Correlates of lower respiratory tract infections and nutritional state in children with severe generalized cerebral palsy and intellectual disability

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Correlates of Lower Respiratory Tract Infections and Nutritional State in Children with Severe Generalized Cerebral Palsy and Intellectual Disability

Correlaten van lage luchtweginfecties en voedingstoestand bij kinderen met ernstige meervoudige beperkingen

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Chapter 1

General Introduction

Children with severe generalized cerebral palsy and intellectual disability represent a small part of the general Dutch population. Their share in healthcare, however, is disproportionally large. Due to their disabilities they are particularly susceptible to various medical problems, which cause much distress, and may even shorten their life expectancy. Many children do not reach adulthood,[1-4] the main cause of death in this population being lower respiratory tract infections.[3,5,6]

The present study was initiated in 2001 in reaction to the need to gain insight into causes of pulmonary infections in these children, as expressed by paediatricians and intellectual disability physicians in the Netherlands. Although children were treated with antibiotics (as a prophylaxis and/or as treatment in case of acute pulmonary infection), recurrent lower respiratory tract infections continued to cause much morbidity and mortality. Preventive measures were needed. This study was set up to evaluate the incidence and correlates of pulmonary infections in this population, and should be considered as a first step that may lead towards the development of a guideline for the prevention of lower respiratory tract infections. The present dissertation is the second of two, resulting from this study. The first dissertation was written by Rebekka Veugelers, and dealt primarily with feasibility of diagnostic methods in this population.[7]

POPULATION OF INTEREST

The term 'cerebral paralysis' was first used by an English orthopaedic surgeon, named William Little, to describe joint contractures and deformities resulting from long-standing spasticity.[8] Little indicated that the cause of this spasticity was often brain damage during infancy. Since then, the definition of cerebral palsy has been described and revised by a large number of authors and working groups. The multitude of definitions merely reflects the difficulty of grasping the essence of the condition. The most recent conceptualization of cerebral palsy has resulted in the following description. "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems".[9]

In the Netherlands, the estimated prevalence of cerebral palsy was 2.4 per 1000 live births in 1986-1988.[10] Although the cause of cerebral palsy in a child frequently remains unknown, many conditions have been described as risk factors. The most important risk factors are low birth weight, intrauterine infections and multiple gestations.[11] However, other conditions, such as premature birth, sepsis, intracerebral haemorrhage, meningitis, hydrocephalus, placenta pathology, intrapartum asphyxia, coagulation disorders, or genetic disorders have been mentioned as well.[12-15]

The primary disorder in cerebral palsy is motor disability, which may vary from mild to severe. The majority of persons with cerebral palsy experience gross motor disability, and 30% to 50% need help in various activities of daily living.[16] Intellectual disability is estimated to be present in 35% to 50% of all persons with cerebral palsy.[16,17]

This study focuses on health-related problems in children with severe generalized cerebral palsy and intellectual disability. In 2000, the number of children and adolescents with severe generalized cerebral palsy and intellectual disability in the Netherlands was estimated at 2100.[18] Most of these children and adults live at home and visit a day-care centre. Many medical and paramedical professionals are involved in the everyday care for these children: family doctors, intellectual disability physicians, paediatricians, speech-language pathologists, occupational therapists, physical therapists, dieticians, and nurses. For most of the parents, the first professional to turn to in case of health problems is the family doctor or the intellectual disability physician. However, because these children are frequently affected by a multitude of health problems, paediatricians are often consulted as well.

MAJOR COMORBIDITY

Apart from motor- and intellectual disability, children with cerebral palsy are at risk of a range of comorbid disorders. Frequently observed problems are sensory disorders (cerebral visual and hearing impairment), and epilepsy.[17] Other frequently occurring disorders are gastrointestinal problems: dysphagia,[19-22] gastro-oesophageal reflux,[23-27] delayed gastric emptying,[23] constipation,[24,28-30] and the development of a poor nutritional state,[20,31-33] and osteoporosis.[34] In the present study, the primary health problems of interest are lower respiratory tract infections. Although, from literature, we know that these infections are the primary cause of death in children with cerebral palsy,[3,5,6] little is known about the incidence and correlates of pulmonary infections in this population.

STUDY GOAL

Lower respiratory tract infections are a major health risk in children with severe generalized cerebral palsy and intellectual disability, and their prevention may have an important impact on general health, quality of life and life expectancy in these children. At present, however, little is known about the distribution of pulmonary infections and their risk factors among this population. Without this knowledge it is impossible to evaluate preventive measures and their effects on the incidence of lower respiratory tract infections and related mortality. Therefore, in the present study, the incidence of pulmonary infections was assessed in a population-based sample of children with severe generalized cerebral palsy and intellectual disability.

Furthermore, the correlation of recurrent lower respiratory tract infections with general child characteristics (age, gender, severity of motor disability, etc) and important comorbid disorders that are hypothesized to be risk factors, such as dysphagia, gastro-oesophageal reflux, constipation and poor nutritional state, has been evaluated. Because the prevalence of dysphagia, gastro-oesophageal reflux, constipation and poor nutritional state has never been evaluated in a representative, population-based sample of these children, the presence and characteristics of these disorders have been evaluated and described in detail as well. Although the association of constipation with pulmonary infections is discussed in the present dissertation, the diagnosis, prevalence, and characteristics of the disorder have already been discussed elsewhere.[35]

The main questions to be answered in this dissertation were:

– "What is the incidence of lower respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability?"

– "What are the characteristics of children at risk of recurrent pulmonary infections, and which comorbid disorders are associated with an increased risk of recurrent pulmonary infections?"

– "What is the distribution of dysphagia, gastro-oesophageal reflux and poor nutritional status in the study population, and which child characteristics are associated with their presence and severity?"

THE OUTLINE OF THE PRESENT DISSERTATION

The design of the present study, in particular the recruitment of the study population and its representativeness, is described in chapter 2. The following three chapters describe the epidemiology of dysphagia (chapter 3), gastro-oesophageal reflux (chapter 4) and poor nutritional state (chapter 5) in the studied population. Apart from a description of nutritional status, in chapter 5 an evaluation of the association of energy intake with nutritional status is discussed as well. Chapter 6 answers the main study questions: "What is the incidence of lower respiratory tract infections in these children", and "Which children are at risk of recurrent pulmonary infections, in terms of child characteristics and comorbid disorders". In chapter 7 the most important findings of the present dissertation are summarized and discussed in a broader perspective, and implications for everyday practice and future research are made.

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Chapter 2

A population-based nested case control study on recurrent pneumonias in children with severe generalized cerebral palsy: ethical considerations of the design and representativeness of the study sample

BMC Pediatr 2005;5(1):25

ABSTRACT

Background

In children with severe generalized cerebral palsy, pneumonias are a major health issue. Malnutrition, dysphagia, gastro-oesophageal reflux, impaired respiratory function and constipation are hypothesized risk factors. Still, no data are available on the relative contribution of these possible risk factors in the described population. This paper describes the initiation of a study in 194 children with severe generalized cerebral palsy, on the prevalence and on the impact of these hypothesized risk factors of recurrent pneumonias.

Methods / Design

A nested case-control design with 18 months follow-up was chosen. Dysphagia, respiratory function and constipation will be assessed at baseline, malnutrition and gastro-oesophageal reflux at the end of the follow-up. The study population consists of a representative population sample of children with severe generalized cerebral palsy. Inclusion was done through care-centres in a predefined geographical area and not through hospitals. All measurements will be done on-site which sets high demands on all measurements. If these demands were not met in "gold standard" methods, other methods were chosen. Although the inclusion period was prolonged, the desired sample size of 300 children was not met. With a consent rate of 33%, nearly 10% of all eligible children in the Netherlands are included (n=194). The study population is subtly different from the non-participants with regard to severity of dysphagia and prevalence rates of pneumonias and gastro-oesophageal reflux.

Discussion

Ethical issues complicated the study design. Assessment of malnutrition and gastro-oesophageal reflux at baseline was considered unethical, since these conditions can be easily treated. Therefore, we postponed these diagnostics until the end of the follow-up. In order to include a representative sample, all eligible children in a predefined geographical area had to be contacted. To increase the consent rate, on-site measurements are of first choice, but timely inclusion is jeopardised. The initiation of this first study among children with severe neurological impairment led to specific, unexpected problems. Despite small differences between participants and non-participating children, our sample is as representative as can be expected from any population-based study and will provide important, new information to bring us further towards effective interventions to prevent pneumonias in this population.

BACKGROUND

Children with severe generalized cerebral palsy often have a combination of motor and intellectual disabilities. They frequently experience co-morbidity and their life expectancy is low,[1-11] with respiratory disease as a main cause of death.[1-3,8,10,12] Although it is common clinical knowledge that children with neurological impairment often have respiratory problems,[13-17] and get hospitalised for this with a major impact on their quality of life and life expectancy,[14,18] prevalence rates have not been studied prospectively. Retrospective prevalence estimates of pneumonias range from 31% per 6 months; 38% single episodes to 19% recurrent pneumonias per year.[19,20] Although several clinical specialists presume several conditions to be risk factors for pneumonias, population-based studies on this subject are lacking. Epidemiological identification of such risk factors will bring us further towards effective interventions to prevent pneumonias.

Hypothesized risk factors of respiratory disease in children / adolescents with neurological impairment / intellectual disabilities from the literature are listed in Table 1. These factors may co-exist and interact with each other. On top of this, normal childhood factors may exist, such as asthma or passive smoking. Pneumonias can be infectious or chemical of nature. To prevent pneumonias, adequate function of the protection mechanisms of the airways is essential. But in children with severe generalized cerebral palsy this protection system is often compromised or endangered due to several conditions.[14,15,20-29]

We hypothesize that malnutrition, dysphagia, gastro-oesophageal reflux, decreased respiratory function and constipation are the most relevant risk factors for recurrent pneumonias. Since scientific evidence for a relationship between these disorders and the occurrence of pneumonias is lacking, we aim to evaluate this in a large-scale epidemiological study. Our

Table 1 Hypothesized risk factors of pulmonary disease in children with neurological impairment / intellectual disabilities

recurrent aspiration (dysphagia, gastro-oesophageal reflux)[14-16,20,28,53,54]
inefficient cough / poor cough reflex[14,15,28]
poor airway clearance (immobility and retained secretions)[14,15]
respiratory muscle weakness and in-coordination[14,15,28]
chest wall or spinal deformities (poor pulmonary reserve)[14,15,28]
inadequate nutritional status (feeding problems, gastro-oesophageal reflux)[14,15]
miscellaneous factors[2,8,10,14-17]
bronchopulmonary dysplasia in preterm survivors
immune problems (Down's syndrome)
lipid aspiration in mineral oil treatment of constipation
reduced lung growth in skeletal dysplasias
normal childhood factors (e.g. asthma, passive smoking)[14,15]
immobility[3,10,27,28,55,56]

research questions are the following: (1) What is the prevalence of pneumonias in children with severe generalized cerebral palsy? (2) Are malnutrition, dysphagia, gastro-oesophageal reflux, decreased respiratory function and constipation risk factors for pneumonias in this group of children? The design of the study also allows us to determine the prevalence and presentation of the studied hypothesized risk factors.

This article describes the study design, diagnostic methods and the study population. Attention is paid to adaptations in the study design arising from ethical considerations as well as from the diagnostic methods required to study medical conditions in children with severe generalized cerebral palsy.

METHODS / DESIGN

Study design

This study has a nested case-control design and will be conducted in a representative group of children with severe generalized cerebral palsy, recruited through care centres (specialized day-care centres and residential facilities) and through specialized schools. In our study population, the hypothesized risk factors dysphagia, respiratory function and constipation will be assessed at baseline. However, for ethical reasons explained in the discussion paragraph, malnutrition and gastro-oesophageal reflux will be assessed at the end of the follow-up period. Cases are defined as children with recurrent pneumonias, and controls as children without pneumonias during a follow-up of 18 months. Cases and controls are matched on age, gender and GMFCS[30] level. A duration of the follow-up period of 18 months was considered sufficient, since we defined recurrent pneumonias as 2 or more episodes within a year. The study will not interfere with common medical practice and interventions in the study population during the follow-up period. Thus, children might be diagnosed and treated by their own physicians during the course of the study. The study design is depicted in Figure 1.

Setting

All diagnostic assessments in this study will be carried out on-site at the different care centres and specialized schools. In order to obtain a complete inclusion and therewith a representative study population, we had to keep the burden for the participants as small as possible. Hospital visits were considered an obstacle for participation. Furthermore, performing measurements in a familiar setting might improve cooperation of the children.

