occurs in several waves (stage I to V) in an inside-out fashion; neurons that migrate later, migrate through neurons that have migrated earlier. The migration of neurons is guided by their

movement along glia fibres, which extend from the ventricular matrix to the cortical plate.[95] Neocortical migration can also be classified into radial-proceeding from the ventricular to the pial surface and tangential-proceeding parallel to the surface of the brain.[96] According to a model the migrating cell can move by adding new membrane components.[96] Most investigators agree that glial and neuronal cell surfaces contain binding molecules. These molecules prompt cell-to-cell binding; lack or alteration of these molecules may result in neuronal migration disorders. According to the radial unit hypothesis neurons originating from a given part of the proliferative zone form a specific cytoarchitectonic area. Probably, final organisation is reached by a combination of intrinsic genetic properties of the neurons and axonal input from the subcortical structures during migration. The findings of light and electron microscopy with Golgi impregnation in the human fetus suggests an early maturation of layer I in cortical genesis.[16] The early establishment of a pial-glial barrier and the early maturation of Cajal-Retzius cells within the marginal zone appear to be of importance in the development of the neocortex.[16] During the 6th week the cerebellar tubercle begins to grow at the rostral end of the 4th ventricle. During the 7th and 8th week the lateral limbs become paired masses on both sides of the brainstem and the lateral rhombic lips thicken rapidly. At 8 weeks cells begin to migrate along several pathways. One is directed dorsally to form the external granular layer of the cerebellum. The others follow a ventral pathway to form the pons (with the inferior olives and the pontine nuclei) and the medulla oblongata.[105]

Little is known about the intra-uterine factors, responsible for the convoluted form of the human brain. Cerebral sulci become visible at the end of the fourth fetal month and continue their development until birth.[15,18] The first sulci to appear are the primary and secondary sulci. They are relatively constant in location and configuration. The tertiary sulci begin to develop in the third trimester, appearing in a more random fashion.

From experimental studies we know that convolitional development is dependent on events in the cortex itself. The developing cerebral cortex of sheep was surgically isolated in utero at a time before the appearance of cerebral convolutions, but after the completion of cellular migration. At term all animals had cerebral sulci of normal size and configuration.[5]

Various degrees of abnormal growth of the inner and outer cortical layers may be responsible for gyral malformations. In a study based on mathematic and mechanical hypotheses, the predicted minimum intersulcal distance (= gyral thickness) is eight times the cortical thickness in normal brain, and equal to the cortical thickness in polymicrogyria. In lissencephaly the relative growth of the cortex is assumed to be smaller than normal, and the relative growth from the centre of the brain to be greater than normal. The forces in the cortex are then not sufficient to exceed the critical value necessary to form sulci, resulting in a smooth brain.[99]

## **PATHOLOGY OF NEURONAL MIGRATION**

Neuronal migration disorders can be classified as follows: lissencephaly, microgyria, verrucous dysplasia of the neocortex, heterotopia, and others.[7]

In 1975 an extensive architectonic and topographical analysis of a lissencephalic brain was given.[110] Macroscopically a smooth brain surface is seen; sometimes a few broad gyri are present. Opercularisation is absent, resulting in an absence of the Sylvian fissure. The claustrum and capsula extrema are absent. The corpus callosum is thin or absent. Sometimes midline calcifications are described. There are multiple heterotopia of the olives. Microscopically the grey mantle in agyria can be divided into four layers: the (1) molecular, (2) superficial cellular, (3) cell-sparse and (4) deep cellular layers (see Figure 5 in Chapter 3). The molecular layer is slightly thicker and more cellular in agyria than in a normal brain. The superficial cellular layer contains pyramidal and polymorphic cells identical to the normal cell layers III, V, and VI, but reduced in number. In pachygyria the superficial cellular layer contains two additional cellular sublayers: a narrow layer of small pyramidal neurons, identical to normal layer II and a deeper sublayer of small granular cells identical to normal layer IV. The cell sparse layer as well as the deep cellular layer are wider in agyria than in pachygyria and absent in the normal brain. The deep cellular layer contains non- or partially migrated neurons radially aligned in columns. This type of neuronal migration disorder is one of an extreme regularity. The pathologic layers are lying at regular distances of the cerebral surface, resulting in subsurface lines. Stewart et al. noticed that most reported cases of lissencephaly had a similar topographic distribution with an occipital predominance of agyria and some sulci present in the frontotemporal areas. He suggested that the cell-sparse zone was due to laminar cortical necrosis, resulting from hypoxia or perfusion failure. This would perhaps explain why agyria was found more often in the parieto-occipital watershed area, where ischaemia might be more severe than elsewhere. The cerebral peduncles, corticopontine and corticospinal tracts are small. The olivary nuclei are seen partly in their normal location, with heterotopic cell groups located in their migration pathway. The cerebellum is smaller than normal. The external granular layer of the cerebellum is absent. There are no Purkinje cell heterotopia.

The ratio of heterotopic neurons to those in the superficial cellular layer suggests that in lissencephaly migration is arrested at some time during the process. In agyria, there is a disturbance during stage III of neocortex formation, between the 11th and 13th gestational week. In pachygyria the disturbance occurs in early stage IV of neocortex formation, around or after the 13th week of gestation. In addition, absence of the claustrum, heterotopia of the olivary nuclei and hypoplasia or absence of the corpus callosum are developmental disturbances occurring between the 11th and 14th week [105], and so confirming their association with lissencephaly.

A quantitative analysis of the cell-densities of the cerebral cortex in a case of lissencephaly, showed that the total number of nerve cells was only slightly reduced compared to the normal brain.[101] In 1984 the above described form of lissencephaly was called classical or type I lissencephaly.[34] In contrast, type II lissencephaly shows complete loss of horizontal lamination.[34] In 1942 Walker reported such a patient with agyria and other abnormalities: hydrocephalus, microphthalmia and retinal dysplasia.[123] Microscopically the cortex was made up of masses of irregularly arranged cells. The cerebellar peduncles were small, the pyramids were practically absent and the inferior olivary nucleus was seen as an irregularly convoluted mass. In lissencephaly type I the migration to the neocortex and to the corpus pontobulbare is

especially disturbed. The involvement of the other major pathways of migration, namely in the cerebellum and to the corpus gangliothalamicum is relatively small. In type II lissencephaly glial, vascular and mesodermal proliferation is found in addition to migration disturbances.[37] Microgyria refers to small gyri. This term is synonymous with polymicrogyria. Histological abnormalities in layer formation are seen, showing four layers. The etiology of polymicrogyria is heterogeneous.

## CLASSIFICATION AND CLINICAL SIGNS

The first two cases of lissencephaly were reported by Erhardt [43] and Culp.[21] They described two cases, one of which had been described before by Matell.[74] Matell described a brain which has to be classified with our present knowledge in mind as a combination of pachygyria and polymicrogyria. The patient was a microcephalic 27 year old woman, who had suffered from seizures since the age of two years. She learned to read and write, but soon lost these capabilities. She died from a status epilepticus. Most of the later publications - until 1970 - are case reports, in which lissencephaly was diagnosed at autopsy.[9,20,28,41,57,63,65,69,81,126] The children were microcephalic, severely retarded, and suffered from seizures; most of them died before the age of two years, often from pulmonary tuberculosis or another infection. Their brains were small showing agyria or pachygyria, absence of the claustrum and capsula extrema, sometimes absence or hypoplasia of the corpus callosum and heterotopia of the inferior olives. Six patients became older, 5 to 11 years of age; they showed pachygyria rather than agyria. Kulczycki described four patients: a girl of 4 months with agyria, a girl of 6 years with pachygyria and two patients with focal polymicrogyria, a man of 53 years old and a boy of 5 years old.

In 1963 Miller reported two siblings with lissencephaly whose parents were not consanguineous. Both children, a girl and a boy, were microcephalic and had similar dysmorphisms of the face. They were cyanotic, failed to thrive and were retarded in motor development. The girl died at the age of 3 months, the boy at 4 months. Autopsy showed in addition to the lissencephaly abnormalities of heart, kidney and gastrointestinal tract. In 1969 Dieker et al. described a 'lissencephaly syndrome' in four patients, resembling the patients reported by Miller. These four patients included two described previously.[24] One case was sporadic, but the other three were related, two brothers and a female cousin.

Jellinger and Rett [61] described the clinical features of four patients with agyria, three with pachygyria and one with a combination of agyria and pachygyria. All except one were microcephalic, and had mental retardation, facial anomalies, feeding difficulties, hypotonia and subsequent seizures. They postulated several possible etiologic factors in lissencephaly, either hereditary, environmental or an intrauterine perfusion disorder. In 1978, two sisters were described with lissencephaly.[48] The diagnose was made at autopsy in the first, and in the second child by the CT scan. The term 'Miller-Dieker Syndrome' (MDS) was introduced, to distinguish the so-called autosomal recessive form of lissencephaly from other types of lissencephaly.[62] The clinical manifestations of the MDS are the following: polyhydramnios,



postnatal growth deficiency, profound mental retardation, early hypotonia, later hypertonia, opisthotonus, seizures, microcephaly, relatively high forehead, bitemporal hollowing, wrinkling of the forehead, wide nasal bridge, epicanthal folds, anteverted nares, micrognathia, ear anomalies, cardiac defects, polydactyly, syndactyly, and other visceral anomalies. In 1984 Dobyns et al. began classifying lissencephaly and separated classical or type I lissencephaly from type II lissencephaly.

All patients with the Miller-Dieker Syndrome (MDS) have a type I lissencephaly. Patients with only a type I lissencephaly without facial dysmorphisms or other somatic abnormalities as described in the MDS are classified as Isolated Lissencephaly Sequence (ILS). Dobyns proposed a severity scale for lissencephaly type I. Grade 1 meant no sulci, grade 2 some sulci visible and grade 3 a mixture of agyria and pachygyria. All MDS patients apparently had a lissencephaly grade 1 or 2.[33] However other authors disagree and include also patients with focal pachygyria and polymicrogyria in the MDS.[2,120]

Some patients with lissencephaly type I do not fit in either the MDS or the ILS.[1,67,91,98,100] They are actually classified as lissencephaly type I in association with: spastic paraplegia, turriccephaly, hare lip, spina bifida, club feet, hypertelorism, abnormally high crossing of the pyramidal tract, hypodontia and a polyarthritis-like condition. This might be a heterogeneous group of patients, which needs further classification. Lissencephaly type I and a normal brainstem (without heterotopia of the olives) was described by Norman et al in 1976.[85] Dobyns et al.[33] proposed to use the eponym Norman-Roberts for this syndrome, despite the absence of more reports of this condition. It is further important to realize that some cases reported as lissencephaly are related to intra-uterine cytomegalovirus infection. These patients show diffuse calcifications with polymicrogyria.[85]

Type II lissencephaly is combined with hydrocephalus, sometimes an encephalocele, and abnormalities of eyes and muscles. Dobyns et al.[34] initially proposed the eponym (after the first two authors) Walker-Warburg Syndrome (WWS).[123,124,125] Familial recurrence was reported by Chemke et al.[14] and by Pagon et al.[90]; the latter introduced the term HARD +/- E syndrome (Hydrocephalus, Agyria, Retinal Dysplasia, with or without an Encephalocele). Krijgsman et al.[68] and Damska et al.[22,23] reported the combination of lissencephaly type II with congenital muscular dystrophy; it was named COMS (Cerebro-Oculo-Muscular Syndrome). In a recent review the diagnostic criteria for the autosomal recessive Walker-Warburg syndrome were expanded with congenital muscular dystrophy and cleft lip or palate.[39] Another syndromal combination of lissencephaly is the autosomal recessive Fukuyama-type Congenital Muscular Dystrophy (FCMD). It was originally reported almost exclusively in Japan.[47] It shows widespread pachygyria combined with polymicrogyria and small areas of agyria. There are some other rarer forms of lissencephaly: Cerebro-Cerebellar-Lissencephaly (CCL) [6,33], and the Neu-Laxova-Syndrome (NLS).[33] Both syndromes probably have an autosomal recessive inheritance.

## GENETIC STUDIES

Initially, MDS was considered to be an autosomal recessive disorder. The observation of an enlarged short arm of chromosome 17 (17p) in unbanded metaphases of one child was at that time interpreted as a normal variant, also occurring in the healthy father and some other relatives.[30] Jellinger and Rett [61] subsequently also found a slight enlargement of chromosome 17p in a patient with lissencephaly; the significance of this finding remained unexplained. In 1983 Dobyns et al. described a ring chromosome 17 in one patient with MDS and in another a partial monosomy 17p13. using high-resolution banding. In a review of lissencephaly type I, Stratton [111] proposed that monosomy 17p13.3 was the possible cause of the MDS in eight patients instead of an autosomal recessive inheritance. Six additional MDS patients with a deletion of 17p were described.[10,49,51,52,104] However some MDS patients had no microscopically detectable deletion of 17p even in high resolution banding preparations [31], which might suggest a submicroscopical deletion. The relation between microscopical and submicroscopical deletions in MDS was addressed by Van Tuinen et al.[119] and Schwartz et al.[103,119] A molecular dissection of the critical region of 17p, was done using a human cell panel, including hybrids obtained from three MDS patients. Three DNA markers, YNZ22.1 (D17S5), YNH37.3 (D17S28), and 144-D6 (D17S34), were deleted in four patients with microscopically visible deletions. Two MDS patients with normal chromosomes also showed deletions for the probes YNZ22.1 and YNH37.3.[103] The latter findings were confirmed in three other MDS cases with normal chromosomes.[119] (Chapter 6)

The cause of ILS is unknown, but probably heterogeneous. Proposed mechanisms were viral infection or maternal uterine bleeding during pregnancy [32], attempted abortion [20], or medication.[75,87] There is one report of a family with three affected brothers with ILS.[93] Autopsy was performed in one patient and was typical for type I lissencephaly grade 3, except for the unusual six-layered cortex in temporal and occipital regions, and the absence of olivary heterotopia. Another ILS patient with a lissencephaly grade 2 was born from first cousins. Descriptions of affected sibs of type I lissencephaly with unusual associated signs might also give the impression of an autosomal recessive inheritance.[1,85,91,98] Another hypothesis is a deletion within the critical region for the Miller-Dieker syndrome. This may fit in the concept of a contiguous gene syndrome, where the cause of ILS is hypothesized to be the expression of involvement of less genes than in the MDS.[106] It is likely to suppose a gradual transit from lissencephaly grade 1 to 4. However, until now no deletion at the chromosomal or DNA-level has been found in patients with ILS.

## **EPIDEMIOLOGY**

Epidemiologic data on lissencephaly are not available. Crome [20] observed ten cases of polymicrogyria and two of pachygyria in a consecutive autopsy series of 137 microcephalic brains. Untill recently, no large series of lissencephaly were described.[40]

This raises the impression that lissencephaly is a rare disorder.



## Chapter 2

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# EPIDEMIOLOGY OF LISSENCEPHALY TYPE I

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## INTRODUCTION

Lissencephaly is a rare developmental disturbance of the cerebral cortex, with either an absence or reduction of cerebral sulci. When the developmental disturbance manifests in early pregnancy (11th-13th week) the sulci are lacking, and when it occurs by the end of the 13th week pachygyria results. In the normal situation more than 30 sulci are present in the newborn.[15] The amount of sulci in lissencephaly is expressed in grades 1 to 4, grade 1 meaning no sulci and grade 4 about 10 sulci.[26,33] The development of the Sylvian fissure is always disturbed in lissencephaly. Two types (I, II) of lissencephaly, are recognized.[32] In type I, facial dysmorphisms (bitemporal hollowing, midfacial hypoplasia, short nose with upturned nares, micrognathia, and furrowing of the forehead) is seen in varying degrees.[38] These patients exhibit the Miller-Dieker Syndrome (MDS), caused by a (submicroscopical) deletion of the short arm of chromosome 17 [71]; the others have the Isolated Lissencephaly Sequence (ILS) or unclassified forms. In type II lissencephaly, hydrocephalus and dysgenesis of the cerebellum are also present in combination with abnormalities of the eyes and muscles.