Sample size

Calculating a required sample size for this study was hampered, since valid prevalence numbers of both pneumonias and most of the supposed risk factors in this population were lacking in the literature. Prevalence numbers were estimated based on the available literature and

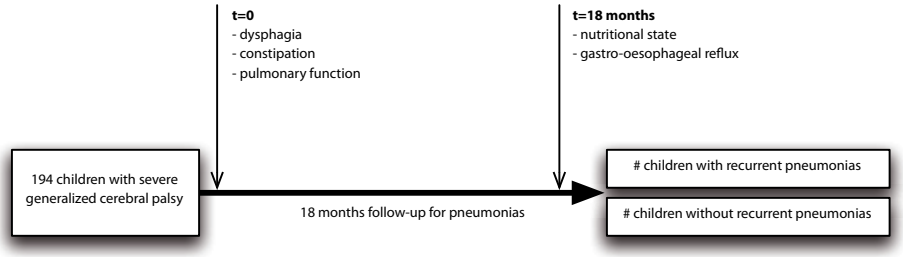

Figure 1 Study design
In this nested case-control study, a cohort of 194 children with severe generalized cerebral palsy is followed up for 18 months in order to record recurrent pneumonias (2 or more episodes per year). Possible risk factors are measured during the follow-up. Dysphagia, constipation and pulmonary function are diagnosed at baseline, while nutritional state and gastro-oesophageal reflux are diagnosed at the end of the study period.

on clinical experience. We calculated the required sample size for a univariate analysis, since the number of children required for a multivariate analysis including five separate variables will probably be quite large. In addition, we estimated that for logistical purposes a maximum number of 300 children could be included in this study. Required sample size was calculated for each possible risk factor separately, assuming a prevalence rate of recurrent pneumonias of 30% with a required power of 0.80 and an alpha of 0.05. The analysis for dysphagia, based on an estimated prevalence of dysphagia of 19% in the controls and 38% in the cases, resulted in the highest sample size (n=260). Assuming a loss-to-follow-up rate of 13%, recruitment numbers were set to 300 participants.

Inclusion criteria

In this study we aimed to include children (2 to 18 years), who have a combination of moderate to profound intellectual disabilities and a severe motor disability. The intellectual disability was defined as an IQ below 55 (or estimated by dividing the developmental age by the calendar age times 100). The motor disability was defined by hypertonic or hypotonic generalized cerebral palsy or a motor developmental delay to such an extent that a child can at best crawl. This corresponds to a Gross Motor Function Classification Scale (GMFCS) level IV or V.[30] These broad criteria, resulting in a heterogeneous cohort with regard to aetiology and disabilities, was chosen deliberately, because in daily practice, it is this heterogeneous group that causes a lot of concern for parents and physicians regarding the studied illnesses. Furthermore, the inclusion criteria had to be clear to non-medical personnel, to ascertain they could identify the eligible children.

Consent procedure

We approached all children with severe generalized cerebral palsy in a certain geographical area, an important prerequisite when studying a prevalence rate, to obtain a representative

sample of the total population. For pragmatic reasons, we chose an area of 50 kilometres around the cities of Rotterdam and Utrecht. We estimated that we could reach 500 children in this area. With an assumed consent rate of 0.60, this would provide the desired 300 participants. Within this area, we traced all facilities that might provide care to children and adolescents with severe generalized cerebral palsy, using the Dutch address guide for disability care. These centres were contacted and asked to participate in the study if they indeed provided care for such children. In the participating centres, parents or guardians of all children that met the inclusion criteria were informed, unless children were in a critical health status, when home situations were considered very unstable, or if parents were known to have a strong aversion to research. Information for parents was available in Dutch, English, and Turkish. For Moroccan families, a spoken introductory compact disc was available, since Berber is only a spoken language. Because gastro-oesophageal reflux can only be measured properly using an invasive method, parents had the opportunity to give consent with or without this measurement.

Inclusion period

Of the 93 care centres and specialized schools that had been contacted, 61 provided care for one or more children with severe generalized cerebral palsy. Fifty-six of these centres agreed to participate in our study. The other centres did not cooperate due to personnel shortage and besides this, one centre also considered the burden of the study for parents, children and personnel too large.

Participants

Within the participating care centres and specialized schools, 593 children were eligible for participation. Parents of 573 children were informed while the parents of 9 children were not contacted based on the previously mentioned reasons and 11 were not contacted because of ineffective internal procedures of care centres. Four children, for whom consent was given, appeared not to meet our inclusion criteria at first visit and were excluded. After a prolonged inclusion period of 20 months, this resulted in the informed consent for 194 children (consent rate of 33%). Although recruitment numbers were set to 300 participants, we stopped the inclusion for practical reasons. We had included nearly 10% of the Dutch population of children with severe generalized cerebral palsy.[31] Parents of 98 children gave consent including assessment of gastro-oesophageal reflux (Figure 2). Because of the broad inclusion criteria, not all children fulfilled the strict definition of cerebral palsy,[32] but all children had comparable disabilities. The different aetiologies of the disabilities of the participants are depicted in Table 2. Basic characteristics of the participants are listed in Table 3. All participating parents that gave consent preferred the questionnaires in Dutch, even when their native language was Turkish.

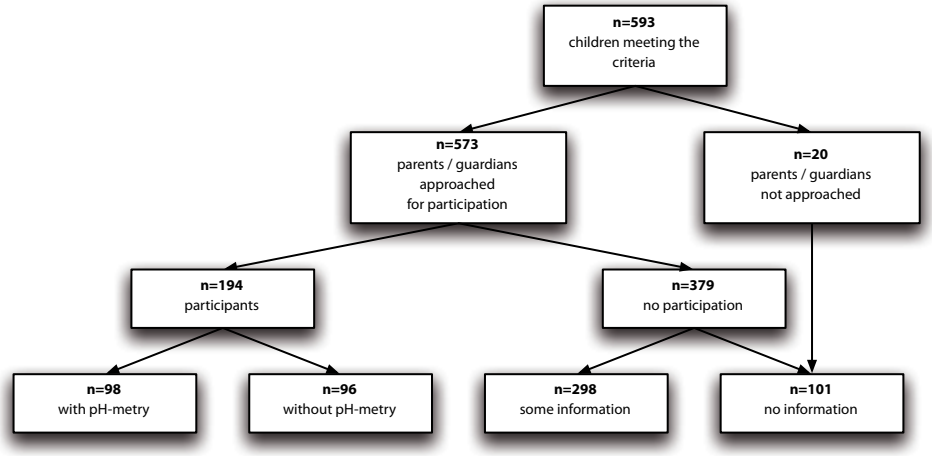

Figure 2 Flow chart of inclusion period
This figure depicts the inclusion of eligible children in the study from a predefined geographical area. 593 children met our inclusion criteria and parents or guardians of 573 children were informed. For several reasons, parents of 20 children were not informed. For 194 children informed consent was obtained and for 98 of those with additional consent for assessment of gastro-oesophageal reflux. For 379 children no consent was obtained. Carers of 298 of these children filled in a small questionnaire. Of 101 children no information was obtained.

Representativeness

Global written information on children that did not participate was obtained from parents, care centres or specialized schools, concerning reasons for no consent, frequency of pneumonias, gastro-oesophageal reflux, body mass index and diet. To our clinical experience, parental judgement of eating skills is unreliable. Therefore we asked which food types the child received and reformulated this into a rough scale of dysphagia. Children were categorised as severely dysphagic if they received daily tube feeding, with or without additional oral food. Children with dietary restrictions (liquid, solid, ground, pureed) were categorised as having moderate dysphagia. All other children were categorised as having "no or mild" dysphagia.

Brief written information on children's characteristics was acquired for 298 of the non-participants (for 169 children from parents and for 129 children from the care centre and school personnel). Information from 101 children that were asked to participate (17%) is lacking. The main reported reason for not participating was that parents were reluctant to any additional "hassle" with their child, mostly because of the extended medical history. Parents also considered the burden too large for themselves. Table 4 shows that the children that participate are slightly younger of age, and therewith have shorter height and lower body weight than the eligible children not participating in the study (BMI is not different between the groups). Gender is equally distributed. According to the parents' reports, the participating children have more severe dysphagia, more lower respiratory infections, and more gastro-oesophageal reflux than the non-participants.

Table 2 Aetiology of disabilities

	n	%
Congenital diseases		
Miller Dieker Syndrome / lissencephaly	7	
corpus callosum agenesis	5	
Cornelia de Lange syndrome	2	
Walker-Warburg syndrome	2	
unspecified abnormal brain development	16	
other non progressive syndromes	6	
other chromosomal abnormalities	9	
Rett syndrome	3	
Alpers syndrome	4	
Aicardi-Goutieres syndrome	2	
other progressive syndromes	5	
other congenital diseases	4	
	65	33.5
Pre and perinatal complications		
perinatal asphyxia	18	
cerebral palsy e.c.i.	13	
cerebral haemorrhage	6	
intra uterine CMV infection	5	
other infections	4	
other causes	7	
	53	27.3
Acquired		
meningitis / encephalitis	5	
trauma	3	
near drowning accident	2	
other	2	
	12	6.2
Combinations of causes		
congenital and acquired disease	6	
congenital disease and perinatal complications	5	
perinatal and acquired	3	
perinatal and hereditary progressive	1	
	15	7.7
Unknown cause	25	12.9
Missing	24	12.4
Total	194	children

Table 3 Characteristics of the participants

		%	valid*
GMFCS level V		82.7	0.95
Can communicate "yes" and "no"		20.6	0.87
Can verbally communicate "yes" and "no"		3.1	0.87
Living with parents at home		81.4	1
Intentional movements	none	34.8	
	little	27.9	
	regularly	37.7	0.66
Involuntary movements	most of the day	29.6	
	regularly	35.2	
	< 2 hours a week	35.2	0.64
Seated > 3 hours / day		84.5	0.68
Standing < 30 minutes / week		38.3	0.59
Activity < 30 min / day		51.3	0.58

* Fraction of the population with known information
GMFCS Gross Motor Function Classification System

Table 4 Comparison of the parent-reported characteristics between the participants and non-participants

		Non-participants		Participants	
			valid*		valid*
Total number		379		194	
Mean Age (years)		10.6 (4.3)	0.67	8.9 (4.4)	1
Gender (% of boys)		50.2	0.7	53.1	1
Mean Height (cm)		130.3 (21.9)	0.52	124.0 (20.1)	0.91
Median Weight (kg)		28.0 [17.0]	0.59	24.7 [16.1]	0.88
Median BMI (kg/m2)		16.4 [4.2]	0.51	15.9 [4.0]	0.85
Dysphagia	severe (%)	27.3		37.8	
	moderate (%)	17.7		51.2	
	no / mild (%)	55.0	0.68	11.0	0.65
Lower respiratory tract infections (%)		16.9	0.68	27.3	0.45
	recurrent** (%)	12.5	0.67	18.2	0.45
Reported gastro-oesophageal reflux (%)		25.1		44.3	0.72

Standard deviations are between brackets, inter quartile range is between square brackets
* Fraction of the population with known information
** Two or more episodes per year
BMI body mass index

Diagnostic methods

Diagnostic methods had to be chosen with great care. Because all assessments are performed on-site, diagnostic methods should be ambulatory available. Moreover, standard methods are often not feasible, due to the severity of the handicaps of these children, and the required level of cooperation. The Dutch ethics committee also demanded methods to be non invasive, if possible.

Pneumonia

In clinical practice, pneumonia is diagnosed based on a chest X-ray together with symptoms and signs. In the present study however, we needed to use a definition that could be used without requiring extra diagnostic procedures. A previous study showed that retrospective examination of medical files was not accurate for detection of pneumonias.[33] Therefore, the research team agreed upon the following definition for an episode of pneumonia: fever (> 38.5°C, or 1.5°C above basal temperature) during more than 24 hours, likely due to a pneumonia, characterized by: (increase of) dyspnoea (tachypnoea, use of assistant respiratory muscles, wheezing) during the last 6 hours, and / or (increase of) hyper secretion of mucus, and / or, tachypnoea and regular coughing. In addition, no other explanation for fever (such as a middle ear infection or a urinary tract infection) should be present. Because this is a population-based study, participating children all have their own treating physicians. To limit the number of people that are involved in gathering data on pneumonias, parents were asked to complete a questionnaire whenever their child has a fever and airway symptoms. If a physician is contacted, parents ask him or her to fill in a questionnaire for physicians. Every 4 months, parents will be reminded to complete the questionnaires if their child was ill.

Respiratory function

The gold standard technique, spirometry, is not feasible for this population due to the low developmental age and motor disabilities.[34] We will measure respiratory function using the interruption technique. A reversibility test will be done using Salbutamol. This is a well-studied technique that is commonly used in infants. Reliability is high and the ambulatory equipment is commercially available.[35-40] In addition, reference values are available for children.[34,41-44]

Dysphagia

In a hospital setting, aspiration can be assessed with videofluoroscopy. Since this technique is not ambulatory available, we will assess severity of dysphagia instead of aspiration. For this epidemiological study we have chosen a standardized observation method: the Dysphagia Disorders Survey (DDS) / Dysphagia Management Staging Scale (DMSS). This method has been developed especially for people with developmental disabilities.[45] We will combine this method with cervical auscultation and measurements of oxygen saturation, to increase accurateness of the observation.

Constipation

To assess constipation, we will use structured parental interviews, a two-week defecation diary and a one-week diary on food intake. This will be combined with a physical examination of the abdomen and the anal area.[46] In clinical practice, the physical examination also includes a digital rectal palpation to assess faecal impaction. However, this was considered too invasive by the ethics committee.

Nutritional state

To assess nutritional state, we will use classical anthropometry in accordance with Gerver & de Bruin[47] and single frequency Bioelectric Impedance Assessment (BIA).[48]

Gastro-oesophageal reflux

Gastro-oesophageal reflux will be assessed using the gold standard method, 24-hour pH-metry.[49] However, to make this test feasible for on-site measurements, catheter placement will not be verified by X-ray, but the step-up method will be used.[50,51]

Analysis and statistics

Incidence of pneumonia will be studied prospectively and the prevalence of the hypothesized risk factors will be studied cross-sectionally. The association between the hypothesized risk factors and recurrent pneumonias will be assessed using logistic regression. A Poisson regression will be used to analyse their influence on pneumonia incidence. In these analyses, only the cases and their controls will be used. The required number of controls will depend on the number of cases. P-values less than 0.05 will be considered significant.

Ethical approval

Ethical approval was obtained (P02.0188C) from the national ethics committee (The Central Committee on Research Involving Human Subjects). Care centres and specialized schools formally consented to participate. Parents or legal guardians gave informed consent, with or without consent for measurement of gastro-oesophageal reflux. Because gastro-oesophageal reflux can only be measured properly using an invasive method, parents had the opportunity to give consent with or without this measurement.

DISCUSSION

Designing and conducting an epidemiological study in children with severe generalized cerebral palsy is associated with characteristic difficulties. Even though we have considerable experience with research through care organisations,[52] the initiation of this first study in children lead to specific, not always anticipated, problems, which caused a substantial delay. In the present study several obstacles needed to be overcome, which will most likely be encountered in future studies as well. This started with the design of a realistic, ethically acceptable study, including the choice of feasible diagnostic assessment methods and was followed by the recruitment of a representative cohort. In addition, one should bear in mind that on-site measurements and therewith inclusion through care centres (specialized day-care centres and residential facilities) and specialized schools can jeopardise timely inclusion due to potential lengthy procedures.

Dealing with encountered obstacles

Designing the study was complicated by ethical issues, which were resolved by a limited concession in the study design. In standard (nested) case-control studies, hypothesized risk factors are determined at baseline. In the present study, indeed, we will determine respiratory function, constipation and dysphagia at the start of the study, as risk factors. However, gastro-oesophageal reflux and malnutrition are disorders that are likely to cause a considerable loss of quality of life, apart from their possible effects on pneumonias, and both can easily be treated. Therefore, it was considered ethically unacceptable to determine the presence of these conditions at the start of the follow-up and then postponing treatment until the study would be finished. For that reason, we decided to perform the diagnostic tests for these conditions at the end of the follow-up period. This theoretically reduces the power of the analysis, but this reduction is relative since both conditions have a chronic character. We consider this design ethically acceptable, even though we purposely will not assess gastro-oesophageal reflux and nutritional state at baseline, because we will not interfere with common medical practice. Therefore, medical diagnosing and treatment of these disorders will not be hampered.

To conduct this study, a group of children with recurrent pneumonias needed to be identified prospectively. It would make sense to do this retrospectively. However, a previously conducted pilot study indicated that medical records, even when combined with interviews of paediatricians and intellectual disability physicians, provided incomplete and therefore unreliable information on pneumonias in these children.[33]

Getting informed consent of the carers of all eligible children in a geographical area within a reasonable time span was difficult. Firstly, there was no clear registration of the centres that provide care for this specific population in the Netherlands, which resulted in a search amongst a range of organisations. Secondly, centres all had their own procedure to decide on cooperation with a study, often including management, medical staff, other personnel, parent boards and ethics committees. In some centres no standard procedure existed, since they had never been asked to participate in a study before. Thirdly, the national ethics committee considered this study as a multi-centre study and required a consent-form from each centre in advance of their final approval. Although this procedure works well in studies with 2 or 3 participating hospitals, for the present study it meant that 56 centres needed to decide on participation in advance. The resulting delay was a new and unsatisfying experience for the national ethics committee as well. Fourthly, privacy regulations lead to great dependence on willingness and organizational skills of the participating centres. The selection of eligible children had to be done by care centre personnel, and information brochures were sent while researchers were blinded for names and addresses. Despite these encountered difficulties, we have approached a representative sample of children with severe generalized cerebral palsy.

All diagnostic measurements should be ambulatory available and require no active cooperation. Therefore, not all diagnostic methods in this study are "gold-standard" methods. To date, only few diagnostic tests are available, validated for this specific population. Some diagnostic

tests used in the present study are applied for the first time in this population, resulting in valuable feasibility data for future validation studies. Since ethical regulations also required methods to be non-invasive when possible, assessment of constipation needs to be done without the rectal digital examination, which will therefore provide less information in comparison to the normal diagnostic procedure.

To ensure that people of different nationalities participate in a prevalence study, information needs to be provided in several languages. However, our experience is that there is no need for translated written information brochures and questionnaires. A spoken introduction on compact disc can provide an introduction and interested parents will ask a family member for translation of the brochure and questionnaires.

Finally, the inclusion period was stopped before target sample size was reached, due to delay because of practical reasons discussed above. By the end of our inclusion period, almost a quarter of the children with severe generalized cerebral palsy in the Netherlands had been approached and nearly 10% of the Dutch population of these children participates. Even with less power than desired, this study will be able to put a subject on the map that got little attention up to now.

Representativeness

To stay close to clinical practice, we used inclusion criteria based on disabilities rather than on aetiology, resulting in a heterogeneous group of children. Obviously, this might also cause more heterogeneity of the results.

The participating children are slightly younger of age than the eligible children that did not participate. However, we do not regard an age difference of less then 2 years with a standard deviation of over 4 years as a clinical relevant discrepancy. Height and weight differences can be explained by age, since BMI is not different in both groups. A relevant discrepancy does seem to be present between the groups with regard to the reported severity of dysphagia, the frequency of lower respiratory tract infections and the presence of gastro-oesophageal reflux. We assume that the parents of the children with more severe health problems were more likely to recognize the health issues of their child in the information brochure and therefore decided to participate more often. Since swallowing strongly depends on motor skills, it seems likely that participants have poorer motor skills in general than the non-participants. Another part of the discrepancy might be explained by the selection of non-eligible children by staff members of the centres. On first visit, we had to exclude four children whose motor or intellectual skills were of a higher level than those defined by our inclusion criteria. This might also have been the case in the group that did not consent to participate. Because of the slight discrepancies in characteristics, the final results, especially prevalence rates, have to be interpreted with caution. Despite the discrepancies, our sample is as representative as can be expected in population-based research.

Implication for future studies

Preventive medicine needs to play a major role in the healthcare for children with severe neurological impairment. Consequently, intervention studies are needed in which effects can be measured in a valid and reproducible way, and reference values need to be established. As in any discipline, intervention studies should be based on epidemiological data. To avoid complex epidemiological studies, a health register seems to be a requisite. In such a registry, data on health status, diagnostic assessments and applied medical treatments of children with severe neurological impairment should be recorded. This would also enable specialists to combine knowledge and to monitor trends.

For every study question, one should contemplate on the choice between diagnostic assessments in hospital or on-site. When a representative cohort of children with severe generalized cerebral palsy is required, one should perform a community-based study to keep the burden low and therewith the consent rate as high as possible, but one can expect to encounter the discussed obstacles. The main disadvantage of a hospital-based study is that a selected population will be recruited, even when performed through an outpatient clinic. Furthermore, one should consider that feasibility of diagnostic assessments might be better on-site, due to the fact that the setting is familiar to the child. On the other hand, in hospital-based studies, logistics are less complicated and hospital assessments, such as X-rays, are easily applied.

In conclusion, this study will fill in some of the lacunas in the knowledge of the health status of these children such as prevalence numbers of several health conditions, and their associations with recurrent pneumonias. It will also provide new information on the diagnostic tools available for these children, and provide experience in performing scientific studies in this specific field.

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Chapter 3

Dysphagia in children with severe generalized cerebral palsy and intellectual disabilities

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ABSTRACT

This study assessed the clinical indicators of presence and severity of dysphagia in a representative sample of children with severe generalized cerebral palsy and intellectual disabilities. A total of 166 children (85 males, 81 females) with Gross Motor Function Classification System level IV or V and IQ<55 were recruited from 54 day-care centres. Mean age was 9 years 4 months (range 2y 1mo-19y 1mo). Clinically apparent presence and severity of dysphagia were assessed with a standardized mealtime observation, the Dysphagia Disorders Survey (DDS), and a dysphagia severity scale. Additional measures were parental report on feeding problems and mealtime duration. Of all 166 participating children, 1% had no dysphagia, 8% mild dysphagia, 76% moderate to severe dysphagia, and 15% profound dysphagia (receiving nil per mouth), resulting in a prevalence of dysphagia of 99%. Dysphagia was positively related to severity of motor impairment, and, surprisingly, to a higher weight for height. Low frequency of parent-reported feeding problems indicated that actual severity of dysphagia tended to be underestimated by parents. Proactive identification of dysphagia is warranted in this population, and feasible using a structured mealtime observation. Children with problems in the pharyngeal and oesophageal phases, apparent on the DDS, should be referred for appropriate clinical evaluation of swallowing function.

INTRODUCTION

Many children with severe generalized cerebral palsy (CP) and intellectual disabilities (ID) have multiple health problems secondary to their neurological disorder. Dysphagia, characterized by deficiencies in oral preparation, oral-pharyngeal and oesophageal phases of swallowing, is a major health problem in these children. It can be caused by oromotor dysfunction, anatomical anomalies (e.g. cleft palate), abnormal neurological maturation, oral sensory impairment, or oesophageal motility disorders, and may worsen due to concurrent gastro-oesophageal reflux disease (GERD).[1,2] Dysphagia has been reported to be related to reduced weight for height and growth impairment,[3-7] as well as to recurrent lower respiratory tract infections (RLRTI) and chronic lung disease, as a result of chronic aspiration.[1,8] Dysphagia also has many consequences for children and their caregivers. Prolonged mealtimes[3,9] may change an activity that is meant to be pleasurable into a troublesome venture.

Proactive identification of dysphagia is important for mitigation of health risks, optimizing management of nutrition and hydration, and habilitation of the dysphagia. Treatment of dysphagia not only focuses on improvement of oromotor function, but also on reduction of secondary comorbidity. It may consist of introducing adapted eating utensils, special food textures (e.g. mashed solids), oral sensorimotor training, treatment of GERD, or optimizing the child's posture during eating with positioning supports.[10] Reduced food intake may be countered by increasing caloric food-content or by adding nasogastric / gastrostomy feeding. An exclusively non-oral diet is imperative in life-threatening, persisting aspiration.

The prevalence of dysphagia in children with CP has been explored in several studies. Using various diagnostic methods, such as parental interviews or review of medical records, signs of dysphagia have been reported in 58% to 86% of children with CP.[3,4,6] However, these methods rely on adequate documentation and accurate reports of feeding competence. Reilly et al[11] introduced a structured mealtime observation, which is reported as being standardized and reproducible. In their study sample of 49 children with CP, aged 1 to 6 years, clinically significant oromotor dysfunction was present in 90% of the children.

To our knowledge, the presence and clinical signs of dysphagia have not yet been assessed in a population-based sample of children with severe CP. The primary objective of the present study was to determine the extent and severity of clinically apparent dysphagia in a representative sample of children with severe generalized CP and ID, using the Dysphagia Disorders Survey (DDS; an observational screening tool) and an assessment of severity. The second objective was to evaluate the association between the presence of clinical signs of dysphagia and parent's judgment of feeding problems.

METHODS

This project is part of a longitudinal study examining risk factors for RLRTI and malnutrition in children with severe generalized CP and ID. The design of the longitudinal study has been described in detail elsewhere.[12] The study protocol has been approved by the local ethics committee and their recommendations were adhered to. Only children whose parents or caregivers gave written informed consent participated in the study.

Participants

Inclusion criteria for participation were: age between 2 and 19 years; IQ<55; and motor impairment defined as hypertonic or hypotonic generalized CP, or a motor developmental delay to such an extent that a child can at best crawl.

Recruitment methods

To obtain a representative sample of children with severe generalized CP, all care centres (specialized day-care centres and residential facilities) and special schools in the western region of the Netherlands that provide services for these children were asked to participate in the study. Of 61 centres contacted, 56 agreed to participate; these centres provide care to a total number of 593 eligible children. To evaluate the representativeness of the study sample, general information (age, gender, weight, height, and RLRTI status) about participating and non-participating children was obtained from parents, care centres and schools.

Measures

From each participant, general information as mentioned above, plus information on the use of tube feeding and the aetiology of the impairment was collected from caregivers, using a questionnaire devised for the current study. Motor ability was scored using the Gross Motor Function Classification System (GMFCS).[13] Weight and height were measured and compared with weight for height reference values of healthy Dutch children.[14] Feeding as experienced by parents and caregivers was evaluated by means of a self-administered questionnaire consisting of three questions on the presence of feeding problems, pleasure of eating, and average mealtime duration (Table 1).