The diagnosis of lissencephaly during life is based upon CT or MR scan findings by using the criteria described by Dobyns and McCluggage (1985).[36] The prevalence of and the risk factors for lissencephaly are largely unknown. This study tries to establish the prevalence at birth of lissencephaly type I in the Netherlands during 1980-1988. The determinants in time and space, the duration of survival and possible predictors of survival are also studied.

## MATERIAL AND METHODS

### Data collection

From March 1986 until December 1989 all patients with lissencephaly in the Netherlands were searched for. This was achieved by individually questioning all child neurology departments, the

clinical genetic centres, and institutions of the mentally retarded. With the parent's consent, medical records were obtained and all patients were examined. In this way 51 possible cases were notified, of whom 22 fulfilled the criteria for lissencephaly type I, and became the subject of this study.

### **Diagnosis**

All diagnoses were reanalysed by reviewing the CT or MR scan or data obtained at autopsy. The diagnosis was made by CT scan in 20 patients and by autopsy in 2 patients. Depending on the number of macroscopically visible sulci, patients were divided into two groups: 11 patients with a grade 1 or 2 (complete agyria and almost complete agyria), and 11 patients with a grade 3 or 4 (combination of agyria with pachygyria and complete pachygyria) lissencephaly.

### **Data analysis**

Data on 22 patients with lissencephaly type I were collected. Three cases born before 1980 were excluded when calculating the prevalence at birth, because criteria for CT scan diagnosis of lissencephaly were not described before 1979.[48] In 16 (73%) of the total series of 22 patients, the diagnosis was made before the age of 13 months. In 16 (84%) of the 19 patients born after 1980, the diagnosis was made before the age of 13 months. Therefore, in calculating the prevalence at birth at least one year of follow-up was necessary. Patients born after January 1989 were excluded for this reason. The prognosis for survival is based on all patients who entered the study, regardless of their date of birth. The 5 year survival rate was calculated by hand according to Kurtzke et al.[70] Patients were observed until death or as long as they were alive during the follow-up period, varying from 1 month to 10 years and one month (mean : 5 years). No patients were lost in the study and 110 patient years could be observed.

### **Clinical characteristics**

The criteria from Dobyns et al.[32] were used to classify the patients. Four patients were classified as having the Miller-Dieker Syndrome, the remainder (18 patients) as having the Isolated Lissencephaly Sequence. The clinical characteristics of 21 patients in this series have been described earlier.[26] In three of the MDS patients a small deletion of the short arm of the chromosome 17 was searched for and confirmed.[27]

### **Family histories**

Family histories were detailed for three generations, with special attention to epilepsy, neural tube defects, leukaemia and breast tumours. The latter information was sought because of the localisation of oncogenes, related to leukaemia and breast tumor, in the close vicinity of 17q21-22 and 17p13.3 on chromosome 17.[25,73] This was done by questioning the parents. The results were compared to the prevalence in the Dutch population.[44]

## RESULTS

### Prevalence

The overall prevalence at birth of lissencephaly type I in the Netherlands in the period 1980 until 1988 amounts to 12 per million births (Table 1). The 22 patients with lissencephaly consisted of 11 males and 11 females.

### Determinants in space

The majority of patients were living in the most densely populated areas of the Netherlands.

### Survival

The 5 year survival rate of patients in this study was 74% (Table 2). No data about the 5 years survival rate in patients with lissencephaly were available in the literature. Patients with the MDS often die before the age of 2 years, but patients with ILS may live longer.[38] In this study 7 patients died at ages from one month to 9 years, with a mean of 3,5 years. The causes of death were intractable seizures or infections.

**Table 2. Life table for patients with lissencephaly type I born in the Netherlands.**

Years	N	Deaths	WA	At risk	Pd	1-Pd	Cum. 1-Pd
0-1	22	3	0	22.0	0.136	0.864	0.864
1-2	19	0	1	18.5	0.000	1.000	0.864
2-3	18	0	2	17.0	0.000	1.000	0.864
3-4	16	1	2	15.0	0.067	0.933	0.806
4-5	13	1	1	12.5	0.080	0.920	0.741
5-6	11	0	1	10.5	0.000	1.000	0.741
6-7	10	1	3	8.5	0.118	0.882	0.653
7-8	6	0	1	5.5	0.000	1.000	0.653
8-9	5	0	3	3.5	0.000	1.000	0.653
9-10	2	1	0	2.0	0.500	0.500	0.328
10-11	1	0	1	0.5	0.000	1.000	0.328

N : number of patients  
 WA : withdrawn alive  
 Pd : proportion of death  
 1-Pd : proportion of surviving  
 Cum. 1-Pd : cumulative survival

**Table 1. Prevalence of lissencephaly type I per 1000.000 births in the Netherlands.**

Year	Female	Male	Total
1980+1981	8.3	5.5	13.8
1982+1983	8.7	11.6	20.3
1984+1985	0.0	2.8	2.8
1986+1987	10.7	2.7	13.4
1988	0.0	5.3	5.3
1980-1988	6.5	5.5	12.0

### Predictors of prognosis

The 5 year survival of the 11 grade 1/2 patients is 54% against 91% for the 11 grade 3/4 patients (Figure 1). The severity of the lissencephaly clearly determined prognosis, with a tendency towards a longer survival in the grade 3/4 patients.

### Family histories

No abnormal prevalences were found for epilepsy, leukaemia, and breast tumours. A high prevalence (4 cases) of spina bifida in the families was suggested, but only among third degree relatives. Parental consanguinity as established by the family history method was not observed in this study. There were no recurrences among siblings. However, within the 22 families only 9 healthy children were born after the

birth date of the patient; the total number of siblings of patients was 17.

The paternal age ranged from 21 to 42 years with a mean of 30,7 and a median age of 30. The maternal age ranged from 17 to 40 years with a mean of 28,6 and a median of 29. The mean paternal age for the general population in the Netherlands is 30 years, and the mean maternal age is 28 years.[44]

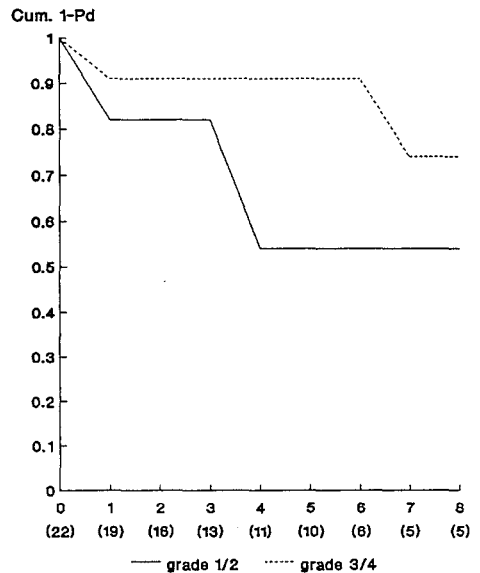
## DISCUSSION

There are no exact data on the prevalence of lissencephaly type I. Dobyns reported about 100 cases from the literature.[38] Over 60 of these cases were type II lissencephaly. Other publications deal with 39 additional cases with lissencephaly type I.[12,29,49] The present study revealed for the first time a prevalence at birth of 12/1000.000, for the type I lissencephaly. Recent data from a regional registration in Europe of congenital malformations [44] gave a prevalence of 5,5/1000.000, for lissencephaly of unidentified type. In a rare disorder, the completeness of ascertainment in a population may be expected to rely upon completeness of diagnosis, referral and reporting, the availability of CT scans and the autopsy rate in mentally retarded children. In the past only one pathology study mentioned 2 brains with pachygyria in a series of 137 microcephalics.[20]

Patients with a grade 1/2 lissencephaly have a worse prognosis than grade 3/4 (Figure 1). This might be expected, from the more severe disturbance of the cortex in grade 1/2 lissencephaly as compared to grade 3/4 lissencephaly. The family histories of lissencephaly patients showed a relatively high number (n=4) of spina bifida patients in third degree relations. This seemed noticeable, since only 3 relatives with epilepsy, a much more common disease, were mentioned in these families. However, the occurrence of spina bifida only in third degree relatives reduces the likelihood of a relation between neural tube defects and lissencephaly. Embryological insights [122] make a relation between neural tube defects and neuronal migration disorders unlikely.

The etiology of lissencephaly type I is generally unknown. No intoxications during pregnancy were mentioned. Most of the patients with MDS have been related to a deletion of the chromosome 17p.[119] This can be caused by a spontaneous deletion, translocation in one of the parents [111] or a germ cell mosaicism.[54] In the ILS patients a chromosomal cause has so far not been found.

Figure 1: Survival for patients with grade 1/2 lissencephaly and grade 3/4 lissencephaly. Number of survivals in parenthesis





# DIAGNOSTIC FEATURES AND CLINICAL SIGNS IN 21 PATIENTS WITH LISSENCEPHALY TYPE I

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## INTRODUCTION

There are at least two types of lissencephaly, according to Dobyns et al.[32], called type I and type II. This study is concerned mainly with type I (Table 1).

### Histology

In type I lissencephaly (sometimes called classical four-layered lissencephaly) the neocortex formation is severely disturbed. This results in a cortex consisting, from inside to outside, of heterotopic non-migrated neurons, a cell-sparse layer, components of layer III, V and VI combined, and a molecular layer. On the outside there is agyria. In pachygyria, small

cellular II and IV layers are found.[110] In agyria, neuronal migration is disturbed between the 11th and 13th week of pregnancy, stage III of neocortical development according to Sidman and Rakic.[105] Pachygyria is presumed to result from a disturbance of neocortex formation after the 13th week but before completion of neuronal migration (stage IV). Often agyria and pachygyria are combined in one brain. Type II lissencephaly is characterized by an almost complete absence of cortical layer formation. It features other cerebral malformations (hydrocephalus, Dandy-Walker malformation and disturbed myelination), combined with abnormalities of the eyes and the muscular system.[34]

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**Table 1. Classification of lissencephaly\***

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### Type I

Isolated Lissencephaly Sequence [ILS]  
Miller-Dieker Syndrome [MDS]  
Non-classified forms

### Type II

Walker-Warburg Syndrome [WWS]  
Fukuyama Congenital Muscular Dystrophy  
Non-classified forms

### Rare forms

Neu-Laxova Syndrome [NLS]  
Cerebro-Cerebellar Syndrome [CCS]

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\* Dobyns et al. 1984 [32]

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### Gross brain morphology

In clinical studies the term lissencephaly is often used for both agyria (meaning no gyri) and pachygyria (meaning few and broad gyri). Dobyns et al.[33] proposed a classification of lissencephaly into three degrees of severity facilitating a correlation of clinical findings

according to pathology and radiology. Because of the close relation between agyria and pachygyria we have added pachygyria to this classification (Table 2).

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**Table 2. Classification of lissencephaly type I according to pathology and radiology\***

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Grade 1: complete agyria  
Grade 2: agyria with some sulci  
Grade 3: a mixture of about 50% agyria and 50% pachygyria  
Grade 4: complete pachygyria

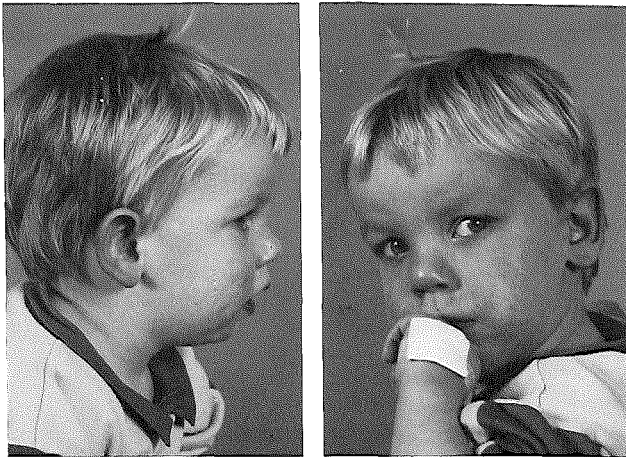
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\* Modified after Dobyns et al. [33]

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**Figure 1. Patient 1, a boy with ILS grade 4, age 3 years: high forehead only, no other facial dysmorphisms.**



### Somatic and facial dysmorphology

Lissencephaly type I, is classified as Miller-Dieker syndrome (MDS) if typical facial and somatic dysmorphic features are present and as isolated lissencephaly sequence if only secondary facial dysmorphisms are found. Sometimes patients with MDS lack somatic dysmorphic features.

### Cytogenetics

In MDS a mini-deletion of the short arm of chromosome 17 is found on prophase chromosome analysis, but this deletion may be too small to be detected under the microscope. Detection of a deletion at the DNA-level in some

cases [103,119] suggests that MDS is always related to a deletion of the short arm of chromosome 17.

### Present study

This study presents 21 children with lissencephaly type I, the largest series reported until now. The clinical characteristics are compared with 55 cases described with sufficient detail in the literature.[2,10,13,19,20,28,30,31,32,41,42,48,51,52,53,57,58,61,62,63,76,80,81,83,85,87,110,117,127,129]

## PATIENTS AND METHODS

A multicentre co-operative study was conducted with the co-operation of all child neurology departments in The Netherlands, so that a nation-wide survey of known children with lissencephaly type I (21 patients) could be made. Lissencephaly was diagnosed by autopsy (2 patients) or by CT scan (19 patients). More precise confirmation was obtained by MRI in five patients and by autopsy in another four. Thus the criterion for inclusion in the study was an abnormal CT or autopsy confirmation of lissencephaly type I.

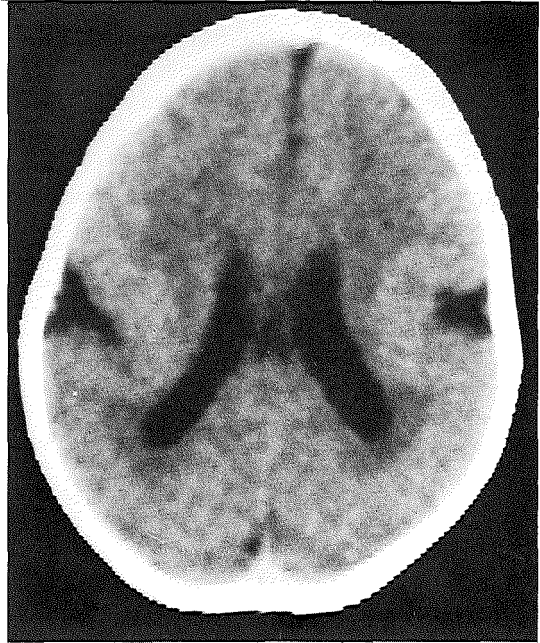
In diagnosing lissencephaly on CT scan, the criteria of Dobyns and McCluggage[33] were followed. In lissencephaly type I the brain surface is smooth and there is no Sylvian fissure, so the brain is shaped like a figure-8. At the same time there is a sharp demarcation between grey and white matter, depending on the severity of lissencephaly. In complete agyria there are no sulci; in grade 2 four sulci are visible, at most; in grade 3 four to six sulci are found, with sometimes a beginning of the formation of the Sylvian fissure. In pachygyria at most ten sulci are seen in all the regions of the brain, but clearly less than the normal number. In all CT scans, the grey matter is relatively enlarged and colpocephaly is seen. Corpus callosum hypoplasia is variably present and occurs mostly in lissencephaly grade 1 and 2. Representative cases are described below.

### Case reports

#### *Patient 1*

This boy with ILS grade 4 (pachygyria) was the second child of unrelated parents; their first child was a healthy girl. He was born at term after an uneventful pregnancy and delivery. His length, weight and head circumference were all on the 50th percentile. His development at the age of 10 weeks seemed to be retarded. An EEG at four months showed unusually high voltages in the beta frequencies. At the age of eight months a CT scan was interpreted as showing cortical atrophy, with widened ventricles. A second EEG at the age of 13 months showed diffuse beta activity of high voltage. At the age of 25 months the boy had periods of head-banging, jerking and losing contact with his environment. He was treated with sodium

Figure 2. Patient 1: CT scan showing thick cortex with open Sylvian fissure and colpocephaly: some sulci are visible.



chromosome 17p13.3. The karyograms of the parents were normal. The girl is now 36 months of age and she has frequently suffered respiratory tract infections. Generalized seizures started at the age of six months, which are at the moment reasonably well controlled with phenobarbital and phenytoin. Her development does not improve; she has no head control and there is no visual tracking.