Dysphagia Disorders Survey

The presence, clinical characteristics, and severity of signs of dysphagia were evaluated using the DDS. The DDS is a screening assessment for dysphagia that was developed and standardized in populations of children and adults diagnosed with intellectual and developmental disabilities.[15] The DDS is administered by observing eating during a typical meal; the users manual[16] provides specific standards for making the observation and for scoring the items. The DDS consists of 15 items in two parts, which are described in Table 2. DDS Part 1 contains

Table 1 Parent questionnaire on subjective feeding experience

Questions	Answer categories
1. Do you consider eating and drinking in your child as a problem?	a. (almost) never
	b. sometimes
	c. often
	d. (almost) always
2. Do you think your child enjoys eating and drinking, regardless of present feeding problems?	a. (almost) always
	b. sometimes
	c. (almost) never
3. How long does an average mealtime last?	a. less than 15 minutes
	b. 15 to 30 minutes
	c. 30 to 45 minutes
	d. more than 45 minutes

Table 2 Contents of the Dysphagia Disorders Survey (DDS)

Sections	Items	Total score
Part 1; Factors related to dysphagia	Weight for height	16
	Diet consistencies / restrictions	
	Independence in eating	
	Use of adaptive utensils	
	Postural alignment for eating	
	Postural stability	
	Use of feeding / swallowing strategies	
Part 2; Task analysis	Orienting for food and drink	22
	Reception	
	Containment	
	Oral transport	
	Chewing	
	Oral-pharyngeal swallow	
	Post swallow signs	
	Gastro-oesophageal signs	

seven items of factors that have been found to be related to dysphagia. DDS Part 2 contains eight task-related items to assess signs of neuro-motor and behavioural competency of the phases of swallowing. This task analysis is applied to three food types (solids that do and do not require chewing, and liquid). Five of the items in Part 2 address task components of the oral preparatory phase of swallowing, two items address the oral-pharyngeal phase and one item addresses the oesophageal phase. DDS scores range from 0 to 38; a higher score indicates more signs of dysphagia.

The final standardization study for the DDS was completed previously on 427 individuals, mean age 33 years, comprising all the inhabitants of a residential facility for individuals with

ID (JJ Sheppard 1988, unpublished data). Standardization of the DDS was based on clinical judgment of presence and severity of dysphagia by speech pathologists who were blinded to DDS screening results. Presence of dysphagia was determined by clinical dysphagia evaluation. Judgment of level of severity was determined by complexity of dysphagia management needs and associated nutritional and respiratory status. The correlation of total DDS score and the speech pathologist's opinion was *r=0.92*. As a test of interrater reliability, six speech-language pathologists, working in pairs, achieved 97% agreement in scoring DDS items for 21 subjects.

Dysphagia severity scale

DDS Part 1 contains dysphagia-related items, which in most cases can be described as consequences of dysphagia, such as reduced weight for height, or the use of adaptive utensils. The information these items provide is of great importance for the general picture of dysphagia in a child. However, the items of DDS Part 1 do not provide the same evidence of presence of dysphagia in a child as the actual task analysis or mealtime observation, as described by DDS Part 2.

Therefore, in the present study, it was decided to use the DDS Part 2 score alone to evaluate the correlation between signs of presence of dysphagia and child characteristics. While the DDS detects the presence of dysphagia, a dysphagia severity scale based on DDS Part 2 scores was developed to assess level of severity. The presence of signs that indicate abnormal bolus motility in the pharynx was defined as severe dysphagia. Aspiration, the most direct life-threatening consequence of dysphagia, is thought to originate from pharyngeal-phase abnormalities, as demonstrated in videofluoroscopy studies of children with severe CP.[17,18] The dysphagia severity scale level is based on the following criteria: presence of dysphagia as indicated by a score of more than zero on DDS Part 2; clinical signs of pharyngeal-phase deficiencies indicated by a score of more than zero on the pharyngeal-phase items of DDS Part 2; and nil by mouth status. See Table 3 for severity scale levels and criteria.

Table 3 Dysphagia severity scale

Severity levels	Criteria
No dysphagia	Score of 0 on DDS Part 2
Mild dysphagia*	Score of >0 on DDS Part 2 Score of 0 on DDS Part 2 items 'Oral-pharyngeal swallow' and 'Post swallow signs'
Moderate to severe dysphagia**	Score of >0 on DDS Score of >0 on DDS items 'Oral-pharyngeal swallow' and 'Post swallow signs'
Profound dysphagia***	Nil by mouth

* Signs of dysphagia are present, however, pharyngeal phase problems are not suspected

** Pharyngeal-phase problems are highly suspected

*** Children in this category were not observed during mealtime, however, because of their exclusively non-oral diet, the presence of severe dysphagia with high risk of aspiration is presumed

DDS Dysphagia Disorders Survey

Procedures

The research team was trained in use of the DDS to meet the validation standards for the test, and was certified in its use. Questionnaires on general characteristics and on parental opinion and feeding experience were sent by mail. Each child was visited at his or her care centre or school by one of three researchers. Researchers scored children on the GMFCS and undertook assessment using the DDS during a normal meal in the school setting. In addition to the standard DDS procedure, a stethoscope was used to evaluate cervical swallowing sounds intermittently during the meal; the stethoscope was used to increase the sensitivity of assessment of the pharyngeal-phase signs of dysphagia specified in the DDS.[19] In children who received nil by mouth, questionnaires were administered, weight and height were measured and motor ability was scored.

Statistical analysis

Data analysis was performed using SPSS (version 14.0). Differences between participating and non-participating children were tested using independent samples t-tests and chi-square (X^2). Associations of general child characteristics, DDS Part 1, and parental questionnaire items with the dysphagia severity scale were evaluated. For normally-distributed variables and categorical variables the following statistics were calculated: F (analysis of variance), z-score (Mann-Whitney U test), and r_s (Spearman's rho). Because the variable DDS Part 1 was not normally-distributed, a Jonckheere-Terpstra (J-T) statistic was calculated for its association with the dysphagia severity scale. For all tests, significance was set at $p<0.05$.

RESULTS

Final population

Of all 593 eligible children, parents of 194 children from 54 different care centres gave informed consent to participate in the study. From these 194 children, 28 were not available for evaluation of dysphagia due to: death (n=6), loss to follow up (n=6), and child absence from day-care centre (n=16). Table 4 presents differences between participating and non-participating children. Participating children were younger than non-participating children, and their body mass index (BMI) was lower. Parents of participating children reported the presence of RLRTI as frequently as did non-participating parents. Characteristics (age, sex, GMFCS levels, ethnicity, and aetiology of the handicap) of the 166 children that were available for dysphagia evaluation are listed in Table 5.

Table 4 General characteristics: non-participants versus participants

	Non-participants	n[3] (%)	Participants	n[3] (%)	Statistics
Age[1]; mean (SD)	9y, 8mo (4y, 4mo)	265 (62%)	8y, 6mo (4y, 2mo)	166 (100%)	t*= 3.014 (df429) p= 0.003
Gender (male); n (%)	142 (51%)	278 (65%)	85 (51%)	166 (100%)	X^{2}**= 0.00 (df1) p= 0.980
Weight (kg); mean (SD)	29.3 (12.0)	239 (56%)	27.6 (10.9)	157 (95%)	t*= 1.379 (df394) p= 0.169
Length (cm); mean (SD)	130 (22)	214 (50%)	130 (19)	156 (94%)	t*= 0.100 (df368) p*= 0.920
BMI (kg/m^2); mean (SD)	16.7 (3.8)	209 (49%)	15.8 (2.9)	154 (93%)	t*= 2.489 (df360) p*= 0.013
Recurrent lower respiratory tract infections[2]; n (%)	35 (13%)	269 (63%)	18 (14%)	133 (80%)	X^{2}**= 0.02 (df1) p= 0.884

[1] Age at start of first inclusion (01-01-2003)

[2] Defined as 2 or more lower respiratory tract infections per year

[3] Number of children with known information

* Independent samples t-test

** Chi-squared test

Table 5 Characteristics of participants

Study participants (n)		166
Age*; mean (SD) Range		9y, 4mo (4y, 4mo) 2y, 1mo -19y, 1mo
Age 2-8 years; n (%)		72 (43%)
Age 8-14 years; n (%)		69 (42%)
Age 14-20 years; n (%)		25 (15%)
Males; n (%)		85 (51%)
Females; n (%)		81 (49%)
GMFCS level IV; n (%)		27 (16%)
GMFCS level V; n (%)		139 (84%)
Ethnicity	Caucasian; n (%)	106 (64%)
	Other; n (%)	60 (36%)
Aetiology of handicap; n (%)		
	Congenital	56 (34%)
	Perinatal	46 (28%)
	Acquired	12 (7%)
	Combination**	14 (8%)
	Unknown	38 (23%)

* Age at mealtime observation period

** All children with congenital and / or perinatal and/or acquired syndromes

GMFCS Gross Motor Function Classification System

Dysphagia Disorders Survey

Of all participating children, 18% were partially tube fed, whereas 15% received nil by mouth, and were therefore not evaluated using the DDS. Median scores of total DDS, DDS Part 1, and DDS Part 2 were 24 (range 2-37), 9 (range 2-16), and 15 (range 0-22) respectively.

On the dysphagia severity scale, 1% of all 166 children was classified as having no dysphagia, 8% mild dysphagia, 76% moderate to severe dysphagia, and 15% profound dysphagia (receiving nil per mouth), resulting in a prevalence of 99% for all participating children with clinically apparent signs of dysphagia.

Associations between child characteristics and the dysphagia severity scale are described in Table 6. Both GMFCS level V and the presence of partial tube feeding were significantly associated with a more severe level of dysphagia. Neither age nor sex showed a significant correlation with dysphagia severity.

Of all participating children, 15% had a weight for height between the 25th and the 10th percentile, and 28% had a weight for height lower than the 10th percentile.

There was a significant association between DDS Part 1 score and the dysphagia severity scale (Standard Jonckheere-Terpstra= 4.267, p< 0.001). Associations of separate DDS Part 1 items and the dysphagia severity scale were tested without the nil-by-mouth group (Table 7). Item 1 of the DDS, weight for height, negatively correlated with severity of dysphagia, i.e. children with more severe dysphagia appeared to have a higher weight for height. This correlation held when repeated including the nil-by-mouth group (r_s= -0.171, p= 0.034). In addition, there was a significant association between the severity level of dysphagia and most of the remaining DDS Part 1 items: diet restrictions, feeding dependence, use of adaptive utensils, postural instability, and the use of feeding / swallowing strategies. Only postural alignment for eating did not correlate significantly with severity of dysphagia.

Table 6 Association between general child characteristics and dysphagia severity scale

Child variable	Categories	Dysphagia severity scale				Statistics
		none	mild	moderate to severe	profound	
Age, mean (SD)	---	10y, 8mo (2y, 1mo)	9y, 2mo (5y, 1mo)	9y, 4mo (4y, 3mo)	9y, 1mo (3y, 8mo)	F*= 0.080 p= 0.778
Sex	male (n)	2	7	64	12	Z**= -0.372 p= 0.710
	female (n)	0	7	62	12	
GMFCS	IV (n)	2	5	20	0	Z**= -3.593 p< 0.001
	V (n)	0	9	106	24	
Tube-feeding	no (n)	2	12	92	0	Z**†= -2.092 p= 0.036
	partial (n)	0	0	30	0	
	non-oral (n)	0	0	0	24	

* F based on ANOVA

** z-score based on Mann-Whitney U test

† Correlation of tube feeding versus the dysphagia severity scale is tested without the nil-by-mouth group

GMFCS Gross Motor Function Classification System

Table 7 Association between DDS Part 1 items and dysphagia severity scale*

Items	Categories	%	Dysphagia severity scale			Statistics
			none (n)	mild (n)	moderate to severe (n)	
1. Weight for height						
	within normal limits^	55%	1	3	68	r_s**= -0.180 p= 0.040
	low^^	16%	0	2	19	
	very low^^^	29%	1	6	31	
2. Diet consistencies / restrictions						
	normal diet	47%	2	13	52	Z***= -3.952 p< 0.001
	mashed / restriction on liquids	53%	0	1	74	
3. Independence in eating						
	self fed	2%	1	2	0	r_s**= 0.424 p< 0.001
	assisted self feeder	13%	1	5	13	
	dependent oral eater	85%	0	7	113	
4. Use of adaptive utensils						
	no	19%	1	6	20	Z***= -2.675 p= 0.007
	yes	81%	1	8	106	
5. Postural alignment for eating						
	upright independent	3%	1	0	3	r_s**= 0.146 p= 0.083
	upright assisted	60%	1	11	74	
	recline	37%	0	3	49	
6. Postural stability						
	stable	6%	1	2	6	Z***= -2.230 p= 0.026
	unstable	94%	1	12	120	
7. Use of feeding / swallowing strategies						
	no	38%	2	10	42	Z***= -3.251 p= 0.001
	yes	62%	0	4	84	

* Associations are evaluated without nil-by-mouth group

** Spearman's rho

*** z-score based on Mann-Whitney test

^ Weight for height > 25th percentile

^^ 25th percentile ≥ weight for height ≥ 10th percentile

^^^ Weight for height < 10th percentile

Weight for height reference values of Dutch schoolchildren[14]

Parental subjective feeding experience

Of all participating parents, 84% returned the questionnaire. Correlations of the three items as discussed in the subjective feeding questionnaire (Table 1) with the dysphagia severity scale were all calculated without the nil-by-mouth group. Data and statistics are presented in Table 8. None of the following three items correlated significantly with severity of dysphagia: problems during feeding as experienced by parents, parents' opinion on their child enjoying mealtime, and mealtime duration. Only 31% of parents of children with moderate to severe dysphagia

Table 8 Association between parental feeding experience and dysphagia severity scale*

Child variable	Categories	Dysphagia severity scale			Statistics**
		none (n)	mild (n)	moderate to severe (n)	
Eating and drinking considered as a problem					
	(almost) never	1	3	35	r_s*= 0.009 p= 0.926
	sometimes	1	4	35	
	often	0	4	19	
	(almost) always	0	0	12	
Child enjoys eating and drinking					
	(almost) always	2	7	73	r_s*= -0.031 p= 0.744
	sometimes	0	3	21	
	(almost) never	0	1	5	
Mealtime duration					
	<15 minutes	0	0	18	r_s*= -0.151 p= 0.111
	15-30 minutes	1	8	60	
	30-45 minutes	0	2	18	
	>45 minutes	1	1	4	

* Associations are evaluated without nil-by-mouth group

** Spearman's rho

reported experiencing feeding problems in their child on a regular basis (i.e. often / almost always).