#### *Patient 21*

This girl with clinical MDS but no 17p deletion was the first-born of parents who were related 10 generations ago. Two children with a spina bifida had been born in the father's family. The pregnancy was complicated by slight hypertension. The girl was born, without complications, at 41 weeks. Head circumference, weight and length were on the 50th percentile. Apart from two sacral dimples, there were no other abnormalities. At age three months there was no ocular fixation or tracking, there was head-lag and hypotonia with extensor plantar reflexes. Routine blood, urine and cerebral spinal fluid analyses were normal. There were no signs of congenital infections. CT showed classical type I lissencephaly with colpocephaly and a complete lack of sulci. High-resolution chromosome studies in the prophase were normal. Later, the girl had periods of jerking, especially of the arms, for which she was treated with phenobarbital. At age 25 months she still had severe head-lag, did not roll over, and made only little eye contact. Her head circumference was 45 cm; she had become microcephalic, with bitemporal hollowing and retrognathia.

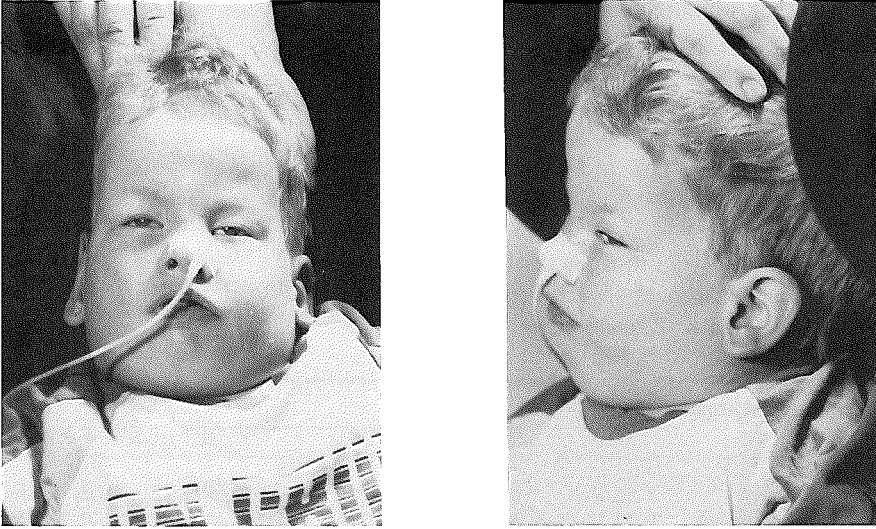
Figure 5. Patient 2: abnormal cerebral cortex with layer of ganglion cells (a) followed by cell-sparse layer (b) and columns of non-migrated neurons (c) (Bodian staining).



## RESULTS

The diagnoses of the patients studied in our series and those previously described are summarized in Table 3. To allow comparison of diagnostic techniques, we separated patients studied with standard chromosome banding techniques from those analyzed with high-resolution techniques. All the chromosome deletions were found in MDS patients. Table 4 lists the clinical signs in the patients studied in the present series. Ten patients had lissencephaly grade 1 or 2, four of whom had MDS. The other 11 had lissencephaly grade 3 or 4 (six grade 3, five grade

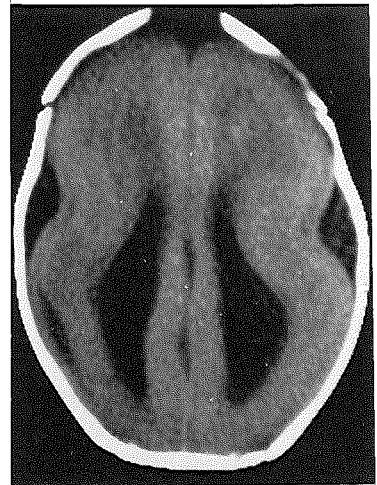
Figure 6. Patient 7, a girl with MDS: peculiar face with a high forehead, bitemporal hollowing, and micrognathia.



4). Table 5 compares the clinical findings of the ILS patients with proven normal prophase chromosomal studies from Table 3 with those of patients who had a deletion of the short arm of chromosome 17 (our study and the literature combined). We did this to compare the clinical signs of patients with lissencephaly, with and without microscopically visible chromosome 17 deletion. Patients with a 17p deletion have more facial dysmorphisms than those with lissencephaly without 17p deletion. Table 6 summarizes the somatic abnormalities in patients with 17p deletion. Table 7 compares ILS patients with and without prophase chromosomal studies in this series with patients described in the literature. The most striking feature is that microcephaly does not always occur.

In the literature, only 18 patients with MDS had a proven deletion of chromosome 17p, but chromosome studies were inadequate for 14 of the other patients with clinical MDS. Two patients have been described with MDS and normal chromosomes studied in the prophase: these are patients 2 and 6 of Dobyns et

Figure 7. CT scan of patient 7: no sulci, characteristic figure-of-eight appearance, with colpocephaly.



al.[32] Patient 2 was considered to have MDS, although the features were less pronounced than in other cases and there were no other somatic abnormalities.[31,32] Patient 6 was the only MDS patient without microcephaly.[32] There were two MDS patients in our series (13 and 20) with normal chromosomes in the prophase. We also classified patients 7, 14 and 20 as MDS, because patient 7 had syndactyly of the toes, patient 14 had corneal clouding and patient 20 had two sacral dimples, beside the lissencephaly. In addition to these somatic abnormalities, these patients had clearly dysmorphic faces. Patient 13 was classified as MDS because of severe facial dysmorphism, but without other somatic abnormalities.

**Table 3. Patients diagnosed on basis of clinical signs**

	Present series	Literature
ILS patients	17 (13)*	21 (2)
MDS patients	4 (3)	34 (20)
Deletion 17p	1	18

\* Numbers in parentheses indicate patients studied with high resolution chromosome binding.

**Table 4. Clinical aspects of patients.**

	MDS				ILS grades 1+2					ILS grades 3+4											
Case number	7	13	14	20	2	5	10	12	17	21	1	3	4	6	8	9	11	15	16	18	19
Age (mths) last report	36	61	1*	25	6	73*	48*	99	41	34	68	57	91	81	93	122*	27	7*	72*	24	87
Age (mths) last seizure	6	6	1	3	2	5	3	2	5	5	25	5	39	8	5	5	3	5	2	1	5
Epilepsy <6 mths	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+
Infantile spasms	-	-	-	-	-	+	-	-	+	+	-	+	-	-	-	+	-	+	-	+	-
Growth deficiency	+	-	+	-	-	+	-	-	+	+	+	-	-	-	+	-	-	+	-	-	+
Recurrent infections	+	-	-	-	-	+	-	+	-	+	+	-	-	-	-	+	-	+	-	-	+
Hypotonia	-	+	+	+	+	-	+	+	-	+	-	+	+	-	-	+	+	+	+	-	+
Spasticity	+	-	-	-	-	+	-	+	-	+	+	-	-	+	+	-	+	+	+	+	-
Microcephaly	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	-
Bitemporal hollowing	+	+	-	+	-	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-
Micrognathia	+	+	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
Malformed ears	-	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Karyotype in prophase	**	~	-	#	~	#	-	#	~	~	~	#	-	-	#	-	#	#	-	~	~

\* These patients have died

\*\* 46XX 17p-;

~ 46XY;

# 46XX

## DISCUSSION

Four main points for discussion emerge from this study. The first is that ILS is apparently much more common than MDS in the present study. Only two other studies suggest this [29,49], but neither study permits division into grades 1 to 4. The second point is that there tend to be more severe abnormalities in gross brain morphology in MDS than in ILS. All patients with MDS in our study and all except one in the literature [110] had lissencephaly grade 1 or 2, whereas in ILS the grades are from 1 to 4. The less severe grades probably occur more often than has been

supposed hitherto. The third point concerns the clinical picture, about which the following observations can be made.

**Table 5. Clinical signs of patients with prophase chromosomal studies in present series and literature.**

	17p deletion (N=19)	ILS grades 1 + 2 (N=7)	ILS grades 3 + 4 (N=9)
Age (mths) last report (mean)	5-54 (21) (N=7)	2-99 (46) (N=6)	7-93 (57) (N=8)
Age (mths) at death (mean)	3-47 (13) (N=12)	6 (N=1)	7 (N=1)
Retardation	19	7	9
Age (mths) first seizure (mean)	0-7 (3)	1-6 (4)	1-39 (10)
Epilepsy <6 mths	12	5	6
Infantile spasms	5	3	4
Growth deficiency	14	4	5
Recurrent infections	8	2	3
Hypotonia	13	3	5
Hypertonia	12	4	4
Microcephaly	19	7	6
Bitemporal hollowing	14	5	1
Micrognathia	17	3	2
Malformed ears	16	3	0

### **Pregnancy**

Polyhydramnios was only noticed twice in the group of lissencephaly patients described in this study. Maternal age at the time of delivery was between 17 and 40 with a mean of 28 years.

### **Facial dysmorphisms**

Dobyns et al.[32] were the first to describe ILS. According to those authors, facial dysmorphism is less conspicuous in patients with ILS than in those with MDS, who also have more specific facial dysmorphisms, like wrinkling of the forehead. In our study, facial dysmorphism was seen most frequently in MDS patients, followed by grades 1 and 2 ILS and finally by grades 3 and 4 ILS. However, no facial dysmorphism was specific to MDS. Microcephaly is almost always present in MDS and lissencephaly grade 1 and 2. All of our MDS patients were microcephalic, and in the literature, there are only three patients with lissencephaly grade 1 and 2 who were

not microcephalic (patient 1 of Harper [58]; patient 6 of Dobyns et al. [32], patient 2 of Motte et al.[80] Only one patient with lissencephaly grade 4 was not microcephalic (patient 6 from Jellinger and Rett.[61] From the present study, it appears that 36 percent of patients with lissencephaly grades 3 and 4 might not be microcephalic. Remarkably few ILS patients reported by Gastaut et al.[49] and Dhellemmes et al.[29] were microcephalic: five of 14 (36 percent) in the former study and three of 10 (30 percent) in the latter. This suggests that those two studies included more patients with lissencephaly grades 3 and 4 than with grades 1 and 2.

We conclude that neither microcephaly nor facial dysmorphism can be considered specific to either MDS or ILS, but microcephaly in combination with facial abnormalities should increase suspicion of MDS.

### Distinction between ILS and MDS

It is clear from Table 3 that our series contains more ILS patients with adequately performed chromosome analysis, whereas the literature contains many more MDS patients. Only two patients with ILS and normal chromosomes in the prophase have been well described (patients 7 and 8 of Dobyns.[32] We describe 13 patients with clinical ILS and normal prophase chromosomal studies. The distinction between ILS and MDS is made on clinical grounds, because MDS patients have more facial dysmorphisms and in most cases also have somatic abnormalities.

Table 7. Clinical signs of ILS patients in present series and in literature.

	ILS grades 1 + 2		ILS grades 3 + 4	
	Present series (N=6)	Literature (N=13)	Present series (N=11)	Literature (N=8)
Retardation	6	13	11	8
Age 1st seizure (mean)	1-6 (4)	0-18(16)	1-39 (9)	0-36 (8)
Epilepsy < 6 months	6	8	8	6
Infantile spasms	3	8	4	3
Growth deficiency	3	3	4	2
Recurrent infections	3	5	4	3
Hypotonia	4	3	7	3
Spasticity	2	6	6	5
Microcephaly	6	11	7	7
Bitemp. hollowing	2	7	1	1
Micrognathia	0	4	1	1
Malformed ears	1	2	0	0

Table 6. Somatic signs of 19 patients with a deletion 17p.

	N
Malformed fingers	8
Congenital heartdefect	8
Sacral dimple	7
Cryptorchidism	4
Malformed kidneys	3
Corneal clouding	1
Duodenal atresia	1

### Age

Patients with lissencephaly may live longer than was previously thought. Our oldest patient died at the age of 10 years, and six other patients were aged six years or more. It has been thought that the majority of these children will die before the age of two years.

### Retardation

All the children in this study were severely retarded. Those with lissencephaly grades 1 and 2 are bed-bound and have little



contact with their environment. Patients with a grades 3 and 4 also are severely retarded but have some contact with their environment, and some are able to crawl. The majority cannot speak, but some of the patients with a pachygyria can say one or two simple words. These findings are in agreement with other reports in the literature.

### **Epilepsy**

Eighteen of our 21 patients (86% percent) developed epilepsy early, before the age of six months, and about one-third have infantile spasms. Patients with lissencephaly grades 3 or 4 may have their first epileptic attack later than those with grades 1 or 2. It is important to realize that the absence of epilepsy does not exclude lissencephaly, but lissencephaly without epilepsy is uncommon. These patients' EEGs showed some more or less characteristic patterns.[27] The different occurrences of microcephaly and epilepsy may be explained by the difference in relative frequency of lissencephaly grades 1 and 2 compared with grades 3 and 4, in the literature and in our series. We presume that grades 3 and 4 has been under-represented in the literature published so far. As long ago as 1956, Crome suspected that pachygyria would be much more frequent than agyria, but this has never received much attention in clinical studies.

The fourth main point for discussion referred to above is the chromosomal and genetic aspects. We were interested to correlate the size of the deletion in MDS with the clinical symptoms. There are 19 well-described patients with a deletion of chromosome 17p (Table 3), 18 in the literature and our patient 7. Their somatic abnormalities are shown in Table 6. Thirteen of these patients had an unbalanced translocation, two had a ring-chromosome and only four had an isolated deletion of the short arm of chromosome 17. This situation makes it difficult to describe the signs of an isolated deletion of 17p. Of the four patients with an isolated 17p deletion, two had a deletion of 17p13. (patient 1 of Bordarier et al.[10]; patient 1 of Cordes et al.[19] The third as patient 5 of Dobyns et al.[32] and Stratton et al. [111], and the fourth was our patient no. 7 (see case report). Chromosome analysis of Dobyns and colleagues' patient 5 showed a deletion of 17p13.1 [111], and in our patient 7 there was a deletion of 17p13.3. Patient 5 described by Dobyns [32] and the patient described by Bordarier et al.[10] had a sacral sinus in addition to the lissencephaly. The patient described by Cordes et al.[19] showed bilateral cryptorchism in addition to lissencephaly. These signs are very non-specific. More case histories are needed to establish the minimum number signs caused by the smallest possible deletion of 17p13.3 associated with lissencephaly.

In our study, the chromosomes of the parents of three MDS patients were normal. Patients with clinical MDS and normal prophase chromosomes are mentioned in the literature, but not extensively described, and they may have had a submicroscopical deletion. This may also apply to patients 13 and 21 in our study, who both fitted the MDS criteria. In future, DNA analysis may detect these hidden deletions.[103,119] Patients with lissencephaly grades 1 or 2 and submicroscopical deletion of chromosome 17p may have few symptoms of MDS, so some cases classified as ILS may prove to be MDS after DNA analysis. In the literature one patient with a deletion 17p in prophase chromosome analysis did not have somatic abnormalities (patient 2 of Garcia et al.[48] This stresses the need for further investigations to facilitate separation

of these two conditions. The occurrence of ILS has been considered an isolated event and no family with more than one child with ILS has been found. Consanguinity between parents of an ILS patient was mentioned by Dobyns [37], and he suggested the possibility of autosomal recessive transmission. More family studies are needed in to judge the risk of recurrence of ILS in one family, but the data obtained in our series do not support the suggestion of an autosomal recessive transmission.

#### **Unclassified forms of type I lissencephaly**

Apart from MDS and ILS other conditions are known who feature lissencephaly type I together with other signs, as yet unclassified.[1,83,91,98] This is probably a heterogeneous group of patients. In addition to the lissencephaly type I, they had such signs as severe spastic paraplegia, hypertelorism, turricephaly, spina bifida, club feet, cleft palate and congenital nephrosis. Unfortunately none of these cases was studied with special chromosome techniques to detect a small deletion.

We conclude that the diagnosis of lissencephaly can be made with confidence on combined clinical and neuroradiological grounds together. Moreover, clinical distinction between MDS and ILS is possible and most cases can be classified as one or the other before the results of the chromosome analysis become known. For the small group of patients for whom it is very difficult to decide, DNA analysis may offer the opportunity to make a more exact distinction.

# EEG AND EVOKED POTENTIALS IN A SERIES OF 21 PATIENTS WITH LISSENCEPHALY TYPE I

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## INTRODUCTION

Lissencephaly is a disturbance in the neuronal migration toward the neocortex resulting in a total or partial absence of sulci. The patients are often microcephalic and always severely retarded. Epileptic seizures are common in early in life. Lissencephaly is subdivided into two types, I and II.[32] Type I may be either an Isolated Lissencephaly Sequence (ILS) or lissencephaly combined with facial dysmorphisms and often somatic malformations (Miller-Dieker Syndrome, MDS). The latter is related to a deletion of the short arm of the 17th chromosome.[31] In lissencephaly type II, other cerebral abnormalities such as hydrocephalus, Dandy Walker malformation and disturbed myelination are found combined with abnormalities of the eyes and muscles.[34] This study concerns lissencephaly type I only. Excluding our own series of 21 patients, as yet only 59 patients with lissencephaly type I have been described in detail.[26]

At present the diagnosis lissencephaly type I can be made by CT or MRI. In imaging studies as well as at autopsy the severity of lissencephaly type I is assessed in four grades ranging from grade 1 (complete agyria) to grade 4 (complete pachygyria).[26,33,35] The EEG in lissencephaly is the subject of only a few publications. Hypsarrhythmia was demonstrated [24,30,48,53,61] in ten cases. Only two of these patients suffered from infantile spasms. Dulac et al.[42] described four patients with agyria; two of them showed an alpha rhythm with high amplitude. In a larger series of 15 patients [44] all EEG's were characterized by fast activity with high amplitudes between 150 and 350uV. In young patients widely distributed theta activity was seen also, either alternating or mixed with this alpha and beta activity. The frequencies of the theta rhythms increased with age. Spike- and wave-complexes were seen also. Generally no reaction occurred on eye opening or on photic stimulation. Sleep had no influence on the EEG.[49] Hiura et al.[59] described the occurrence of REM sleep in 3 patients, albeit reduced

in comparison to normal subjects. Mizuguchi et al.[79] performed polysomnography in 2 patients, showing highly abnormal sleep patterns. As far as we know, no studies exist on evoked potentials in lissencephaly. The aim of our study was the description of EEG's and evoked potentials as well as the extraction of neurophysiological features typical for lissencephaly, which eventually might be useful in the diagnosis of this disorder.

## MATERIAL AND METHODS

### Patients

In the Netherlands a study was done in cooperation with all centres for child neurology. In this way a series of 21 patients with lissencephaly type I was collected. In 19 patients the diagnosis was made by CT, in the other two at autopsy. The radiological diagnosis was confirmed by microscopy in 4 patients. Ten patients were classified as lissencephaly grade 1 or 2 (complete agyria or some sulci present) and eleven patients were classified as grade 3 or 4 (mixture of agyria and pachygyria or complete pachygyria). Four patients had the Miller-Dieker syndrome, the others the ILS form of the disease. All patients were severely retarded and had epilepsy. In 7 patients infantile spasms occurred. All patients were on anti-epileptic medication. Plasma levels were in the non-toxic range in all. Our 21 patients were compared to a group of 21 patients with an atypical cortical dysplasia different from lissencephaly. This is also called "pachygyric-like changes".[116] In the latter group of patients the diagnosis was made on the CT scan and confirmed at microscopy in 4 patients. Epilepsy was seen in 11 of these patients; two patients suffered from infantile spasms. All patients with seizures used anti-epileptic medication. These two groups of patients (patients with lissencephaly or an atypical cortical dysplasia) were compared to a control group of 823 consecutive patients, seen at the department of Clinical Neurophysiology in the Juliana Children's Hospital. The reasons for the EEG in these patients were: (epileptic) seizures, retardation, trauma, infection, anoxia and headache.

Table 1. EEG patterns of 21 lissencephaly patients (Liss) compared to 21 patients with an atypical cortical dysplasia (A.C.D.) and a control group (Con.), consisting of 823 patients who underwent an EEG for various reasons.

	Liss	A.C.D.	Con.
Number of EEG's	114	52	882
Number of patients	21	21	823
	Percentage of EEG's		
Abnormal EEG	100#*	81	37
Abnormal background pattern	95#*	76	23
Generalized fast activity > 50uV	45#*	8	0.1
Generalized fast activity > 150uV	25#*	2	0
Generalized slow activity > 300uV	24*	10	1
Asymmetrical background pattern	4	0	9
Sharp- and slow-wave complexes > 800uV	37#*	0	0.1
Continuous epileptic activity	8*	2	0.3
Alternating pattern**	11#*	2	0

# Fisher Exact test,  $p < 0,05$ ; Liss.tested against A.C.D.

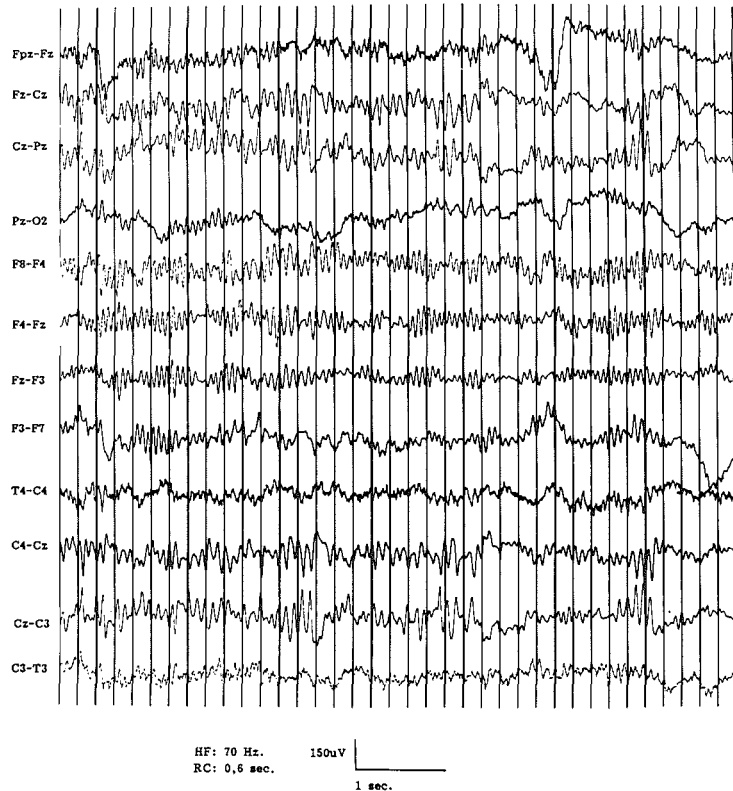
\* Fisher Exact test,  $p < 0,0001$ ; Liss.tested against Con.

\*\* See text

### Acquisition and analysis of EEG's and Evoked Potentials

The EEG's were recorded in our own hospital or in the contributing centres. All EEG's were recorded with 16 or 21 channel EEG machines using several derivations. The technical quality of all recordings was according to the standards set by the IFSECN. In the 21 lissencephaly patients 114 EEG's were recorded (range: 2 to 11 EEG's for each patient). The age of the patients at recording of the EEG was between 1 and 85 months (median: 8 months), 59% of the EEG's were made in the first year of life. In the group of 21 patients with another cortical

Figure 1-a. A girl with lissencephaly grade 3/4 at the age of 23 months; generalized fast activity with amplitudes of 150uV.



dysplasia, 52 EEG's were reviewed. Fifty-eight percent of these recordings were done in the first year of life (the median age at recording was 7 months). In the control group 57% of the 882 EEG's were recorded under the age of 12 months. Special attention was given to features of the background pattern, such as the amount of generalized fast and slow activity and asymmetries, and to epileptic activity i.e. sharp waves and sharp- and slow-wave complexes. An EEG was classified as continuously epileptic when epileptiform activity was seen throughout the entire period of recording. As some patients used medications known for enhancing fast (beta) activity, this EEG feature was taken into account only when amplitudes were higher than 50uV. Short latency somatosensory evoked potentials (SEP's) were recorded in 10 lissencephaly patients in our department. The median nerve was stimulated with electric pulses of 0,1 ms duration at a stimulus frequency of 5/s. The following derivations were used: point of Erb-Fz, Neck (at vertebra C7)-Fz, C3-A1 or C4-A2, C3-Fz or C4-Fz. In the first few children tested a derivation to a non-cephalic reference electrode was tried. Due to the many artifacts during

such recordings, this practice had to be abandoned in favor of the less sophisticated choice of Fz as a reference. The filters were set at 10 and 3000 Hz. Twohundred and fifty-six sweeps of 50 ms duration were recorded with a stimulus delay of 12,5%. Automatic artifact rejection precluded severe distortion of the average obtained from these sweeps.

Figure 1-b. A girl with lissencephaly grade 1/2 at the age of 12 months; sharp- and slow-wave complexes with amplitudes up to 2900uV.



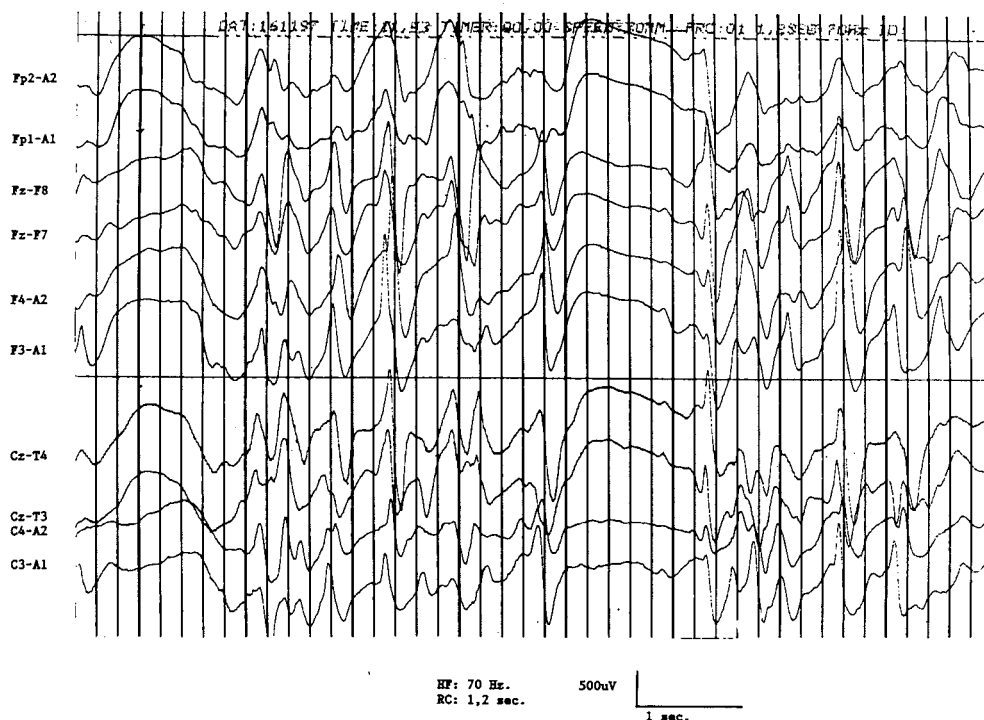
## RESULTS

The results of the assessment of the EEG's are summarized in Table 1. All EEG's of the lissencephaly patients and 81% of the EEG's of the patients with an atypical cortical dysplasia were abnormal. Striking features in the group of lissencephaly patients were:

- generalized fast activity (8-18/s) with high amplitude (range 50-400uV), see Figure 1a.
- continuous generalized slow activity with high amplitude (above 300uV)
- sharp- and slow-wave complexes with high amplitude (range 500-3000uV), see Figure 1b.
- an alternating pattern consisting of bursts with a duration of several seconds consisting of sharp waves with amplitudes from 500uV to 2000uV alternating with relative depression of EEG

activity with amplitudes of 100 $\mu$ V or less, see Figure 1c. The patterns (a), (c) and (d) were found significantly more often in patients with lissencephaly than in patients with an atypical cortical dysplasia (Fisher Exact test  $p < 0.05$ ). These patterns, as well as pattern (b), were seen very seldom in EEG's recorded of patients suffering from other pathology (Fisher Exact test  $p < 0.0001$ ).

**Figure 1-c.** A girl with lissencephaly grade 1/2 at the age of 19 months; an alternating pattern consisting of paroxysms of sharp waves for several seconds with amplitudes up to 2000 $\mu$ V alternating with periods of depression for several seconds.



In 95% of the lissencephaly patients and in 82% of their EEG's pattern (a) or (c) or both were recorded, compared to only 5% of the patients with an atypical dysplasia (8% of their EEG's). In the control group pattern (a) or (c) were seen rarely (in 0,4% of the EEG's). In 11% of the EEG's recorded from the lissencephaly patients the alternating pattern (d) was seen, compared to 2% of the EEG's recorded from patients with an atypical cortical dysplasia. This pattern was absent in the control group. Recordings with pattern (a) followed by pattern (c) or vice-versa occurred in nine lissencephaly patients. In 3 patients a full cycle with return to the initial pattern was found (a)-(c)-(a) or (c)-(a)-(c). There was no clear relation between age at recording and one of the EEG patterns described. The differences between the group of lissencephaly patients grade 1 and 2 and the group with lissencephaly grade 3 and 4 can be seen in Table 2.

Generalized fast activity with high amplitudes was seen more often in lissencephaly grade 3 and 4. In contrast sharp- and slow-wave complexes with high amplitude and the alternating pattern occurred more frequently in lissencephaly grade 1 and 2 patients. Most lissencephaly patients had a high frequency of epileptic attacks. A high frequency of epileptic attacks was not limited to those patients whose EEG's were characterized by epileptiform activity. In 21 of the 114 EEG's from 10 patients with lissencephaly periods of sleep were recorded. During sleep, background-slowing as well as sleep spindles were seen. K complexes did not occur. Two of

these 21 EEG's were characterized by paroxysms of sharp activity. Continuous epileptic activity was found in only one of the sleep recordings.

The results of the SEP studies are summarized in Table 3. The latencies of the SEP components at the point of Erb and the neck were normal according to age for all children.[115] The cortical components N20, P27, and N35 were absent in 7 out of the 10 patients (an example is given in Figure 2). Only four times cortical components, probably the N20 peak, could be recorded. The configuration of the cortically generated complexes was highly abnormal; the latencies were prolonged compared to normal children.