DISCUSSION

The aim of this study was to evaluate the clinically apparent presence and severity of dysphagia in a population of children, representative of the general population of children with severe generalized CP and ID in the Netherlands. Participating children had a lower BMI than non-participating children, which presumably reflects their lower age rather than a poorer health status. This is supported by the finding that recurrent lower respiratory tract infections, as reported by parents, were equally present in both participating and non-participating children. We therefore consider the study population to be representative.

This study confirms the findings of previous studies that children with severe generalized CP are very often severely affected by dysphagia. As much as 99% of the study population was to some extent affected by dysphagia, and 91% had signs of pharyngeal-phase involvement or were exclusively fed by tube. This is concordant with the findings of Reilly et al.[11] who found clinical signs of dysphagia in 90% of a cohort of young children.

This study demonstrates the feasibility of screening identification of dysphagia in this population. Proactive identification of the clinical signs of dysphagia may facilitate case management

and support referral for clinical and instrumental evaluation and treatment. Assessment of feeding problems by a multidisciplinary team (caregiver, speech therapist, dietician, paediatrician) has been proposed in literature.[20] Multidisciplinary teams would be able to evaluate specific causes and consequences of dysphagia and to provide a tailored plan of interventions. However, a team approach is not suitable for screening purposes, because of logistical and time constraints. Mealtime observation tools for use in classroom and day-care settings, such as the DDS, or the Schedule for Oral Motor Assessment as used by Reilly et al.[11], appear to be quite suitable for proactive detection of dysphagia in this population at risk. They are completed quickly, can be performed in the natural environment of the child, and are non-invasive, which are all important features of a diagnostic tool in this population.

Ideally, a mealtime observational method would be applied in everyday practice by professionals who already provide medical care for these children. In the UK, community nurses who specialize in intellectual disabilities[21] might be the designated professionals for this purpose, as they provide medical care for institutionalized children and children living with their parents.

Although the DDS correlated well with the speech pathologist's opinion in the original standardization study (r=0.92), the correlation of the DDS and features of dysphagia as assessed by imaging diagnostic methods, such as video fluoroscopy, has not been evaluated. It should be noted that detailed information on the exact mechanisms that lead to dysphagia in an individual child and, more importantly, the presence of aspiration, cannot be established by mealtime observation. Therefore, children with signs of pharyngeal phase swallowing involvement, who may be at high risk of aspiration, need to be referred for imaging diagnostic techniques, possibly in the context of a multidisciplinary team.

In the present study, parents' opinions on the presence of dysphagia did not correlate with the actual presence of clinical features of dysphagia as assessed by standardized mealtime observation. Parents tended to underestimate the severity of dysphagia in their child. The discrepancy between actual severity of dysphagia and reported feeding problems might be due to habituation or low expectations of feeding performance for children with severe CP and ID. This shows that the use of parental initiative alone may not be sufficient for pro-active detection of dysphagia and referral for diagnostic assessments. Further study is needed to explore these issues.

Many children in the present study population were underweight. This deficient nutritional state has frequently been reported in children with CP,[22,23] and has been shown to be associated with dysphagia.[3-7] Surprisingly, dysphagia in the present study correlated to a higher weight for height. A possible explanation would be that children in the present study population, who were affected by dysphagia to such an extent that they were malnourished, had already been adequately treated with partial or complete tube feeding. This might indicate a positive shift towards active detection and treatment of malnutrition. This matter, however, was not explicitly evaluated in the present study. In previous studies, performed between 1993 and 2002, only 4 to 24% of children received gastrostomy feeding,[4,6,11] whereas in the present study 44%

was on a partial or complete tube feeding diet. Also, in the present study 81% of the children already used special utensils and 62% special feeding techniques. Although data on dysphagia diagnostics performed in the participating children were not available, it could be concluded that, given the above mentioned measures taken, feeding difficulties were already suspected in many of the children.

CONCLUSION

Children with severe generalized CP and ID are at considerable risk of dysphagia. Clinicians should not wait for parental concern to address feeding problems; proactive detection of the disorder in this population is justified and desirable. A standardized mealtime observation is a child-friendly and relatively easy to perform screening for dysphagia. The DDS is one such tool for evaluating clinical signs of problems in all phases of swallowing. When apparent swallowing difficulties are established, referral should be considered to evaluate specific causes of the dysphagia and to determine appropriate management strategies. In particular, when problems in the pharyngeal or oesophageal phases of swallowing are suspected, imaging diagnostic techniques should be used to assess the risk of aspiration.

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Chapter 4

Pathological gastro-oesophageal reflux in children with severe generalized cerebral palsy and intellectual disability is often undetected

Submitted

ABSTRACT

Background

Many children with severe generalized cerebral palsy and intellectual disability suffer from gastro-oesophageal reflux. Although standard 24-hr pH-measurements are recommended in this population, diagnosis and treatment are often still symptom-based. Present study evaluated the correlation of gastro-oesophageal reflux with symptoms, and described treatment-status in 25 children.

Materials and methods

24-hr pH-measurements, and parental questionnaire on symptoms.

Results

Mean age 11 years 11 months (SD 4 years 2 months), 12 males, 4 GMFCS level IV, 21 GMFCS level V. Fourteen children had gastro-oesophageal reflux. Eight of them used anti-reflux medication, as well as five children without gastro-oesophageal reflux. Symptoms did not correlate with gastro-oesophageal reflux.

Conclusions

A large proportion of children with severe generalized cerebral palsy and intellectual disability suffering from gastro-oesophageal reflux remain untreated. A pro-active detection of gastro-oesophageal reflux with 24-hr pH-measurements is recommended since symptoms do not correlate with the presence of gastro-oesophageal reflux in this population.

INTRODUCTION

Pathological gastro-oesophageal reflux (GER) is a disorder that affects many children with severe generalized cerebral palsy (CP) and intellectual disability (ID). Former studies in neurologically impaired children, mainly performed in hospital settings or in symptomatic children, have reported prevalence rates ranging from 55% to 91%.[1-4] One study, performed in a large population of institutionalized, intellectually disabled children and adults, found a prevalence of 48%.[5] The prevalence of pathological GER in the intellectually disabled is probably much higher than the prevalence in the general non-neurologically impaired paediatric population, although detailed information on pathological GER in non-disabled children is lacking. One study, however, performed in 3 to 17 year-old children in general practice showed a prevalence of GER-related symptoms of 1 to 8% dependent on age and type of symptom.[6] Multiple factors may contribute to the increased risk of developing pathological GER in children with severe generalized CP and ID. For example, several conditions related to their disability, like the use of anti-convulsive drugs, and scoliosis correlate with presence and severity of pathological GER.[5] The effect of gastrostomy feeding as a possible causal factor is controversial.[7] Early detection and treatment of pathological GER is of utmost importance, because when longstanding, it may lead to serious complications in this frail population, such as malnutrition, recurrent lower respiratory tract infections, and oesophagitis, which may result in anaemia and oesophageal stenosis.[1,8-11] In clinical practice, several approaches are available towards the assessment of pathological GER in the general paediatric population, ranging from empirical therapy with anti-reflux medication to 24-hr pH monitoring, or endoscopy. Recommendations have been made in guidelines for the detection and treatment of pathological GER developed by the North American and the European Society for Pediatric Gastroenterology and Nutrition (NASPGAN / ESPGAN).[12,13] Generally, it is stated that in a child whose history is typical for uncomplicated pathological GER, an initial trial of anti-reflux therapy is appropriate. This means that in a patient with typical symptoms, such as heartburn and regurgitation, further diagnostics, such as endoscopy or 24-hr pH monitoring, are postponed until pharmaceutical treatment fails. Children with severe generalized CP and ID, however, are unable to communicate symptoms like pain or heartburn. This may lead to a treatment-delay in this population, and the presence of pathological GER may not be established until more overt symptoms occur, such as frequent vomiting and haematemesis, indicating development of oesophagitis. The need for a different approach towards the detection of pathological GER in intellectually disabled persons has been recognized by a Dutch multidisciplinary consensus group that developed a guideline for the diagnosis and treatment of pathological GER in intellectually disabled persons.[14] The recommendations in this guideline were primarily based on a large study in institutionalized persons.[5] It was recommended to perform oesophageal endoscopy in case of alarming symptoms, such as haematemesis, frequent vomiting, or unexplained anaemia, and in case of symptoms such as recurrent respiratory tract infections, nutritional problems, rumination, regurgitation and

dental erosions. Because spasticity and low IQ were found to be risk factors for presence and severity of pathological GER, 24-hr pH-monitoring was also recommended in non-symptomatic persons with an IQ<35, or with spasticity of at least two limbs. This last recommendation implies a routine 24-hr pH-monitoring for every child with severe generalized CP and ID.

In spite of these previous recommendations, today, in the Netherlands, routine 24-hr pH-monitoring is not yet a standard procedure in this population. The diagnosis and treatment of pathological GER are still symptom-based. Hypothetically, this may leave many children with pathological GER untreated, although evidence is lacking. Therefore, in the present study, we aimed to evaluate the presence and current treatment status of pathological GER in a non-clinical population of children with severe generalized CP and ID in the Netherlands. Furthermore, we explored the relation between symptoms and presence of pathological reflux as measured by pH-monitoring in this population.

MATERIALS AND METHODS

Children with severe generalized CP and moderate to severe ID were recruited through 23 care centres (specialized day-care centres, special schools, and residential facilities) in the western part of the Netherlands. All children already participated in a larger, longitudinal study on incidence and risk factors of recurrent lower respiratory tract infections in this population,[15] and participated in the present study after their parents had given additional informed consent. Ethical approval was obtained for the study protocol of the longitudinal study including the present sub-study, from the national ethics committee (P02.0188C, Central Committee on Research Involving Human Subjects). Inclusion criteria were: age between 2 and 20 years, IQ below 55 (documented developmental age divided by calendar age times 100) and motor disability defined as hypertonic or hypotonic generalized cerebral palsy or a motor developmental delay to such an extent that a child could at best crawl. This corresponds to a Gross Motor Function Classification System (GMFCS) level IV or V.[16] From all children, background information (gender, age, and aetiology of the handicap) was collected. Parents were asked to fill out a questionnaire on the current use of anti-reflux and anti-epileptic medication, presence of tube feeding, former anti-reflux surgery, and former pH-measurements or oesophageal endoscopy performed. Furthermore, they were asked to complete a questionnaire on symptoms, hypothesized to be related to pathological GER, that had been developed by the researchers for the present study. This questionnaire included symptoms that have been described to correlate to GER in intellectually disabled persons, such as emesis,[5] rumination,[8] and low weight for height,[1,8] as well as symptoms such as hiccups and arching, that have been found to correlate to GER in healthy infants.[17] Furthermore, several symptoms we frequently observe in

clinical practice, such as food refusal, poor sleeping and acid breath smell were included in the questionnaire. Each symptom was scored as either currently present or not present.