## DISCUSSION

Our study of 114 EEG's from 21 lissencephaly type I patients is in partial agreement with the results of Gastaut et al.[49] We also found generalized fast activity (8-18/s.) with high amplitudes (pattern a) and generalized slow activity with high amplitude in the awake patient (pattern b). New EEG patterns in our study were: sharp- and slow-wave complexes with very high amplitudes (in 55% over 500uV and in 37% 800uV or more) (pattern c), the alternating pattern as described in the Results section (pattern d), the results of sleep analysis, and the changes in EEG patterns over time. Frontally localized beta activity with amplitudes up to 200uV, is described in children with mental retardation and cerebral palsy.[50] This EEG

**Table 2. Patterns in the EEG of lissencephaly patients. Lissencephaly patients with grade 1 and 2 compared to patients with grade 3 and 4.**

	Lissencephaly grade 1+2	Lissencephaly grade 3+4
Number of EEG's	48	66
Number of patients	10	11
	Percentage of EEG's	
Abnormal EEG	100	100
Abnormal background pattern	92	97
Generalized fast activity > 50uV	27	58*
Generalized fast activity > 150uV	17	30
Generalized slow activity > 300uV	29	21
Asymmetrical background pattern	8	2
Sharp- and slow-wave complexes > 800uV	52*	26
Continuous epileptic activity	8	8
Alternating pattern**	17	6
# Fisher Exact test, p < 0,05		
** See text		



feature often occurred in sleep, but quite commonly also in the awake state. Generalized fast activity with high amplitude is also seen in children suffering from infantile neuroaxonal dystrophy [46] and, albeit with low amplitude, in progressive encephalopathies due to aminoacidopathies.[78] In the control group of 823 patients with various pathology, these patterns were rare. The two basal patterns (a) and (c) noticed in 20 of the 21 lissencephaly patients, were on the contrary seen in only one of the 21 patients with an atypical cortical dysplasia. Thus, though not specific for lissencephaly the presence of patterns (a) and/or (c) suggests the diagnosis. In nine patients a more or less cyclical pattern between patterns (a) and (c) was noticed. There may be a relation between the high amplitude fast and slow activity found in our patients and the anatomic configuration of the lissencephalic cortex. Due to the lack of sulci, electric activity of a relatively large part of the cortex might be picked up by a scalp electrode. Similar to the hypothesis put forward by Ferris et al.[46] in children with neuroaxonal dystrophy and Ichikawa et al. [60], deafferentiation of the cortical neurons resulting in denervation supersensitivity could also be an explanation. For lissencephaly the latter possibility was mentioned before by Gastaut et al.[49]

Another explanation for the generalized fast activity with high amplitudes could be an abnormal reaction of the lissencephalic cortex to the use of benzodiazepines. Forty-five percent of the EEG's from the lissencephaly patients were recorded when the patient used benzodiazepines. Forty-one percent of these cases showed generalized fast activity with high amplitudes. EEG's of patients not using benzodiazepines showed such fast activity in 48%. Thus, the use of benzodiazepines seems to have no influence on the occurrence of generalized fast activity in the lissencephalic brain.

In addition to the EEG, evoked potentials may be useful for the diagnosis of lissencephaly. The absence of cortical SEP components suggests disease limited to the supratentorial grey matter. In this respect the absence of the "N20 component" in physiologically lissencephalic brains such as that of the rabbit is of interest.[17] Using the criteria of Dobyns and McCluggage [33] differentiation between an atypical cortical dysplasia and lissencephaly can be made by CT and/or MRI. In addition to radiological criteria, EEG and evoked potentials can be of diagnostic value also when one considers the diagnosis of lissencephaly type I. Even in the

**Table 3. Overview of the SEP after median nerve stimulation in 10 patients with lissencephaly type I.**

Age at recording	Side of stimulation					
	Right			Left		
months	N9	N13	N20	N9	N13	N20
3	nd	?	24.0	nd	8.8	24.0
16	7.5	8.5	-	7.5	8.0	-
19	?	8.5	-			
20	5.2	11.6	-	5.2	11.8	-
36	6.0	8.4	-	5.4	8.8	-
53	nd	9.0	-	nd	9.0	-
56	6.6	10.2	-	6.2	9.0	-
84	7.2	10.2	-	?	10.7	19.0
87	6.8	10.2	-	7.6	9.5	-
102	7.4	9.2	21.6	7.6	9.0	-

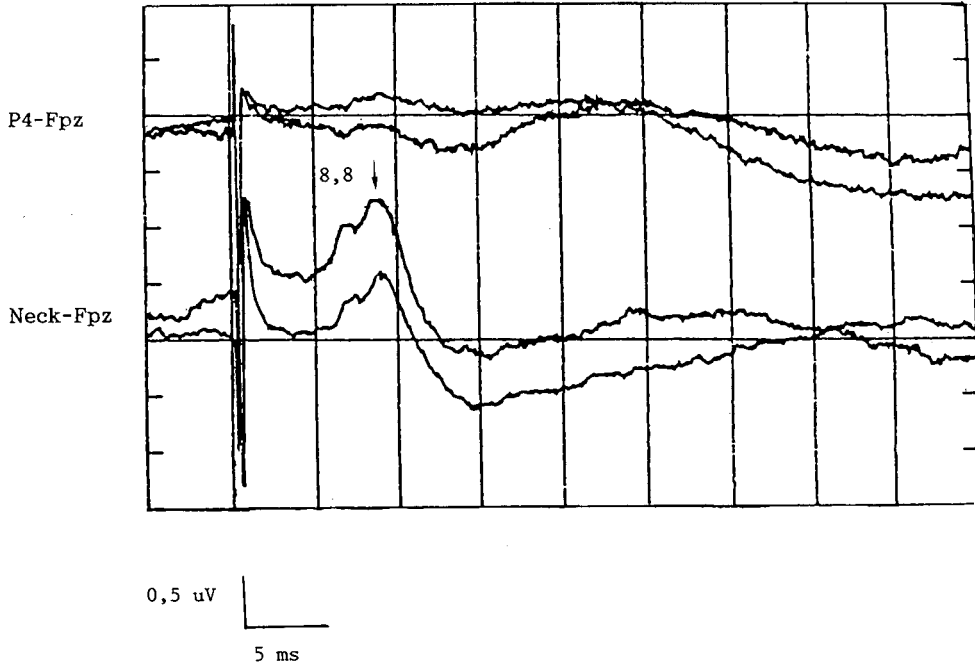
nd: not done

? : too many artefacts

- : repeatedly no response

EEG's recorded from the patients with an atypical cortical dysplasia the patterns described for lissencephaly were only sporadically present, suggesting discriminative power for the EEG to differentiate lissencephaly type I from other cortical disorders.

Figure 2. Left median SSEP at age 53 months in a boy with lissencephaly grade 4. Normal latency of the cervical components, and absence of a cortical response.



# NEUROIMAGING IN LISSENCEPHALY TYPE I

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## INTRODUCTION

Lissencephaly is a developmental disorder of the cerebral cortex, in which sulci are not or only partially formed. There are two types of lissencephaly: type I, in which the disturbance mainly concerns the cerebral cortex, and type II, in which disturbances of the cerebellum, eyes and muscles are present as well.

In 1966 it was suggested that arteriography should be performed to diagnose lissencephaly.[127] Before 1979 lissencephaly could only be diagnosed by autopsy.[61] In 1979 lissencephaly was diagnosed for the first time during life by CT scan.[48] In 1985 the characteristic CT features of lissencephaly type I were described systematically including [35]:

- \* a smooth brain surface (figure 'eight' shape) or a decreased number of sulci.
- \* absent or few grey/white interdigitations
- \* absent or incomplete opercular development
- \* enlarged posterior ventricles (colpocephaly), no hydrocephalus
- \* sometimes agenesis or hypoplasia of the corpus callosum
- \* sometimes small midline calcifications
- \* no infratentorial abnormalities or at most slight hypoplasia of the cerebellar hemispheres.

The aim of this study was to obtain more quantitative criteria for the diagnosis of lissencephaly type I by measuring a number of cerebral structures. The relationship between the number of sulci and cortical thickness was also examined. We also tried to find out whether MRI has advantages above CT scanning.

## MATERIAL AND METHODS

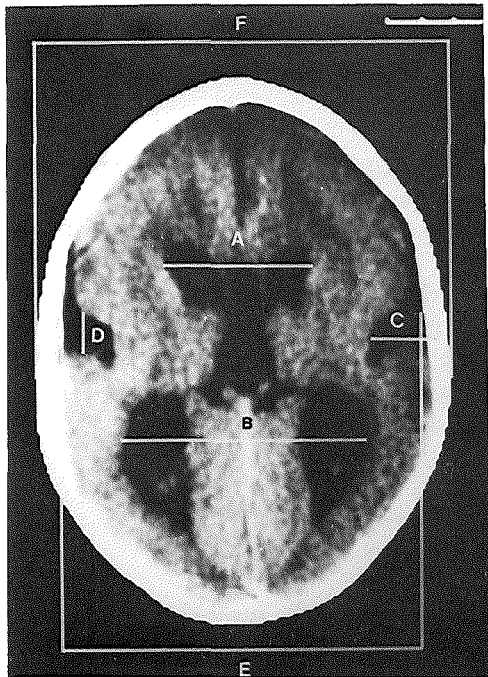
### Data collection of patients

Two groups of patients were studied:

(1) 22 children with lissencephaly type I: 12 boys and 10 girls.

(2) 44 children with a normal CT scan and 5 children with a normal MRI: 30 boys and 19 girls.

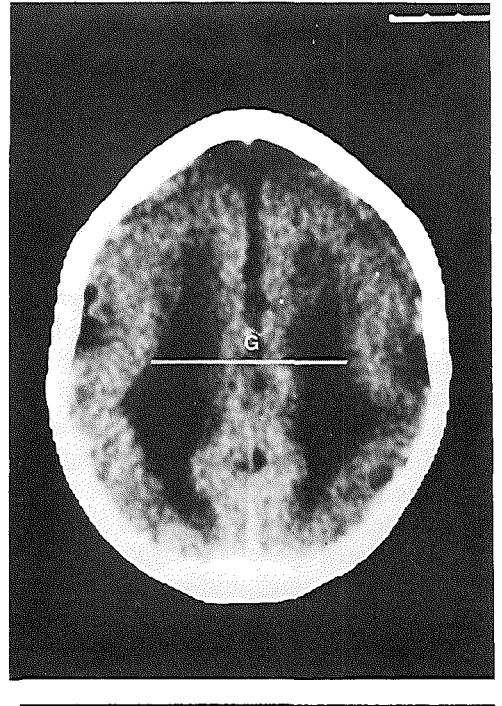
Figure 1A. CT scan of a 22 month old boy with lissencephaly



- A = frontal horn width
- B = occipital horn width
- C = depth of the Sylvian fissure
- D = width of the Sylvian fissure
- E = maximum internal width of the skull between the temporal bones
- F = maximum external width of the skull between the temporal bones

In 6 patients MRI was performed. In 4 patients, the diagnosis was confirmed by autopsy. The age at which the CT was made, varied from 1 to 218 months, with a median age of 8 months.

Figure 1B. G = minimum width of the ventricular system at the cella media level



ad (1)

Twenty-two patients with lissencephaly type I were collected from several child neurology departments in the Netherlands.[26] They were classified as lissencephaly, according to the criteria of Dobyns and McCluggage.[33]

Nineteen of the 22 CT scans were performed before the age of 12 months. MR scans were performed between 9 and 82 months of age.

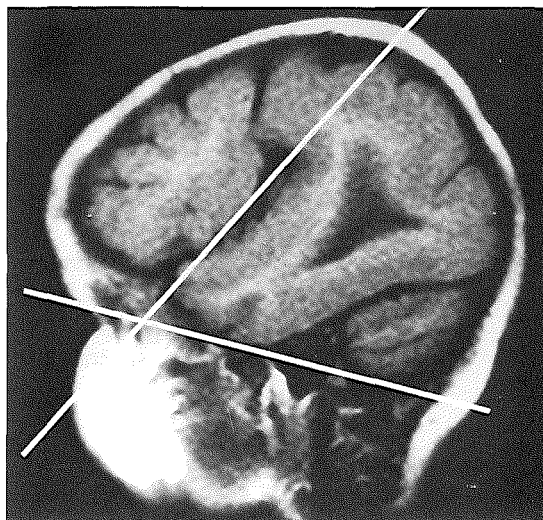
ad (2)

A consecutive control group consisted of patients derived from the Westeinde Hospital and the Juliana Children's Hospital in The Hague (CT) and the Free University Hospital in Amsterdam (MRI). Their MR or CT scans were reported to be normal. The indications for the investigation were epilepsy, mental retardation, or trauma. Their neurological examination was normal, apart from developmental retardation in a number of patients. The age of these patients at the time of the CT scan varied from 2 to 116 months; 31% were made before the age of 12 months. MR scans were made from 5 to 81 months of age.

### Measurements

CT scans of the patients with lissencephaly were made in the contributing centres. This implicated that different CT-scan machines were used. When more than one CT scan was made from one patient, the scan with the highest quality was chosen for the measurements. Consecutive slice thickness was usually 6 mm. The CT-scans of the patients in the control group were all performed in the Westeinde Hospital on a Siemens Somatom DR apparatus. Consecutive slice thickness was 8 mm. All MR scans were performed in the Free University Hospital, Amsterdam, on a 0,6 T con II apparatus. Slices of 7.5 or 10 mm thickness were made. Measurements were done on the inversion recovery (IR) pictures. All measurements were performed by one investigator to avoid interobserver variability. The patients were divided into two groups, younger and older than 3 years. This age limit was chosen because the maturation of the brain, the myelination and change of the cellular components takes place in the first 2 to 3 years of life.[94]

Figure 2. MR scan of a 42 month old boy with lissencephaly. (SE: TR 405, TE 32, TI 0). The angle of the sylvian fissure with the inferior part of the temporal horn and the cerebellum is shown.



The following measurements on axial slices were made (Figure 1):

the total number of sulci; the patients were classified in grades: grade 1 meaning no sulci or only one visible sulcus, grade 2 meaning two to four visible sulci, grade 3 meaning five or seven visible sulci, and grade 4 meaning eight to ten visible sulci.

- TC : Frontal and occipital Cortical Thickness on both sides (in mm.).
- DSF/TBW : Depth Sylvian Fissure / Total Brain Width at that level
- WSF/DSF : Width of the Sylvian Fissure / Depth of the Sylvian Fissure
- FEVI : Frontal Evans Index = frontal horn width / maximum internal width of the skull between the temporal bones
- OEVI : Occipital Evans Index = occipital horn width / maximum internal width of the skull between the temporal bones.
- VR : Ventricular Ratio = OEVI / FEVI
- CMI : Cella Media Index = maximum external width of the skull between the temporal bones / minimum width of the ventricular system at the cella media level.
- VA : Ventricular Angle = angle between the axis of the frontal horn and the axis of the occipital horn of the ventricular system.
- LOP : Length of the operculum, this is the temporofrontal separation measured on an axial scan through the thalamus ( in mm.).

Additional measurements were made when sagittal images were present (Figure 2)

- ASF : Angle of the Sylvian Fissure with the inferior part of the temporal horn and the cerebellum.
- LSF : Length of the Sylvian Fissure (in mm.).

**Table 1. The 5th, 50th and 95th percentiles of measurements on the CT scan in patients younger and older than three years with lissencephaly compared to the control group.**

	Lissencephaly (N=17)			Controls (N=24)		
Younger than 3 years	P5	P50	P95	P5	P50	P95
FEVI*	0.15	0.29	0.43	0.19	0.25	0.31
OEVI*	0.43	0.59	0.75	0.32	0.52	0.62
VR	0.96	2.11	3.26	1.48	2.10	2.72
CMI**	2.30	3.23	4.16	3.06	4.26	5.46
Mean VA (grades)	97	113	129	107	115	123
Mean DSF/TBW	0.12	0.19	0.26	0.07	0.17	0.27
Mean WSF/DSF**	0.29	0.88	2.80	0.09	0.16	0.25
Mean LOP (mm)**	5.4	13.5	21.0	1.6	2.5	4.6
Mean TC (mm)**	8.1	12.7	17.3	2.19	3.17	4.15
	Lissencephaly (N = 3)			Controls (N = 20)		
Older than 3 years	P5	P50	P95	P5	P50	P95
FEVI**	0.22	0.33	0.44	0.16	0.22	0.28
OEVI*	0.42	0.58	0.74	0.35	0.47	0.59
VR	1.62	1.74	1.86	1.41	1.77	2.85
CMI*	2.30	2.86	3.92	2.88	3.88	6.44
Mean VA (grades)	108	118	128	108	97	124
Mean DSF/TBW*	0.12	0.18	0.24	0.10	0.16	0.12
Mean WSF/DSF**	0.34	0.68	1.25	0.13	0.11	0.18
Mean LOP (mm)**	7.5	11.2	16.1	1.0	2.1	3.2
Mean TC (mm)**	11.0	12.7	14.4	2.42	3.5	4.50

The 5% confidence is given by the 5th and the 95th percentile by 2 times + or - the standard deviation. In case of the WSF/DSF and the LOP the P50 is given with the lowest and highest value measured. \*: T-test p < 0.03, \*\*: T-Test p < 0.0001

In the tables the 5th, 50th and 95th percentiles are given of FEVI, OEVI, VR, CMI, and of the mean of the measurements on both sides of VA, DSF/TBW index, WSF/DSF index, and LOP. The same was done with the mean Cortical thickness, measured on four locations, namely frontally on both sides and occipitally on both sides. In case of the WSF/DSF and the LOP only the 50th percentile was given, with the lowest and highest range. This was done, because in calculating the 5th percentile a negative value resulted.

**RESULTS**

In Tables 1 and 2 the results of the measurements on the CT and MR scan in patients with lissencephaly compared to the control group are presented. In lissencephaly patients the absolute value of the cortical thickness was always more than 10 mm on CT and MR scans. This contrasts to the control group in which the cortical

**Table 3. Relation between grades of lissencephaly and the cortical thickness TC, measured on the CT scan.**

Grades	1	2	3	4
Values	10.5	10.5	11.6	10.4
	10.8	10.8	11.7	11.9
	11.0	11.6	12.0	13.1
	11.4	12.4	13.9	
	12.1	12.5	14.9	
	12.8	13.2	15.4	
			16.7	
Mean	11.4	11.6	12.4	12.3
SD	0.8	0.9	1.7	1.6

**Table 2. The 5th, 50th and 95th percentiles of measurements on the MR scan in patients with lissencephaly compared to the control group. In case of the WSF/DSF and the LOP the P50 is given with the lowest and highest value measured.**

	Lissencephaly (N = 6)			Normal (N = 5)		
	P5	P50	P95	P5	P50	P95
FEVI*	0.27	0.35	0.43	0.10	0.24	0.38
OEVI*	0.59	0.69	0.79	0.30	0.42	0.54
VR	1.42	2.02	2.62	0.80	1.96	3.12
CMI**	3.80	4.23	5.84	3.13	3.77	4.41
Mean VA (grades)	100	110	120	111	117	123
Mean DSF/TBW	0.13	0.19	0.25	0.14	0.17	0.20
Mean WSF/DSF**	0.41	0.78	1.30	0.11	0.16	0.25
Mean LOP (mm)**	6.9	14.1	21.3	0.8	2.5	3.6
Mean TC (mm)**	11.4	14.9	18.4	5.6	6.7	7.8
Mean ASF	44.7	77.3	109.9	56	66	76
Mean LSF	3.7	5.7	7.7	4.4	5.9	7.4

\*: T-test p <0.03, \*\*: T-Test p <0.0001

thickness was always less than 5 mm on the CT scan and less than 7 mm on the MR scan. Whereas the DSF/TBW index did not differ between lissencephaly patients and their controls, the WSF/DSF index was significantly larger in lissencephaly patients than in the control group. In all lissencephaly patients this index was higher than 0,29 and in the control group this index was always smaller than 0,25. The WSF/DSF index is a variant of the measurements on the temporofrontal separation, which is described as being abnormal when this distance is 3 mm or more.[114] We calculated the WSF/DSF index, to exclude the magnification factor in our measurements. In fact, the frontotemporal distance (LOP) was more than 3 mm on the CT scan of all lissencephaly patients. In the controls this distance was smaller.

In Table 1 and 2 we can also see that the ventricular system (FEVI, OEVI and CMI) is significantly larger in patients with lissencephaly than in the normal situation. This did not concern the occipital horns only, since the VR was not larger in the lissencephaly patients than in the controls. In Table 3 one can see that there is no clear relationship between the grade of

lissencephaly and the cortical thickness. The WSF/DSF index seems to be higher in grade 1 lissencephaly than in grade 2 or 3 lissencephaly, and is the smallest in grade 4 lissencephaly (see Table 4). In lissencephaly patients, no focal heterotopia's were seen, the cerebellum had a normal aspect, or was only slightly hypoplastic. Absence of the corpus callosum was seen in 3 patients, the corpus callosum was thin in 11 patients. If present, sulci were predominantly seen in the frontotemporal area. No intracranial calcifications were present.

## DISCUSSION

The morphologic criteria on the CT scan described by Dobyns and McCluggage in 1985 [33], may be complemented by exact measurements, which are abnormal on the CT or MR scan in all lissencephaly patients. This study presents some values to differentiate more accurately the image of lissencephaly from normal. When on every CT or MR scan of a severely retarded child the mean TC, and the mean WSF/DSF is measured, it will be virtually impossible to miss the diagnosis of lissencephaly. The WSF/DSF index is a measurement of the extent in which opercularisation has taken place. As expected a relation between the WSF/DSF index and the severity of lissencephaly was found. It was also possible to differentiate between lissencephaly and the control group by measuring the cortical thickness. We had thought that a relation could exist between the grade of lissencephaly and the cortical thickness, however this seemed not to be the case. In difficult cases, MR scan has advantages above the CT scan in visualizing the cortical surface and detecting heterotopia's. This is especially the case in atypical cortical dysplasia's, schizencephaly and polymicrogyria.[4,88] In most cases, however, the diagnosis of lissencephaly can be made on a CT scan, when all characteristics described above are present. The predominance of lissencephaly in the occipitoparietal region has already been described.[20] This is in contrast to the frontal pachygyria found in some patients.[116] Neither one of these predominances can be explained by our knowledge about gyral development.[15]

We conclude that is possible to diagnose lissencephaly reliably on the CT scan by measuring the cortical thickness and the index WSF/DSF in addition to the criteria of Dobyns and McCluggage.[35]

Table 4. Relation between grades of lissencephaly and WSF/DSF index measured on the CT scan.

Grades	1	2	3	4
WSF/DSF	0.70	0.60	0.45	0.29
	0.76	0.60	0.48	0.34
	1.25	0.70	0.50	0.41
	2.30	0.71	0.74	
	2.40	0.71	0.80	
	2.80	0.83	0.82	
			0.83	
Mean	1.70	0.69	0.66	0.35
SD	0.83	0.08	0.16	0.05



# **STUDIES WITH DNA-MARKERS IN PATIENTS WITH LISSENCEPHALY TYPE I AND OTHER CORTICAL DYSPLASIAS**

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## **INTRODUCTION**

Lissencephaly type I is a severe brain malformation resulting from a disturbed neuronal migration to the neocortex. Macroscopically, sulci are completely or partially absent; agyria and pachygyria are often present within the same brain. A classification scale was developed ranging from grade 1 (complete agyria) to grade 4 (complete pachygyria).[26,33] Patients with lissencephaly type I suffer from severe retardation and epilepsy and are often microcephalic. Lissencephaly type I may occur as an isolated malformation, designated as Isolated Lissencephaly Sequence (ILS), or as a part of the Miller-Dieker syndrome (MDS). Patients with MDS show more or less specific facial dysmorphisms and often have somatic abnormalities.[32] MDS is associated with a mini-deletion of the chromosome 17p13.3 [31,111], because this is the common abnormality in MDS patients described with: unbalanced translocations (13 cases), pericentric inversions (2 cases), de-novo deletions (7 cases), and ringchromosomes (2 cases); five patients with normal karyotypes showed the deletion at DNA-level.[8,10,13,19,31,51,52,71,103,104,111,119] Ledbetter et al.[71] suggests that this deletion found in 15 out of 15 MDS patients is diagnostic for MDS patients. Whether any deletions occur in ILS has not been reported.

We describe DNA studies in a large number of patients with lissencephaly type I and a more heterogeneous group of patients with cortical dysplasia. Molecular genetic analysis of the patients with ILS, was carried out to test the hypothesis that MDS and ILS possibly have a common genetic etiology.[119]

# MATERIAL AND METHODS

## Clinical data

Twenty-one patients with lissencephaly type I, collected from departments of Child Neurology and Clinical Genetic Centers in the Netherlands, were subject of this study. Details of 15 patients are presented elsewhere.[26] The diagnosis of lissencephaly was made in all patients on the CT scan using the criteria made by Dobyns and McCluggage.[33] The diagnostic criteria for MDS and ILS were used according to Dobyns et al.[32] One case of lissencephaly was diagnosed at autopsy, but did not fit in either the type I or the type II lissencephaly.

Figure 1. Chromosome analysis in patient 7 with MDS. A deletion 17p13.3 is shown.

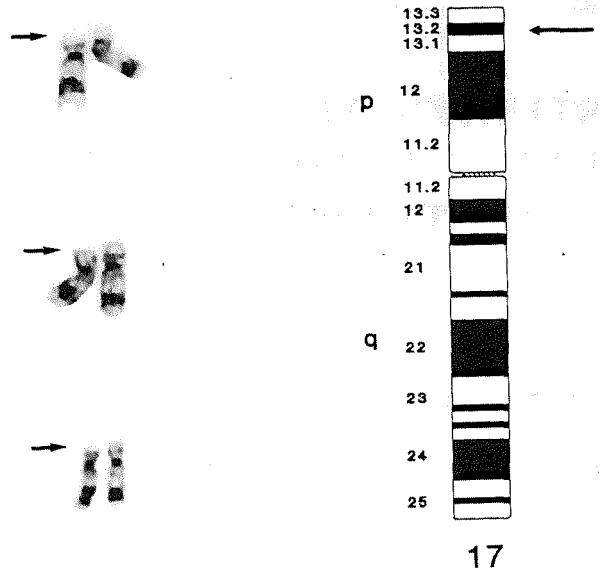
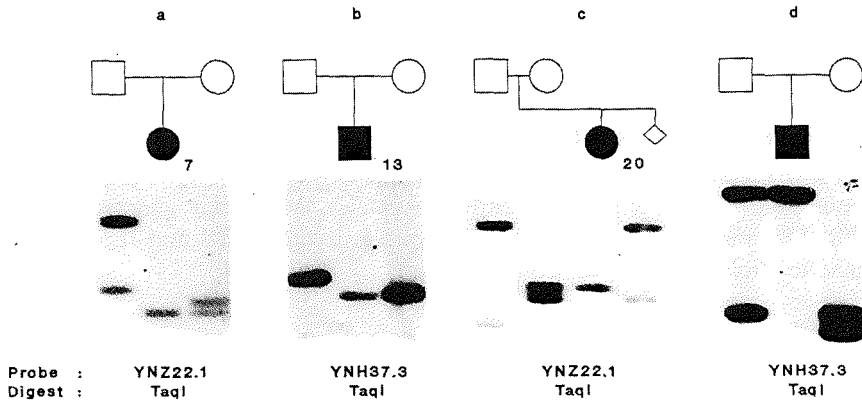


Figure 2. Hybridization of YNZ22.1 and YNH37.3 in MDS families. a) absence of paternal allele YNZ22.1 in patient 7 with MDS. b) absence of paternal allele YNH37.3 in patient 13. c) absence of paternal allele YNZ22.1 in patient 20, d) absence of maternal allele of YNH37.3.



Nine other patients with different types of cortical dysplasia, were studied, including schizencephaly with localised pachygyria (2 patients), atypical cortical dysplasia (5 patients), polymicrogyria (one patient) and a mixture of polymicrogyria and pachygyria (one patient).

### Methods

Peripheral blood lymphocytes were obtained from patients, parents and siblings for chromosome and DNA analysis. In some cases cultured fibroblasts were used. Chromosome preparations were made according to standard techniques and analyzed after trypsin Giemsa banding. For DNA analysis the following probes were used: YNZ22.1 (D17S5), YNH37.3 (D17S28) [82], 144-D6 (D17S34) [66] and VAW (D17S128).[71] The order of markers is: centromere - VAW508 - YNZ22.1 - YNH37.3 - 144D6 - telomere.[72] Total genomic DNA was isolated from human leucocytes or cultured cells.[77] DNA samples were digested to completion with restriction endonucleases, fractionated by agarose gel electrophoresis, and subjected to Southern blot analysis.[108] DNA fragments to be used as probes were labelled by the random primer method.[45] After prehybridization and hybridization the filters were washed to 0.1xSSC at 65°C.

Table 1. Summary of the DNA analysis using three DNA probes.

Marker	F	7	M	F	13	M	F	20	M	P	F	.	M	F	.	M
144-D6	1.3	1.2	2.4	1.1	1.2	2.3	4.3	3.1	1.2	3.2	1.2	1.1*	1.2	2.4	1.3	2.3
YNZ22.1	1.2	-4	4.3	1.3	-4	4.2	1.4	-2	2.3	1.3	1.4	-3	2.3	2.4	-2	1.3
YNH37.3	1.2	-3	3.3	1.1	-2	2.2	1.1	-2	2.1	1.1*	1.2	-2*	1.2	1.2	-1	2.3
VAW508	1.1	-1*	1.1	1.2	-1*	1.1	1.2	-1*	1.1	2.1	1.1	1.2	1.2	1.1	1.2	1.2

F/M=father/mother; P=pregnancy tested by chorionic villus sampling; numers refer to cases described by de Rijk-van Anel et al.[26]

\* the number of alleles was determined on the basis of relative dosage of the band present on autoradiograph.

## RESULTS

Five patients were classified as MDS, and 17 patients as ILS. All the MDS patients had a lissencephaly grade 1/2 (complete or nearly complete agyria). In the group of ILS patients 10 patients had a lissencephaly grade 1/2 and 8 a grade 3/4 (a mixture of agyria with pachygyria or complete pachygyria). In one patient with lissencephaly classification was not possible. Nine other patients showed other types of cortical dysplasia. Chromosome analysis showed a deletion on 17p in only patient 7 with MDS (Figure 1). DNA analysis, with DNA markers for the 17p13.3 region, showed a deletion of paternal origin in some MDS patients. Figure 2a and 2b show the absence of a paternal allele of YNZ22.1 and YNH37.3, respectively, in the affected children. In one patient the deletion was found in the maternal chromosome (Figure 2d). In the five MDS patients two alleles of the telomeric probe 144D6 were present. We conclude that the deletions are interstitial (Table 1).

In the family with the MDS patient no 20, DNA analysis after chorion villus sampling was performed in a subsequent monoamniotic twin pregnancy. Chromosome analysis showed a normal karyotype. Two alleles of DNA markers YNZ22.1 were detected in contrast to the single allele found in the DNA of the index patient (Figure 2c); two normal children were born (Table 1). In 17 patients with ILS and one patient with non-classified lissencephaly no deletion could be detected with the four markers used. In all but two patients two different alleles were found for one of the markers YNZ22.1 or YNH37.3. In one patient dosage analysis favored the presence of 2 alleles. In one patient the DNA analysis was non-conclusive. Also, in the patients with other types of cortical dysplasia no deletions were found with the probes YNZ22.1, YNH37.3, 144-D6 and VAW508.

## DISCUSSION

This study extends the expectation that all patients clinically classified as having MDS have a DNA deletion involving 17p13.3.[71,103,119] In 9 MDS patients (5 in the literature and 4 in this study) this deletion was submicroscopical and invariably included a deletion of the markers YNZ22.1 and YNH37.3. A deletion of the DNA markers 144-D6 and VAW508 was only seen in some MDS patients. In 4 MDS cases described here the deletion was seen in the paternally contributed chromosome. In one patient, however, the deletion was found to be of maternal origin. Only a single case has been observed before.[103] Apparently, the parental origin of the deletion in MDS is not determinant. This is in contrast to 15q11-13 deletion where the clinical outcome is dependent on the parental origin of the deletion: Prader-Willi Syndrome (PWS) in case of paternal deletion and Angelman Syndrome (AS) in case of a maternal deletion.[64] There, genomic imprinting does not play a role in MDS as is suggested for PWS and AS.[84,128] Since in the region between YNZ22.1 and 144-D6 in males a five times higher recombination frequency as compared to females has been observed, this might be related to the cause of interstitial deletions and their preference for a paternal origin.[71]

This is the first large series of ILS patients studied by DNA analysis. Neither YNZ22.1 and YNH37.3, which are deleted in all MDS patients tested so far, nor VAW508 and 144D6 which are localised on either side of the MDS critical region were found to be deleted in DNA from ILS patients. Therefore it remains to be determined whether ILS and MDS have (partly) a common etiology. The deletion responsible for MDS is estimated to be around 300kb.[71,72] The probes YNZ22.1 and YNH37.3 span a region of about 20 kb. If the deletion, that might be responsible for ILS is very small, it may very well reside in the part not covered by these DNA markers. Among the other cases of cortical dysplasia (a clinically heterogeneous group) no deletion was found. In this group, a boy and a girl from consanguineous parents, having a combination of polymicrogyria and pachygyria may in fact have an autosomal recessive disorder. If the deletion on 17p13.3 in the MDS patient is caused by one de novo event in one germ cell, the risk of recurrence will be very small. However, a deletion involving 17p may also originate from a somatic mutation in the germ cell of the parents, as has been demonstrated in other

clinical entities such as the Duchenne muscular dystrophy [3] (for review see Hall).[54] This may lead to the recurrence in siblings, whereas constitutional DNA of the parents does not show the deletion. In the Duchenne muscular dystrophy the recurrence risk in mothers of patients with new mutations is calculated to be 14%.[3] Byers et al. hypothesized that 6% recurrence risk of de novo mutations of autosomal dominant osteogenesis imperfecta can be explained by gonadal mosaicism in one of the parents.[11] The number of patients in the families studied is very small, and until now no recurrences of MDS have been described in families with cytogenetically normal parents. However, prenatal DNA analysis offers the opportunity to exclude recurrence.