The presence of pathological GER was evaluated by 24-hr pH-monitoring, using a glass electrode (SME F8 / IR Blue Line, or LOT 440 M3; Medical Measurement Systems, Enschede, the Netherlands), and a portable digital recorder (Orion I; Medical Measurement Systems, Enschede, the Netherlands). Prior to the measurement, current use of anti-reflux medication was recorded, and parents were asked to withhold this medication for one to five days prior to the 24-hr pH-measurement (ranitidine, omeprazole and pantoprazole five days, cisapride three days, and alginic acid one day). Furthermore, parents were asked not to feed their child during the three hours prior to the measurement. Before start of the measurement the system was calibrated using pH 4 and pH 7 solutions. Catheter introduction and placement was done at each child's care centre, in a setting familiar to the child in order to minimize discomfort. The pH electrode was introduced through the nose into the stomach, while the child was sitting in its own wheelchair. If a child preferred to lie down, the probe was introduced in the supine position. To minimize the disturbance of the children, no more than two attempts were made to introduce the probe. The probe was positioned using the step-up method,[18] i.e. once the tip of the probe reached the stomach, causing the pH to drop towards 1, it was pulled back 0.5 cm at a time until a sudden rise in pH above 4 occurred, reflecting the location of the lower oesophageal sphincter (LES). Subsequently the probe was pulled back 3 cm in children younger than 10 years and 5 cm in children aged 10 years and older.[19] The distance from the tip of the probe to the nares was noted, and the probe was fixed to nose and cheek. Children were prevented from taking anti-reflux medication or acid foodstuffs or drinks during the entire measurement, and were not allowed to swim or take a bath. Parents, and other caregivers, were asked to fill in a diary to record the positioning of their child (upright, supine), mealtimes, and special events during the measurement (such as crying, vomiting). After 24 hours of measurement the distance from the tip of the probe to the nares was noted again by the researcher, and the probe was removed. pH data were analyzed with proprietary Orion I software from Medical Measurement Systems. All pH curves were evaluated by one of the co-authors (J.E.), a trained paediatric gastroenterologist. Results were not included in the analyses if the probe was likely to have been pulled up or had drifted down into the stomach during measurement. Movement of the probe was suspected on the basis of a difference in distance probe-nares before and after measurement, or on the basis of a typically deviant pH curve. The presence of pathological GER was defined as pH less than 4 during more than 4% of recording time. The nature of the GER was described by conventional reflux parameters: reflux index (RI), defined as the percentage of total measured time during which pH < 4, number of acid reflux episodes, number of acid reflux episodes lasting > 5 minutes, and duration of longest acid reflux period.

Analysis

The relation of pathological GER with general child characteristics, presence of tube feeding and use of anti-epileptic medication was tested using an independent t-test, a Chi-square test and Fisher's exact test for tables with small expected frequencies. The relation between pathological GER and symptoms was tested using Fisher's exact test. For all tests, significance level was set at $p< 0.05$. Analysis was done using SPSS version 14.0 software.

RESULTS

Thirty-nine out of 194 children, participating in the longitudinal study on incidence and risk factors of recurrent pulmonary infections, participated in the present sub-study on gastro-oesophageal reflux. In 25 children, a 24-hr pH-monitoring was successfully performed. Figure 1 presents a flow chart that describes the number of children from inclusion to final measurement. In 14 children, the pH monitoring failed due to problems with the positioning of the pH-electrode: in seven children the introduction of the electrode failed, in two children the electrode was malpositioned (as shown by the pH registration), and five children accidentally pulled back or removed the electrode after the measurement had started. General characteristics of the children with a successful pH-monitoring, and of the 169 other children from the

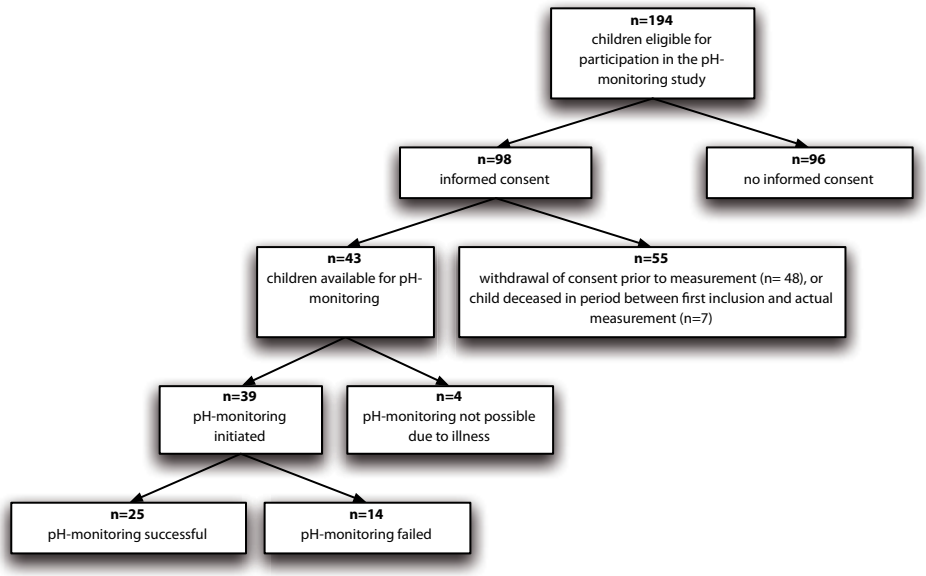

Figure 1 Flow chart: number of children from first inclusion in the longitudinal study to pH-monitoring (two-year period).

Table 1 General characteristics: children with successful 24-hr pH-monitoring versus children without successful pH-monitoring

		Children with successful pH-monitoring (n=25)	Children[a] without successful pH-monitoring (n=169)	Statistics
Age[b] (mean, SD)		11 years 11 months (4 years 2 months)	11 years 4 months (4 years 5 months)	t= 0.582[c] p= 0.561
Minimum		5 years 2 months	4 years 5 months	---
Maximum		19 years 11 months	22 years 5 months	---
Male (n)		12	90	X^2= 0.241[d] (df 1) p= 0.623
Female (n)		13	79	
GMFCS level IV (n)		4 (16%)	29 (17%)	p= 1.0[e]
GMFCS level V (n)		21 (84%)	140 (83%)	
Aetiology (n)	congenital	8 (32%)	58 (34%)	X^2= 6.290[d] (df 3) p= 0.098
	perinatal	6 (24%)	57 (34%)	
	combination[f]	5 (20%)	10 (6%)	
	missing	6 (24%)	44 (26%)	

[a] Combination of children whose 24-hr pH-monitoring failed (n=14), and of children who were originally eligible for participation in the present pH-monitoring study, but did not have a 24-hr pH-monitoring for the following reasons: no informed consent (n=144), illness (n=4), deceased (n=7)

[b] Age on 01-01-2006

[c] Independent t-test

[d] Chi-square test

[e] p-value based on Fisher's exact test

[f] Combination represents a combination of congenital, and / or perinatal, and / or acquired

longitudinal study are presented in Table 1. Children with successful pH-measurements did not significantly differ from the others in terms of age, gender, GMFCS level, and aetiology of the disability. Mean duration of pH-recording was 22.5 hrs (min 20.0 hrs, max 24.7 hrs). Fourteen children had pathological GER (GER+). In Table 2, all conventional pH-parameters, together with present treatment status, former GER surgery and former GER diagnostics are described for both GER+ children, and children with no pathological GER (GER-). Of all GER+ children, eight currently used anti-reflux medication, and out of all GER- children, five used anti-reflux medication. Of the six GER+ children not using medication, three had had GER diagnostics in the past. Unfortunately, the results of the pH-measurements or endoscopies performed in the past have not been retrieved. Of all five GER- children using anti-reflux medication, two had had GER diagnostics at an earlier moment in their past. Whether these tests detected pathological GER could not be retrieved either. The presence of pathological GER did not relate significantly with age, gender, GMFCS level, presence of tube feeding or use of anti-epileptic medication (Table 3).

Of all symptoms, arching and poor sleeping were present most frequently: in more than 60% of the children (Table 4). Rumination, however, was only observed by one parent. None of the reflux-related symptoms significantly related to the presence of pathological GER.

Table 2 Conventional pH-parameters and diagnostic history and treatment status; presented for children with and without pathological GER separately

	GER+[a] (n=14)	GER-[b] (n=11)
PH-parameters		
RI[c] (%); mean (SD)	10.4 (6.9)	1.6 (1.2)
Number of reflux periods[d] in 24hrs; mean (SD)	55 (30)	22 (16)
Number of reflux periods > 5 minutes in 24hrs; mean (SD)	7 (6)	1 (1)
Duration of longest reflux period (min); mean (SD)	25.9 (21.7)	4.8 (4.9)
Present treatment status and diagnostic history		
Present use of anti-reflux medication[e]	8 (57%)	5 (45%)
Anti-reflux surgery in past	2 (14%)[1,2]	1 (9%)[1]
24-hr pH-measurement or oesophageal endoscopy in past (n, %)	9 (64%)	4 (36%)

(GER= pathological gastro-oesophageal reflux; RI= reflux index)

[a] GER is present as assessed by 24-hr pH-monitoring

[b] GER is absent as assessed by 24-hr pH-monitoring

[c] Percentage pH < 4 of total measured time

[d] Reflux period= pH < 4 during ≥ 10 seconds

[e] Ranitidine, omeprazole, pantoprazole, cisapride, alginic acid, domperidone

[1]Nissen-fundoplication

[2]Thal-fundoplication

Table 3 Relation between age, gender, GMFCS level, tube feeding and anti-epileptic medication and the presence of pathological GER

	Categories	GER+[a] (n=14)	GER-[b] (n=11)	Statistics
Age; mean (SD)	---	12 years 10 months (4 years 1 month)	11 years 1 month (4 years 6 months)	t= -0.656[c] p= 0.518
Gender	male (n)	8	4	X^2 = 1.066[d] p= 0.302
	female (n)	6	7	
GMFCS level	IV (n)	4	0	p[e]= 0.105
	V (n)	10	11	
Tube feeding[f]	yes (n)	3	4	p[e]= 0.656
	no (n)	11	7	
Anti-epileptic medication	yes (n)	11	8	p[e]= 1.0
	no (n)	3	3	

(GER= pathological gastro-oesophageal reflux)

[a] GER is present as assessed by 24-hr pH-monitoring

[b] GER is absent as assessed by 24-hr pH-monitoring

[c] Independent t-test

[d] Chi-square test

[e] Based on Fisher's exact test (two-sided)

[f] Adjuvant or exclusive tube feeding

Table 4 Relation between reflux-related symptoms and the presence of pathological GER

Reflux-related symptoms	GER+[a] n (%)	GER-[b] n (%)	p-value[c]
Emesis once or more per day	3 (25%)	2 (20%)	1.0
Rumination	0 (0%)	1 (13%)	1.0
Food refusal	2 (18%)	5 (56%)	0.160
Difficulty in maintaining weight	4 (31%)	5 (50%)	0.417
Crying during mealtime	0 (0%)	1 (9%)	0.458
Regular hiccups	1 (8%)	3 (30%)	0.293
Arching	7 (64%)	6 (60%)	1.0
Poor sleeping	6 (46%)	9 (82%)	0.105
Acid breath smell	4 (31%)	4 (36%)	1.0

(GER= pathological gastro-oesophageal reflux)

[a] GER is present as assessed by 24-hr pH-monitoring

[b] GER is absent as assessed by 24-hr pH-monitoring

[c] Based on Fisher's exact test (two-sided)

DISCUSSION

In the present study, 14 out of 25 children with severe generalized CP and ID had pathological GER, as assessed by 24-hr pH-monitoring. Six children were currently untreated, although pathological GER was present, whereas five children without pathological GER received anti-reflux medication nonetheless. A relation between symptoms and presence of pathological GER was not found. Initially, one of the main aims of the present study was to evaluate the prevalence of pathological GER in children with severe generalized CP and ID. In order to obtain a study population that was representative of the general Dutch population of children with severe generalized CP and ID, children were recruited from non-clinical settings. Unfortunately, the consent rate for the pH-recordings was low, and a prevalence rate could not be extrapolated from the results of the 25 successful pH-measurements performed in this study. Many parents considered 24-hr pH-monitoring to be too much of a burden for their child and refrained from participation, which makes the evaluation of a reflux prevalence rate in this population exceptionally difficult. In our clinical experience, this hesitant attitude towards the use of pH-monitoring is not restricted to caregivers only, but may affect medical practitioners as well. In the present study only half of the participating children had previously undergone either 24-hr pH-monitoring or oesophageal endoscopy. Apparently, a routine 24-hr pH-monitoring in these children with increased risk of pathological GER, as was advocated in the Dutch guideline for the detection and treatment of pathological GER in intellectually disabled persons,[14] is not yet incorporated in clinical practice. This hesitant approach towards the detection of pathological GER, however, is harmful for these children at risk. In the present study, in six out of 14 children, pathological GER was presumably undetected, for it was untreated. This demonstrates that

the detection of pathological GER based on clinical signs and symptoms alone is insufficient in this population. In children without overt symptoms like frequent emesis, which usually emerge only after GER has been present for a longer period, the presence of pathological GER will not be recognized, although they might already experience serious heartburn. On the other hand, a symptom-based diagnosis and treatment of pathological GER might wrongfully diagnose children without pathological GER, and put them on a useless, expensive, and long-term medical treatment. In the present study, five out of 11 children without pathological GER were treated with anti-reflux medication. Apparently, at some point in time, the presence of pathological GER was suspected in these children. Most likely this suspicion was raised on the basis of signs and symptoms, such as frequent vomiting or failure to thrive. In former research, several symptoms have been shown to relate to the presence of pathological GER, like emesis, rumination, and low weight for height.[1,5,8] Also, behaviour-related symptoms, such as hand-mouthing and automutilation / aggression have been suggested to correlate with pathological GER in intellectually disabled children.[20,21] However, it is well known that children with severe generalized CP and ID often suffer from multiple disorders, like epilepsy,[22] and dysphagia,[23] which might cause similar symptoms. In the present study, a significant relation was not found between proposed symptoms and presence of pathological GER. However, any firm conclusion on this matter cannot be drawn, because the number of evaluated children was small. From the present results we may, however, conclude that in this population at high risk of pathological GER and often unable to communicate first stage symptoms like heartburn, routine 24-hr pH-monitoring remains the preferred practice. Since many years 24-hr pH-monitoring is considered the gold standard in the detection of acid intra-oesophageal reflux, and it has been the method of evaluation in most previous research projects that have assessed the prevalence of GER in disabled children.[1-4] 24-hr pH-monitoring can be performed in both clinical and non-clinical settings, which is a major advantage for these children with limited mobility. A newer technique, oesophageal impedance monitoring, is a promising research tool, however, the added value of impedance in everyday practice still needs to be evaluated.[24] When 24-hr pH-monitoring is performed in non-clinical settings, the pH probe cannot be correctly positioned using conventional methods such as manometry or X-ray. The step-up method,[18] which was used in the present study, is quick and easy to perform in any environment. In a former study it was showed that, although there was a difference in average location of the LES (<3cm) located by step-up method as compared to manometry, the use of the step-up method did not bring about any significant differences in the actual diagnosis of pathological GER.[25]