PS. Only recently, we examined a patient with clinical ILS and a deletion of chromosome 17p13.3 (DNA markers YNZ22.1 and YNH37.3). This observation stresses the importance of DNA analysis in all patients with lissencephaly type I. Moreover, it may appear questionable whether the diagnosis of MDS may be rejected in the absence of external signs considered typical for this syndrome.



## Chapter 7

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# CLINICAL AND CHROMOSOME STUDIES IN THREE PATIENTS WITH THE SMITH-MAGENIS SYNDROME

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### INTRODUCTION

As was demonstrated in the previous chapter, the Miller-Dieker syndrome (MDS) is related to a deletion of chromosome 17p13.3.[111] Other patients with a deletion on the short arm of chromosome 17 were searched for to investigate the presence of a possible overlap between contiguous gene syndromes.[106]

It appeared that recently a new syndrome was ascribed to a deletion of chromosome 17p11.2.[56] It is named "Smith-Magenis Syndrome" (SMS) as proposed by Van Tuinen et al.[119] after the first authors, who reported nine cases.[107] Clinical manifestations include dysmorphic facial features, mental retardation and hyperactivity. Twenty one patients have been reviewed elsewhere.[56,92,97,107,109,112,121] Most of the patients were younger than 15 years; the oldest, however, was 65 years old. Three additional patients, aged 1½, 29 and 59 years old, are reported here.

### CASE REPORTS

#### Patient 1

An 18 month old boy was examined because of mild psychomotor retardation. He was born at term as the second child of non-consanguineous parents. The older sibling was normal. Pregnancy and labour were unremarkable. Apgar scores were 7 and 9 after 1 and 5 minutes. Birth weight was 4000 grams. From early childhood he frequently suffered from otitis media and upper respiratory tract infections. Development was slightly retarded: smiling at the age of three months, rolling over from belly to back at eight months, sitting unsupported at 10 months, pulling himself up to a standing position at the age of 14 months, walking with support at the

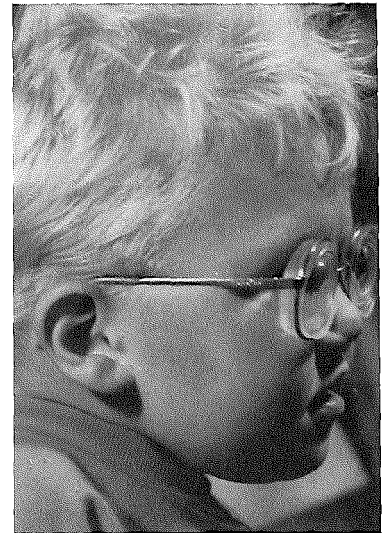
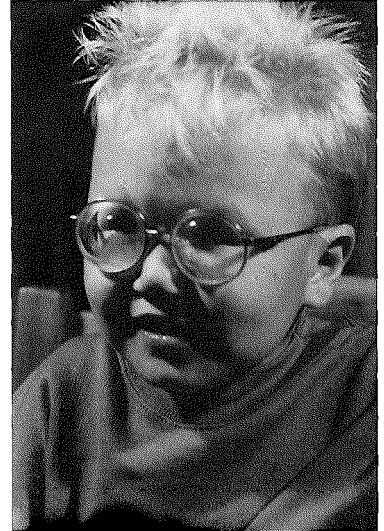
age of 18 months. At this age he produced a few single words. His front teeth started to erupt at the age of 8 months. He showed the following dysmorphic features: brachycephaly, frontal bossing, hypertelorism, epicanthi, down-slanted corners of the mouth, small low set ears (Figure 1) and abnormal palmar creases. Head circumference accorded with the P75, height and bodyweight with the P50. Slight convergent strabismus of the left eye was present as well as severe myopia of -8,5 diopters on the right eye and -6,5 on the left. There was slight generalized hypotonia. Further general and neurological examination showed no abnormalities. He was able to walk with support. At the age of 20 months he began to walk without support. He showed increasingly hyperactive behaviour and at the age of three years there was a distinct speech retardation. Mental retardation was mild. After correction of the myopia his performance improved. Laboratory investigations did not show any signs of congenital infections. Thyroid function was normal. Metabolic screening of a 24 hour urine sample did not show any abnormality. A CT scan showed a slight atrophy of the brain, with a normal ventricular system. Brainstem auditory evoked potentials showed a mixed conductive and perceptive hearing loss of at least 20-40dB in the 3KHz range. Conductive hearing loss corresponded with the presence of middle ear pathology. Chromosome analysis of lymphocytes and skin fibroblasts showed a 46,XY karyotype with an interstitial deletion of the proximal G-negative band of the short arm of chromosome 17(p11.2). Both parents showed normal karyotypes. Additional investigation with the probes pYNZ22, pYNH37.3 and p144D6, specific for the 17p terminal region [71], revealed no deletion in the 17(p13.3) band. Probes in the 17(p11.2) region are not yet available.

### Patient 2

This patient is the second child in a family of three children. The elder and younger brother were normal. Pregnancy and delivery were without complications. Psychomotor development was slow: he started to walk at the age of 3 years and even now, at the age of 29, he does not speak. Because of aggressive behaviour he has been treated with

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Figure 1. Patient 1 at the age of 36 months. There is brachycephaly, frontal bossing, hypertelorism and low set small ears.





neuroleptics. Since the age of 11, he suffered from epileptic fits, several times a year, treated successfully with valproic acid. The EEG showed epileptiform activity in the temporal areas. At the age of 29 years the height was 160 cm (<P3 percentile), and the head circumference 57 cm (at the P50). He could utter some sounds with a deep voice. He was brachycephalic, had thick lips but a normal tongue with normal motility. His vision could not be determined accurately but he seemed to see small objects. He walked on his toes. Apart from general clumsiness, the neurological examinations was normal. Cytogenetic investigation showed a paracentric inversion in the short arm of chromosome 17 with breakpoints in 17(p11.1) and 17(p13). The karyotypes of both parents were normal. Blood for DNA analysis was not available.

### Patient 3

This 59 year old mentally retarded man is the first born of twelve children. Pregnancy and delivery were without complications. The other children are healthy. Up to the age of 55, he was taken care of at home; his mother's death led to his institutionalization. In recent years there have been progressive walking problems. On physical examination a remarkable macroglossia and thick lips with, however, normal motility was noticed. Head circumference was on the P50, his length was 1.64 m (smaller than the P3), and his weight according to length on the P90. His hands were short and broad with clinodactyly of the fourth and fifth fingers bilaterally. He could not walk independently for more than a few steps with a spastic gait of the right leg. He spoke in three or four word sentences. Vision was 70 percent on both sides. He had a hearing device on the right ear because of a perceptive loss of 50 dB. He showed hyperreflexia with an extensor plantar response on the right. Routine blood investigation, including thyroid function, electroencephalogram and visual evoked potentials were normal. X-ray examination of the cervical spine demonstrated osteogenic narrowing of the spinal canal. Psychological tests revealed an I.Q. of 30. His karyotype in prophase chromosomes showed a deletion of the short arm of chromosome 17, with break points in the regions 17p11.1 and 17p11.2. The karyotype of his father was normal. As his mother had died, no information about her karyotype could be obtained. This was also the reason that no study with DNA markers was performed.

**Table 1. Symptoms of patients with the Smith-Magenis Syndrome.**

	1*	2	(%)
Male:Female	11M:10F	3M:0F	14M:10F
Brachycephaly	16/16	3/3	100
Prominent forehead	13/18	3/3	76
Broad face	15/16	2/3	89
Broad nasal bridge	18/21	3/3	88
Flat midface	17/17	3/3	100
Prominent jaw	11/17	2/3	65
Delayed dentition	8/16	1/1	53
Malpositioned ears	8/17	1/3	45
Malformed ears	12/18	1/3	62
Strabismus	7/13	1/3	50
Myopia	1/16	1/3	11
Short broad hands	12/14	2/3	82
Abn. palm. creases	7/18	3/3	48
Cong. heart defect	9/18	0/3	43
Seizures	6/11	2/3	57
Growth deficiency	12/18	0/3	57
Microcephaly	8/17	0/3	40
Mental retardation	20/20	3/3	100
Hyperactive	13/13	3/3	100
Self mutilation	10/13	1/3	69
Speech delay	16/18	3/3	100
Hearing loss	10/18	2/2	60
Hoarse/deep voice	6/11	1/3	50

1\* 56,92,97,107,109,112,121

2 = this series.

Abn.palm.creases: Abnormal palmar creases

Cong.heart defect: Congenital heart defects

## DISCUSSION

Two separate clinical conditions seem to be associated with a deletion of the short arm of chromosome 17: the Smith-Magenis Syndrome (SMS) and the Miller-Dieker Syndrome (MDS).[119] The deletion in the MDS is located distally from the deletion associated with SMS. In the SMS the deletion is interstitial [region 17(p11.2)] whereas in the MDS the deletion is terminal or subterminal [region 17(p13.1-2-3), always including the band 17(p13.3)]. Until now a deletion has been found in every MDS patient with probes lying in the 17(p13.3) band [71], but

sometimes the deletion in the MDS is too small to be detected by chromosome analysis. The extent of the deletion is variable in both syndromes [107,111] and this may explain the variable severity of the clinical pictures. At this moment no specific DNA markers in the region 17 (p11.2) are available. In future, submicroscopical deletions in the SMS may be detected with proper DNA probes. This has already been demonstrated in some MDS patients.[103,119] (Chapter 6) Until now no recurrences within a family have been found. In one patient a translocation has been mentioned.[56] There have been too few cases of the SMS for an adequate estimate of recurrence. Germinal mosaicism for chromosomal abnormalities is known

Table 2. Differences between MDS and SMS

	MDS	SMS
Male:Female	17M:15F	14M:10F
Retardation	profound	mild to severe
Lissencephaly type I	32/32	0/8
Microcephaly	31/32	8/20
Brachycephaly	0/32	19/19
Midface hypoplasia	0/32	20/20
Short, broad hands	0/32	14/17
Congenital heart defect	6/28	9/21
Abnormal palmar creases	10/10	10/21
Hyperactive	0/32	13/13
Seizures	32/32	8/14
Associated chromosome region	17(p13)	17(p11)

according to the literature

[10,13,19,31,51,52,56,71,103,104,111,119,26]

Table 3. Cytogenetics in the Smith Magenis Syndrome\*

	N
Partial deletion 17p11.2	14
Deletion 17p11.2	5
Deletion 17p11.1,p12	2
Deletion 17p11	1
Deletion 17p11.1,p11.2	1
Inversion 17(p11.1,p13)	1
Both normal parents	12
Only one parent studied	5
Neither parents studied	7

\* 107,112,56,109,97,121

to occur, possibly giving rise to up to a 5% recurrence rate in sporadic cases of this type.[54] The clinical signs of the SMS are mentioned in Table 1. Constant findings are mental retardation, speech delay, hyperactive behaviour, brachycephaly with a flat midface and short broad hands. Life expectancy is longer than initially believed. Mental retardation is moderately severe, with relatively adequate language development. The clinical differences between the SMS and the MDS are presented in Table 2. It is easy to separate these two conditions on clinical grounds. Microcephaly is present in almost every MDS patient, in the SMS in only 40%. The neuronal migration disturbances are very severe in MDS leading to complete or nearly complete agyria. In the SMS only one autopsy is known, showing a slight disturbance in neuronal organization.[107]

Recognition of the Smith-Magenis syndrome and detailed analysis of deletions on 17p (including DNA analysis) may identify the minimal size of the deletion in this syndrome. Also, the relation between size of the deletions and symptoms [107] may become classified in this way.



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## GENERAL DISCUSSION

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The observation of two different types of lissencephaly [23] prompted the classification into type I and II.[32] This classification uses the data from histology, gross brain morphology, somatic dysmorphisms and cytogenetics (Chapter 3). This thesis concerns the type I lissencephaly only, involving 27 patients. Lissencephaly type I was considered as a rare congenital malformation of the brain [20,38] and no precise data on its prevalence at birth were known. Studying probably all Dutch patients in the period 1980-1988, we could establish the prevalence at birth.

The grade of lissencephaly is related to life expectancy: patients with a less severe grade of lissencephaly survived longer than patients with (almost) complete agyria. The 5 year survival of 22 patients was 74% . The oldest patient in our studies has now reached the age of 18 years. (Chapter 2)

Clinical characteristics were studied extensively in 21 patients. All patients were severely retarded; many had microcephaly and epileptic seizures. The main causes of death are infections. The 21 patients in our study were classified as cases (n=4) of the MDS, or as cases (n=17) of ILS. Other larger series [49,29] found a similar relative distribution of MDS and ILS (Chapter 3). The diagnosis of lissencephaly type I can be made by the combination of clinical signs and the findings on neuroimaging (Chapter 5) or autopsy (Chapter 3). The EEG may be helpful in making the diagnosis (Chapter 4). The abnormally high voltages seen on the EEG of children with lissencephaly may be partly explained by the smooth brain surface, reducing the distance between the surface electrode and the electrical source.

A genetic origin was suspected after the observation of recurrence in sibs.[30,48,76] Recurrence of MDS in siblings could retrospectively be explained by a balanced translocation in a parent (resulting in risk of unbalanced offspring).[51,52,111] Another possibility of increased risk in cytogenetically normal parents is a germ cell mosaicism for a (submicroscopical) deletion of chromosome 17p13.3. Remarkable findings in MDS are:

\* All patients with a clinically confirmed MDS show a (submicroscopical) deletion of 17p13.3 (with at least a deletion for DNA probes YNZZ22.1 and YNH37.3).

\* In all but two cases, this deletion occurred in the paternal chromosome

\* Future studies are needed to see if there are differences between the effects of similar deletions in the paternal or in the maternal chromosome 17p, as occurs in the Prader-Willi syndrome (paternally derived chromosome 15 deletion) and the Angelman syndrome (maternally derived). The two patients with a maternal deletion for the DNA probes YNZ22.1 and YNH37.3 showed the clinical characteristics of the MDS (Chapter 6). Until now genomic imprinting does not seem to play a role in the MDS.[55]

\* In ILS, no deletion with DNA markers of chromosome 17p is found. It remains to be studied, using additional probes, if no deletions are present in ILS elsewhere.

In the Isolated Lissencephaly Sequence an autosomal recessive genetic transmission has been suggested, because of parental consanguinity in one case, and the description of three affected brothers.[93] However there is no known recurrence of ILS among sibs in our own series. In our series no parents were consanguineous. The cause of the ILS is unknown, but probably heterogeneous. Some hypotheses about the etiology in ILS are mentioned in Chapter 1. In the literature some patients with a lissencephaly type I, who did not fit in either the criteria for the MDS nor in those of the ILS have been reported from consanguineous parents and with affected sibs.[1,85,98] It is obvious that one should consider an increased risk of recurrence until 25% in counselling parents of a child who has the ILS.