CONCLUSIONS

From the present study we conclude that in many children with severe generalized CP and ID pathological GER remains undetected. Furthermore, research on the prevalence of pathological

GER in these children appears to be complicated by the concerns about the burden of 24-hr pH-monitoring in these children among caregivers. The same concerns might hamper proper detection of pathological GER in clinical practice. However, the symptom-based approach towards the detection and treatment of pathological GER, as is still used nowadays, proofs to be insufficient in this population, since GER is not suspected until overt signs of oesophagitis occurred. This necessitates the use of routine 24-hr pH-monitoring in this population at risk, as has been recommended before in the Dutch guidelines for the detection and treatment of pathological GER in intellectually disabled persons.[14]

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Chapter 5

Energy intake does not correlate with nutritional state in children with severe generalized cerebral palsy and intellectual disability

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ABSTRACT

Background & aims

The majority of children with cerebral palsy and intellectual disability has a poor nutritional state compared with their healthy peers. Several studies have found reduced daily energy intake in this population. The hypothesis is tested that low daily energy intake correlates with poor nutritional state.

Methods

In a population-based sample of 176 children with severe generalized cerebral palsy and intellectual disability (mean age 10 years, SD 2 months; 16% GMFCS level IV; 84% GMFCS level V) anthropometric parameters (weight, upper arm and tibia length, biceps, triceps, subscapular and suprailiacal skinfold thickness, mid upper arm circumference) were measured and dietary intake was registered.

Results

No correlation was found between energy intake as a percentage of estimated average requirement and anthropometric Z-scores. Higher age, female gender, mobility, and to a lesser extent the absence of tube feeding predicted lower anthropometric Z-scores.

Conclusions

In children with severe generalized cerebral palsy and intellectual disability nutritional state is not primarily determined by energy intake. Differences in energy expenditure presumably play an important role, although more research is needed to clarify the complex association between energy intake and nutritional state. Individualized nutritional care is suggested, preferably based on energy expenditure, in order to avoid malnutrition, but also overweight.

INTRODUCTION

Many children with cerebral palsy (CP), especially the most severely affected, have a poor nutritional state compared with their healthy peers.[1-4] Their poor growth has been attributed to several non-nutritional factors, such as endocrine dysfunction, immobility and lack of weight bearing, which are all conditions inherent to the underlying brain malformation or injury.[5,6] Also, residential living has been found to relate to a better nutritional state in this population, although the underlying mechanisms have not yet been elucidated.[7] Besides these non-nutritional factors, nutrition plays a substantial role in the development of a poor nutritional state in children with CP, particularly in the most severely disabled.[8,9] Results of several intervention studies in this population have shown that the improvement of food intake by gastrostomy placement or the elevation of energy content of the oral diet may actually induce catch-up growth and improve weight for height.[10-13] These results suggest that energy intake is often insufficient in children with moderate to severe CP, which is also expected in a population that is often unable to communicate hunger and to self-feed in between meals, and one that is notably affected by dysphagia.[14] Indeed, daily energy intake is lower in children with CP than in their healthy peers, ranging from 71% to 96% of the recommended dietary allowance for healthy age- and gender-matched children.[11,15,16] Since poor nutritional state and poor energy intake both have been observed in children with moderate to severe CP, one would expect a correlation to be present between energy intake and anthropometric indices. However, such correlation has not been evaluated before.

In the present cross-sectional study the hypothesis is tested that low daily energy intake correlates with poor nutritional state in children with severe generalized CP and ID. Furthermore, correlates of energy intake and nutritional state are described.

MATERIALS AND METHODS

The present study is part of a longitudinal study evaluating risk factors of recurrent lower respiratory tract infections in 194 children with severe generalized CP and ID. Practical and ethical considerations on the study design have been described in detail elsewhere.[17] In order to obtain a non-clinical, representative study population, children were recruited through 56 centres (specialized day-care centres, special schools, and residential facilities) in the western part of the Netherlands. Ethical approval was obtained for the study protocol from the national ethics committee (P02.0188C, Central Committee on Research Involving Human Subjects). Inclusion criteria were: IQ below 55 (documented developmental age divided by calendar age times 100) and motor disability defined as hypertonic or hypotonic generalized cerebral palsy or a motor developmental delay to such an extent that a child could at best crawl.

After parents had given informed consent, information on age, gender and aetiology of the handicap was obtained from caregivers and from medical records available at the care centres. Gross motor ability was assessed using the Gross Motor Function Classification System (GMFCS).[18] Since mobility in children with GMFCS level V may vary substantially from complete immobility to a certain degree of autonomous movement, additional information on mobility was obtained from parents through the following question: "is your child capable of performing voluntary movements?". Children were subsequently classified as "immobile" when the answer was "never", and "mobile" when the answer was "sometimes" or "regularly". Furthermore, the presence of the following child characteristics was registered: tube feeding (both adjuvant or exclusive tube feeding), frequent emesis (vomiting at least once a day), and dysphagia. The presence of dysphagia was assessed on site by the researchers using the Dysphagia Disorders Survey (DDS), a mealtime observational tool developed for children and adults with intellectual and developmental disabilities.[19] The use and the interpretation of the DDS in the present study population have been described in detail elsewhere.[14] Children were assigned to the following categories of dysphagia: none, mild, moderate / severe and profound, which included children that were exclusively tube fed as a result of dysphagia.

Dietary intake was registered by means of an estimated food diary. Parents and caregivers at the care centres were asked to register all food and drink intake, including energy supplements, for seven consecutive days. They were carefully instructed on the correct registration of the volume of the actually ingested (and not presented) food portions. Also, they were encouraged to add wrappings of food and tube feeding to the diary whenever possible, in order to facilitate the retrieval of information on ingredients. Dietary intake was analyzed by a dietician using appropriate software based on Dutch normative values ("De Eetmeter", 2002, 'Voedingscentrum', The Hague and the 'Consumentenbond'). Micronutrient food supplements were not included in the analysis, because the use of these supplements had not been adequately registered. For each child mean daily intake was computed in terms of energy (kcal), protein (g), calcium (mg), vitamin A (µg), vitamin D (µg), vitamin B6 (µg), vitamin B12 (µg), and folic acid (µg). Furthermore, intake of nutrients was calculated as a percentage of recommended allowances for healthy Dutch children.[20-23] When available, recommended daily allowance (RDA) was used as a reference. If RDA was not available, then other measures such as estimated average requirement (EAR) or adequate intake (AI) were used.

Anthropometric measurements were performed on site by two researchers. In order to assess inter-observer and intra-observer error, 11 children were measured in duplicate by both researchers. All measurements were performed according to general Dutch guidelines, at the left side of the body.[24] Weight was measured with an electronic wheelchair scale (Universal PM 7050, Lopital). Tibia length and upper arm length were measured to the nearest 0.1 cm with a flexible tapeline. Tibia length was defined as the distance from the medial side of the tibial plateau to the inferior edge of the medial malleolus, and upper arm length was defined as the distance from the acromion to the head of the radius. Biceps, triceps, subscapular, and

suprailiacal skinfold thickness was measured with a Harpenden skinfold caliper (John Bull, England). Each skinfold thickness was measured in triplicate, and the mean was taken for the analyses. Mid upper arm circumference was measured to the nearest 0.1 cm with a flexible tapeline. For all anthropometric measurements Z-scores were calculated based on Dutch reference data of the general population,[27] using Growth Analyser version 3.5, Copyright © 2001-2006, Dutch Growth Foundation. Reference data were available only for children under 18 years.

Statistics

In order to evaluate correlates of energy intake as a percentage of estimated average requirement (energy intake$^{\%EAR}$), multiple linear regression analysis was performed including age, gender, GMFCS level, mobility, tube feeding, and dysphagia as covariates, and energy intake$^{\%EAR}$ as dependent variable.

The technical error of the measurement (TE) and coefficient of variation (CV) were computed from duplicate anthropometric measures in 11 children in order to assess inter and intra-observer error.[25] TE is computed as $\sqrt{(\Sigma\ d^2\ /\ 2n\ )}$, where d is the difference between paired measures, and n is the number of subjects. CV is computed as (TE / mean of measures taken)*100.

The correlation between energy intake$^{\%EAR}$ and all anthropometric Z-scores was evaluated using multiple linear regression analysis. Age, gender, GMFCS level, mobility, tube feeding, frequent vomiting, and dysphagia were entered as covariates in order to adjust for possible confounding. In all regression analyses a forward stepwise technique was used and the probability of F was set as follows: entry 0.05 and removal 0.10. For all statistical tests, significance level was set at $p< 0.05$. Analysis was done using SPSS version 15.0 software (SPSS Inc. Chicago).

RESULTS

Study population

A total of 194 children participated in the longitudinal study on recurrent pneumonias. Their data were used for the present study if at least one of the relevant assessments (dietary registration or anthropometric measurement) had been made. Twelve children were therefore excluded from the analyses (reason for lacking data: parental consent withdrawn n=7, deceased n=2, no measurements done n=3). Another six children, with no dietary data, were excluded as well, because for them, anthropometric Z scores could not be computed since they had turned 18 years in the time between original inclusion and measurement. The 176 included children were therefore significantly younger than the 18 children not included in the analyses. However, they did not differ significantly in terms of gender, GMFCS level and presence of tube feeding (data not shown). Table 1 presents the general characteristics of the present study population of 176 children.

Table 1 General characteristics of the study population (n=176)

Age (years / months); mean (SD)		10 years / 2 months (4 years / 0 month)
Minimum (years / months)		3 years / 5 months
Maximum (years / months)		19 years / 1 month
Age 3-9 years; n (%)		74 (42%)
Age 9-15 years; n (%)		78 (44%)
Age 15-20 years; n (%)		24 (14%)
Gender; n (%)	male	92 (52%)
	female	84 (48%)
GMFCS; n (%)	level IV	29 (16%)
	level V	147 (84%)
Mobility[A]; n (%)	mobile	95 (54%)
	immobile	51 (29%)
	missing data	30 (17%)
Aetiology of handicap; n (%)	congenital	60 (34%)
	perinatal	50 (28%)
	acquired	12 (7%)
	combination[B]	14 (8%)
	unknown	40 (23%)
Tube feeding[C]; n (%)	yes	65 (37%)
	no	111 (63%)
Frequent emesis[D]; n (%)	yes	84 (48%)
	no	59 (33%)
	missing data	33 (19%)
Dysphagia; n (%)	absent	2 (1%)
	mild	13 (7%)
	moderate to severe	119 (68%)
	profound[E]	24 (14%)
	missing data	18 (10%)

[A] Mobility was defined by the question: "is your child capable of performing voluntary movements?" Mobile= sometimes or regularly; Immobile= never

[B] Combination represents all children with congenital and / or perinatal and / or acquired syndromes

[C] Tube feeding; Yes= both partial and exclusive tube feeding; No= exclusive oral feeding

[D] Frequent emesis; Yes= vomiting at least once a day; No= vomiting less than once a day

[E] Exclusively tube fed because of dysphagia

Dietary intake

Dietary intake was assessed in 138 children. In five children the diary covered five days, in 15 children six days and in the remaining 118 children seven days were covered. Table 2 presents the daily intake of macro- and micronutrients expressed in absolute quantities as well as in percentages of the recommended quantity for healthy children. Overall, the intake of energy and the majority of other nutrients were considerably lower than the recommended daily allowances. Protein and vitamin B12 intake, however, were substantially higher than the

Table 2 Daily intake[A] of macro- and micronutrients (n=138)

	Daily intake; mean (SD)	% of recommended quantity for healthy children; median (range)
Energy (kcal)	1300 (418)	62% (27-114%) of EAR
Protein (g)	48.0 (17.0)	153% (45-384%) of RDA
Calcium (mg)	801.5 (345.1)	87% (0-326%) of AI
Vit A (µg)	692.3 (547.8)	77% (0-387%) of AI
Vit D (µg)	3.9 (4.3)	73% (0-1133%) of AI
Vit B6 (µg)	2.3 (6.4)	13% (0-442%) of AI
Folic acid (µg)	172.7 (138.5)	78% (0-535%) of AI
Vit B12 (µg)	4.7 (5.3)	164% (0-2170%) of AI

EAR= estimated average requirement
RDA= recommended daily allowance
AI= adequate intake
[A] Food supplements not included

recommended allowances. Only age and mobility significantly predicted energy intake$^{\%EAR}$. Higher age predicted lower energy intake$^{\%EAR}$ (b= -1.115, t= -2.681, p= 0.008), and better mobility predicted a 9% higher energy intake$^{\%EAR}$ (b= 9.247, t= 2.592, p=0.011).