Identifying the deletion in MDS will probably open new insights, also on normal brain development. Further analysis of the critical MDS region may result in isolation of the genes responsible for the MDS phenotype. Maybe a product made by the deleted DNA is important during the process of neuronal cell migration. It is also possible that the clinical criteria for the MDS will be revised. Until now all patients (except one, unpublished data) with a deletion of the DNA markers YNZ22.1 and YNH37.3 showed the MDS, and there are no MDS patients without such deletion (Chapter 6). The one not fulfilling the clinical MDS criteria showed a lissencephaly grade 3. However, the division of lissencephaly into grades of severity is artificial division. From embryogenesis, it follows that a continuum exists from grade 1 to 4. It was therefore predictable that some patients with a lissencephaly grade 3 or 4 would have the same etiology as the MDS. Maybe the DNA analysis will have to be included into the criteria for MDS.

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## SUMMARY

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Lissencephaly type I is a rare developmental disorder of the neocortex. The neuronal migration normally occurring especially between the 8th-16th week of gestation is severely disturbed, resulting in a total or partial lack of cerebral sulci. In Chapter 1 we give a review of the literature. With the cooperation of Dutch departments of child neurology and clinical genetic centres 27 patients with lissencephaly type I were collected between april 1986 and august 1990. These data allowed for the first time to establish the prevalence at birth: 12/1000.000 births. Contrary to older literature indicating a short life expectancy of lissencephaly the 5 year survival of 22 patients in our study was 74%. However the degree of the brain malformation was important: in complete or nearly complete agyria 5 year survival was 54% compared to 91% in cases of mixed agyria/pachygyria or complete pachygyria.

The clinical spectrum of 21 patients with lissencephaly type I (Chapter 3) shows severe retardation and epilepsy in all cases; 19 patients were microcephalic. Four patients fulfilled the criteria of the Miller-Dieker syndrome (MDS): facial dysmorphism, and other somatic abnormalities as syndactyly, corneal clouding, sacral dimples. The other patients were classified in the Isolated Lissencephaly Sequence (ILS), they showed only secondary facial dysmorphisms. All our MDS patients showed lissencephaly grade 1 or 2 (complete and almost complete lissencephaly), patients with ILS also showed lissencephaly grade 3 or 4 (mixture of agyria and pachygyria or complete pachygyria). Patients with lissencephaly grade 1 or 2 developed seizures earlier than patients with a grade 3 or 4. Patients with lissencephaly grade 1 or 2 were always microcephalic and showed hardly any psychomotor development. In 7 from the 11 patients with lissencephaly grade 3 or 4, microcephaly was present. Patients with lissencephaly grade 3 or 4 showed some slight development. During life the diagnosis can be made by using the criteria described in Chapter 5 for the CT or MR scan. The CT and MR scan's of 22 lissencephaly patients were compared to a control group consisting of 49 patients with epilepsy, mental retardation or trauma and a normal CT or MR scan. The lissencephaly patients showed a smooth brain with a cortex thicker than 10 mm, and a foetal form of the Sylvian fissure with an index of the width/depth larger than 0,29. The differences with the control group were significant. The interdigitations of the white matter are lacking or decreased. By counting the number of primary and secondary sulci a division in grades 1 to 4 can be made. There was no

relationship between the grade of lissencephaly and the cortical thickness. If present, sulci were predominantly located in the frontotemporal region. In contrast to the literature no intracranial calcifications were seen in the MDS patients.

EEG studies, scarcely reported in ILS and MDS, may support the diagnosis lissencephaly (Chapter 4). The 114 EEG's obtained from the 21 patients described in Chapter 2 were compared to 52 EEG's from 21 patients with an atypical cortex dysplasia and to a control group of 882 EEG's recorded from 823 children for various reasons. The EEG's of lissencephaly patients showed significantly more often the following patterns: generalized fast activity (8-18/s) with amplitudes above 50uV; sharp- and slow-wave complexes with amplitudes above 500 uV; and sometimes an alternating pattern with amplitudes up to 2000 uV. In lissencephaly the first two patterns were seen in 95% of the patients compared to 5% in patients with an atypical cortical dysplasia and only 0,4% in the control group. SEP's by stimulating the median nerve were recorded for the first time in ten patients. They were severely disturbed, showing normal latencies at the point of Erb and the neck, but absent or prolonged latencies of the cortical component the N20 peak with a highly abnormal configuration.

Cytogenetic studies revealed a microscopical deletion of 17p13.3 in one of the five MDS patients. However, all five MDS patients had at the DNA level a deletion in the chromosome 17 (in four patients paternally derived and in one patient maternally) when tested with the DNA markers YNZ22.1 and YNH37.3. In 17 ILS patients and 9 patients with an another cortical dysplasia similar deletions were excluded. In one family prenatal DNA analysis in chorionic villi excluded the recurrence of MDS in a subsequent pregnancy. All MDS patients showed a deletion for the DNA markers YNZ22.1 and YNH37.3. However, we recently saw a child with a clinical ILS and a deletion of 17p13.3 in DNA analysis, stressing the importance of DNA analysis in all patients with lissencephaly type I.

To investigate the presence of a possible overlap between contiguous gene syndromes all patients with a deletion of chromosome 17p were collected. It appeared that a syndrome different from lissencephaly is related to a deletion more proximal on the short arm of chromosome 17. This syndrome, named the Smith Magenis syndrome, is described in Chapter 7.



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## SAMENVATTING

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Lissencephalie type I is een zeldzame aanlegstoornis van de hersenmantel. Hierbij is de neuronale migratie gestoord, waardoor de hersengroeven niet of slechts gedeeltelijk tot ontwikkeling komen. Het uitwendig aspect van de hersenen is dan geheel of gedeeltelijk glad. Het woord lissencephalie betekent dan ook "gladde hersenen". In de klinische literatuur worden nog twee andere termen vaak gebruikt voor lissencephalie, namelijk agyrie en pachygyrie. Agyrie betekent het ontbreken van hersengroeven en bij pachygyrie zijn er enkele hersengroeven tot ontwikkeling gekomen. De term lissencephalie wordt vaak voor beide gebruikt.

In hoofdstuk 1 wordt een overzicht gegeven van datgene wat er in de literatuur bekend was, voordat er met onderzoek begonnen werd. Migratie van neuronen naar de uiteindelijke hersenmantel vindt bij de mens plaats tussen de 8ste en de 16de week van de zwangerschap. Bij de lissencephalie type I zijn de cellen halverwege dit proces blijven steken. Meestal is er dan ook sprake van een gestoorde migratie van de hersenstam, zodat vaak heterotopien van de olijkernen worden gezien. Het cerebellum is redelijk intact. Bij de lissencephalie type II is de migratie van cellen naar de hersenmantel nog ernstiger gestoord dan bij de type I. Bij de type II lissencephalie zijn de horizontale cellagen dan ook in het geheel niet meer herkenbaar.

Hoofdstuk 2 beschrijft een epidemiologische studie van patiënten met lissencephalie type I in Nederland. Aanleiding om dit onderzoek te doen was het feit dat er geen gegevens in de literatuur waren te vinden betreffende prevalentie bij geboorte en de 5 jaars overleving. De voorgaande literatuur betrof voornamelijk beschrijvingen van enkele patiënten. Dankzij de hulp van de afdelingen kinderneurologie en klinische genetica in de grote ziekenhuizen van ons land, tezamen met enkele grote instituten van de zwakzinnigenzorg, was het mogelijk om in de periode van april 1986 tot augustus 1990 in totaal 27 patiënten met een lissencephalie type I te onderzoeken. Er werd een prevalentie bij de geboorte berekend van 12 gevallen/1000.000 geboorten. In de voorgaande literatuur was er van uitgegaan dat de levensverwachting bij deze kinderen erg kort zou zijn. De 5 jaars overleving werd bij 22 patiënten bekeken en bleek 74% te zijn. Er werd vervolgens gekeken naar factoren die invloed hebben op de 5 jaars overleving. Patiënten met een lissencephalie graad 1 of 2 (volledige agyrie of bijna volledige agyria) hadden

een 5 jaars overleving van 54% vergeleken met 91% bij patiënten met een lissencephalie graad 3 of 4 (een mengbeeld van agyrie met pachygyrie of volledige pachygyrie).

Hoofdstuk 3 geeft de resultaten van het klinische beeld van 21 patiënten met lissencephalie type I. Vergeleken met de vorige literatuur is onze patiënten-groep een van de grootste. Alle patiënten waren ernstig geretardeerd, hadden epilepsie en 19 patiënten waren microcephaal. Vier patiënten in deze serie voldeden aan de criteria van het Miller-Dieker syndroom: duidelijke dysmorfie van het gelaat met meestal andere afwijkingen in het lichaam. De andere patiënten pasten in de criteria van de geïsoleerde lissencephalie: secundaire dysmorfie van het gelaat zonder andere dysmorphe kenmerken. In overeenstemming met de voorgaande literatuur was dat de MDS patiënten een lissencephalie graad 1 of 2 hadden, terwijl de geïsoleerde lissencephalie patiënten een lissencephalie beeld lieten zien variërend van een graad 1 tot 4. In de gehele serie hadden elf patiënten lissencephalie graad 1 of 2 en de andere elf patiënten een graad 3 of 4. Patiënten met een lissencephalie graad 1 of 2 bleken eerder epilepsie te krijgen dan patiënten met een graad 3 of 4. Patiënten met een lissencephalie graad 1 of 2 waren allemaal microcephaal en toonden nauwelijks enige psychomotore ontwikkeling. Microcephalie was afwezig in vier van de elf patiënten met een lissencephalie graad 3 of 4, en deze patiënten toonden enige ontwikkeling: zij hadden enig contact met hun omgeving en konden wisselend kruipen.

Tijdens het leven zal de diagnose lissencephalie bij voorkeur gesteld worden met behulp van de CT of MR scan, met gebruik van bekende criteria. In de literatuur zijn de morfologische criteria hiervoor beschreven. In hoofdstuk 5 werden de CT en MR scan's van 22 lissencephalie patiënten vergeleken met die van een controle groep van 49 patiënten, waarbij het onderzoek als niet afwijkend was afgegeven. De indicatie voor het onderzoek bij de controle groep was als volgt: epilepsie, mentale retardatie en trauma. Bij de lissencephalie patiënten werd er een glad hersenoppervlak gezien met een cortex welke dikker was dan 10 mm, en een foetale vorm van de fissuur van Sylvius met een index van de breedte/diepte van meer dan 0,29. In de controle groep was de cortex dikte altijd minder dan 7 mm, en was de index breedte/diepte van de fissuur van Sylvius altijd kleiner dan 0,25. De interdigitatie van de witte stof was verminderd of afwezig. Door het aantal primaire en secundaire sulci te tellen kon een onderverdeling in graden worden aangebracht lopend van graad 1 tot graad 4. Er werd geen relatie gevonden tussen de graad van lissencephalie en de cortex dikte. Indien er sulci aanwezig waren, dan werden zij voornamelijk in de frontotemporale gebieden gezien. In de literatuur is deze locatie van enkele sulci beschreven, maar dan zowel frontotemporaal als occipitoparietaal. In tegenstelling tot de literatuur werden er geen intracraniele verkalkingen gezien bij onze patiënten met het Miller-Dieker syndroom.

De bijdrage van het EEG in de diagnostiek bij lissencephalie is nauwelijks onderzocht. Er werden 114 EEG's van 21 lissencephalie patiënten vergeleken met 52 EEG's van 21 patiënten met een cortexdysplasie en met een controle groep bestaande uit 882 EEG's van 823 diverse andere patiënten. Bij lissencephalie ziet men significant vaker de volgende patronen: gegeneraliseerde snelle activiteit (8-18/s) met amplituden boven de 50  $\mu$ V., pick-golf varianten met een amplitude boven de 500  $\mu$ V., en een alternerend patroon met amplituden tot 2000  $\mu$ V. De eerste twee patronen ziet men in 95% van de lissencephalie patiënten, in 5% van de

patiënten met een atypische cortex dysplasie en in 0,4% in de controle groep. SEP's werden via de N. medianus geregistreerd in tien lissencephalie patiënten en waren ernstig afwijkend: er werden responsies verkregen met een normale latentietijd bij het punt van Erb en de nek, maar de latentie van de corticale component (N20), indien aanwezig, was sterk verlengd met een afwijkende vorm. In de literatuur waren niet eerder SEP's beschreven in een serie lissencephalie patiënten.

Chromosomaal onderzoek toonde bij een van de vijf geteste Miller-Dieker patiënten een deletie van de korte arm van chromosoom 17. In hoofdstuk 6 zijn de resultaten beschreven van onderzoek met de DNA marker YNZ22.1, YNH37.3 en VAW 508 bij 5 patiënten met het Miller-Dieker syndroom, 17 patiënten met de geïsoleerde lissencephalie, 1 patiënt met een niet te classificeren lissencephalie en 9 patiënten met een atypische cortex dysplasie. Bij vier van de vijf Miller-Dieker patiënten werd er een deletie gevonden voor het paternale chromosoom en in een Miller-Dieker patient een deletie voor het maternale chromosoom met de bovengenoemde markers. Bij de andere patiënten werd dit niet gevonden. Er werd eenmaal prenatale diagnostiek verricht met DNA analyse waardoor herhaling van het Miller-Dieker syndroom in een volgende zwangerschap kon worden voorkomen.

In het hoofdstuk 7 wordt het Smith-Magenis syndroom beschreven, zonder lissencephalie, maar met een deletie op de korte arm van het chromosoom 17p. In een poging om alle lissencephalie patienten te verzamelen werd er namelijk ook gezocht naar patienten met andere deleties van 17p. De deletie in het Smith-Magenis syndroom is meer proximaal gelegen dan de deletie in het Miller-Dieker syndroom. De verschillen tussen beide syndromen zijn in dit hoofdstuk beschreven.



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## LIST OF PUBLICATIONS

The chapters of this thesis were adapted from the following articles

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1. De Rijk-van Andel JF, Arts WFM, Barth PG, Loonen MCB: Diagnostic features and clinical signs in 21 patients with Lissencephaly type I. *Devel Med and Child Neurol* 1990;32:707-717
2. De Rijk-van Andel JF, Arts WFM, De Weerd AW: EEG and Somatosensory Evoked Potentials in a series of 21 patients with Lissencephaly type I. *Neuropediatrics*, in press.
3. De Rijk-van Andel JF, Arts WFM, Hofman A, Niermeijer MF, Staal A: Epidemiology of Lissencephaly type I. *Neuroepidemiol*, submitted
4. De Rijk-van Andel JF, Catsman-Berrevoets CE, Van Hemel JO, Hamel AJH: Clinical and chromosome studies in three patients with the Smith-Magenis Syndrome. *Develop Med and Child Neurol*, accepted
5. De Rijk-van Andel JF, Eussen HJ, Brunner H, van Hemel JO, Halley DJJ, Los F, Niermeijer MF, Oostra BA: Studies with DNA-markers in patients with Lissencephaly type I and other cortical dysplasias. *Am J Med Gen*, submitted
6. De Rijk-van Andel JF, Van de Knaap MS, Valk J: CT and MRI in Lissencephaly type I. *Neuroradiol*, submitted





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## CURRICULUM VITAE

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The author of this thesis was born on 24 March 1957 in Rotterdam. She graduated from the Marnix Lyceum in 1975. After finishing her medical training at the Erasmus University in Rotterdam, she started to work in the department of neurology of the Ikazia Hospital Rotterdam. From October 1982 to September 1983 she worked in the department of neurosurgery of the Academic Hospital Dijkzigt and the Sophia Children's Hospital Rotterdam (prof. dr. R. Braakman). From October 1983 to January 1984 she worked in the department of neurology of the Academic Hospital Dijkzigt Rotterdam (prof. dr. A. Staal). Her neurology training was continued in the Westeinde Hospital, The Hague, and was completed in June 1989 (for the neurology dr. L.C.M. Moll and dr. J.T.J. Tans, for the neurosurgery Dr. M.Th.A. van Duinen, for the clinical neurophysiology dr. E.J. Jonkman, and for the psychiatry E.W. de Regt-Teutscher). She spent one year in the department of paediatrics in the same hospital to be able to become a child-neurologist (G.M. de Jong). On 11 november 1989 she was awarded with the Dr. Eduard Hoelen "award" for her scientific work. Now she works part-time in the department of neurology of the Ikazia hospital in Rotterdam.