Anthropometry

Reliability of the anthropometric measures assessed in 11 children is presented in Table 3. For all measurements TE was under the maximum acceptable TE as defined by Ulijaszek and Kerr.[25] Results of the anthropometric measurements performed in 167 children are presented in Table 4.

Dietary intake versus Z-scores

In 132 children both dietary intake data, as well as anthropometric data were available. Six children started tube feeding after their dietary registration had taken place, but before their

Table 3 Reliability of the anthropometric measures (n=11)

	Inter-observer error: TE; CV	Intra-observer error: TE; CV
Tibia length (cm)	0.64; 2.22	---
Upper arm length (cm)	0.93; 3.26	---
Biceps skinfold thickness (mm)	0.36; 10.16	0.07; 1.91
Triceps skinfold thickness (mm)	0.72; 13.01	0.16; 2.80
Subscapular skinfold thickness (mm)	0.24; 3.46	0.08; 1.16
Suprailiacal skinfold thickness (mm)	0.44; 9.15	0.12; 2.39
Mid upper arm circumference (cm)	0.45; 2.17	---

TE= technical error of the measurement,[25] computed as: $\sqrt{(\Sigma\ d2\ /\ 2n)}$, where d= difference between paired measures, and n= number of subjects
CV= coefficient of variation,[25] computed as: (TE / mean of measures taken)* 100

Table 4 Anthropometric characteristics of the study population; mean Z-scores, and the proportion of children with Z-scores ≤ -2 and ≥ +2

Anthropometric measures	Mean Z-scores[A] (SD)	Z-score ≤ -2 n (%)	Z-score ≥ +2 n (%)
Tibia length for age (n=166)	-1.82 (1.34)	68 (41%)	0 (0%)
Upper arm length for age (n=167)	-0.60 (1.98)	40 (24%)	17 (10%)
Weight for age (n=165)	-1.64 (1.54)	77 (47%)	3 (2%)
Biceps skinfold thickness for age (n=163)	-0.55 (1.45)	17 (10%)	5 (3%)
Triceps skinfold thickness for age (n=162)	-1.47 (1.04)	62 (38%)	2 (1%)
Subscapular skinfold thickness for age (n=143)	0.61 (1.79)	3 (2%)	29 (20%)
Suprailiacal skinfold thickness for age (n=131)	-0.62 (1.23)	10 (8%)	5 (4%)
Sum of four skinfolds for age (n=121)	-0.91 (1.13)	17 (14%)	1 (1%)
Mid upper arm circumference for age (n=166)	-0.08 (1.95)	23 (14%)	25 (15%)

[A] Z-scores based on reference values of Dutch children[24]

Table 5 Multiple regression analysis[A] predicting anthropometric measures

	Anthropometric measures[B]								
	WA	UAL	Tib	Bic	Tri	Sub	Supr	Sum	UAC
Energy intake[%EAR]	**	**	**	**	**	**	**	**	**
Age	b= -0.117 p= 0.004	b= -0.131 p= 0.008	**	**	**	**	b= -0.076 p= 0.014	**	b= -0.130 p= 0.011
Female gender	**	**	**	b= -0.947 p< 0.001	b= -0.469 p= 0.025	**	**	**	**
GMFCS level	**	**	**	**	**	**	**	**	**
Mobility	**	**	**	b= -0.804 p= 0.004	b= -0.934 p< 0.001	**	b= -1.001 p< 0.001	b= -0.960 p= 0.001	**
Tube feeding	**	**	**	**	**	**	b= 0.591 p= 0.019	**	**
Frequent vomiting	**	**	**	**	**	**	**	**	**
Dysphagia	**	**	**	**	**	**	**	**	**
R^{2*}	0.069	0.057	---	0.157	0.161	---	0.252	0.128	0.052

** Not significant

[A] Forward stepwise regression analysis with energy intake%EAR, age, gender, GMFCS level, mobility, tube feeding, frequent vomiting, and dysphagia as independent factors. All anthropometric Z-scores were entered as dependent factor. b= regression coefficient; R^{2*}= adjusted R^2

[B] WA= Z-score weight for age; UAL= Z-score upper arm length for age; Tib= Z-score tibia length for age; Bic= Z-score biceps skinfold thickness for age; Tri= Z-score triceps skinfold thickness for age; Sub= Z-score subscapular skinfold thickness for age; Supr= Z-score suprailiacal skinfold thickness for age; Sum= Z-score sum of four skinfolds for age; UAC= Z-score upper arm circumference for age

anthropometric measurements were taken. These children were excluded from the analysis of the correlation of dietary intake and the anthropometric Z-scores, in order to avoid a bias due to a substantial change in dietary content. The analysis evaluating the correlation of energy

intake$^{\%EAR}$ and the growth and nutritional state Z-scores was therefore performed in 126 children, the results of which are presented in Table 5. Energy intake$^{\%EAR}$ did not significantly predict any of the anthropometric Z-scores. Child variables such as higher age, female gender, mobility, and to a lesser extent the absence of tube feeding, significantly predicted lower Z-scores.

DISCUSSION

The present study is the first to evaluate the correlation between energy intake and nutritional state in children with severe generalized CP and ID. No significant correlation was found between energy intake and anthropometric parameters. Although surprising, this finding is not unique, since earlier research in non-neurologically impaired children evaluated the association between energy intake and obesity and found no correlation.[26,27]

We must bear in mind that the absence of a correlation might have been the result of measurement error. The measurement of dietary intake is particularly prone to error, as has been discussed in former research. An underestimation of actual energy intake was found in non-disabled children and adults.[28] However, Stallings et al. reported a marked overestimation of dietary intake in children with CP as compared to their healthy peers.[16] In their study the overestimation occurred evenly in children with low fat stores and in children with adequate fat stores, which makes bias in the evaluation of the correlation between energy intake and anthropometry caused by overestimation of energy intake unlikely.

Despite the abovementioned reservations, the absence of a correlation between energy intake and all measured anthropometric parameters in the present study is striking. How should such results be interpreted? It is unrealistic to conclude that in these children a correlation between energy intake and nutritional state is non-existent, since it is generally accepted that in all humans food intake is indispensable for growth and preservation of adequate nutritional state. Rather, it is more convincing to conceive of other child-factors that obscure such correlation. Since nutritional state can be considered the result of an equilibrium between energy intake and energy expenditure (EE), variation in EE between children may interfere with the correlation between energy intake and nutritional state. Variation in EE may arise from various genetic and metabolic factors, among which mobility that acts through differences in level of activity. Children that are relatively mobile are likely to have higher levels of total EE (TEE). Even differences in resting EE (REE) have been found between mobile and immobile children, with immobility correlating with lower REE.[29] In the present study, mobile children had relatively low Z-scores of skinfold thickness, even while their energy intake was higher than the energy intake of immobile children, suggesting the presence of higher EE in mobile children. More research is needed to identify correlates of EE in this population. In everyday nutritional care for these children, knowledge of REE and TEE would be of great value for optimizing their nutritional

state. However, we realize that at this moment the use of, for example, indirect calorimetry in all care-settings is still unattainable.

The nutritional state of the present study population is in concordance with results of former research in comparable populations,[1-4] and mean Z-scores of almost all anthropometric indices fell below zero. Although information on the ideal nutritional state in these children is lacking and the appraisal of measured anthropometric indices is complicated, as much as 14% of the present study population had a Z-score of the sum of four skinfolds below −2. This suggests the presence of a large group of relatively malnourished children. However, a small group of children with severe motor disabilities had Z-scores of skinfold thickness of +1 and higher. Their immobility may put them at risk of the development of overweight. Concerns about excessive energy intake in some children with CP, especially the ones that are tube fed, have been discussed previously.[30] Thus, although the risk of malnutrition is more pronounced in children with severe generalized CP and ID, overweight is an actual pitfall, especially in immobile children.

CONCLUSIONS

In the present population of children with severe generalized CP and ID, energy intake, as assessed by a 7-day food diary, did not correlate with anthropometric indices. This implies that in this population, nutritional state is not primarily determined by energy intake. Differences in energy expenditure (EE), however, seem to play an important role. Individualized nutritional care is suggested, preferably based on indices of EE, in order to avoid widespread malnutrition, but also overweight.

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Chapter 6

Lower respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability

Submitted

ABSTRACT

Aim

To determine the incidence of lower respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability, and to evaluate the association with constipation, dysphagia, nutritional state, and general child characteristics.

Methods

In a population-based sample of 180 children (mean age 9 years; 0 months, 97 males, 17% GMFCS level IV, 83% GMFCS level V, IQ< 55), the number of lower respiratory tract infections was recorded using parental questionnaires during 18 months of follow-up. General and health-related characteristics were evaluated by questionnaire. Abdominal examination, and measurement of tibia length and biceps / triceps skinfolds were performed. Dysphagia was assed during mealtime observation.

Results

The incidence of lower respiratory tract infections was 348 per 1000 children per year (95% CI: 281-426), and 19 (11%) children had recurrent chest infections (≥ 2 per year). The presence of recurrent chest infections significantly correlated with dysphagia and signs of severe scoliosis, whereas no association was found with constipation and anthropometric indices.

Interpretation

The incidence of lower respiratory tract infections is much higher in children with severe generalized cerebral palsy and intellectual disability than in the general paediatric population, and children with dysphagia and signs of severe scoliosis are particularly at risk.

INTRODUCTION

Life expectancy of children with severe generalized cerebral palsy (CP) and intellectual disability is low, and many children do not reach adulthood.[1,2] The greater part of these deaths may be attributed to lower respiratory tract infections.[2,3] Besides the negative effect on survival, chest infections constitute a principal reason for hospital admissions, causing much distress in both parents and child.[4] Several studies retrospectively evaluated the frequency of lower respiratory tract infections in selected populations of children with CP and either dysphagia, malnutrition, or scoliosis.[5-9] The presence of at least one pulmonary infection in a 6 to 12 months period was found in 19 to 71% of the children. The incidence of pulmonary infections, however, has never been evaluated in this population.

Therefore, the present study prospectively evaluated the incidence of lower respiratory tract infections in a population-based sample of children with severe generalized CP and intellectual disability. Furthermore, disease episodes are described in terms of frequency of doctor visits, diagnostics and treatment, and hospital admittance. Last, the association of recurrent pulmonary infections with several hypothesized risk factors (constipation, dysphagia, nutritional state) and general child characteristics is evaluated.

METHODS

In this prospective, longitudinal study 194 children with severe generalized CP and intellectual disability were included. Children were recruited through 56 care centres (specialized day-care centres, special schools, and residential facilities) using the following inclusion criteria: IQ below 55 (documented developmental age divided by calendar age times 100) and motor disability defined as hypertonic or hypotonic generalized CP or a motor developmental delay to such an extent that a child could at best crawl. Ethical approval was obtained for the study protocol from the national ethics committee (P02.0188C, Central Committee on Research Involving Human Subjects). Practical and ethical considerations on the study design have been described in detail elsewhere.[10] After parents had given informed consent for participation of their child in the study, information on age, gender, aetiology of the handicap, and tube feeding was obtained from caregivers and from medical records available at the care centres. Also, present treatment by an orthopaedist because of scoliosis was recorded as an indicator of presence of severe scoliosis. Gross motor ability was assessed using the Gross Motor Function Classification System (GMFCS).[11]

The presence of constipation was based on a two-week diary evaluating defecation patterns and laxative use, followed by an abdominal examination. Constipation was defined as scybalous, pebble-like, hard stools in >25% of defecations and defecation frequency < 3 times a week, or large stools palpable on abdominal examination, or laxative use or manual disimpaction of feces.[12]

The presence of dysphagia was assessed using the Dysphagia Disorders Survey (DDS), a mealtime observational tool developed for children and adults with intellectual and developmental disabilities.[13] The use and the interpretation of the DDS in the present study population have been described in detail elsewhere.[14] Children were assigned to the following categories of dysphagia: none, mild, moderate / severe and profound (exclusively tube fed as a result of dysphagia).

The nutritional state was evaluated using anthropometric measurements, performed according to general Dutch guidelines.[15] The following parameters were measured: tibia length, biceps- and subscapular skinfold thickness, and Z-scores were calculated based on Dutch reference data of the general population,[15] using Growth Analyser (version 3.5, Copyright © 2001-2006, Dutch Growth Foundation). Reference data were available only for children under 18 years.

Airway infections; diagnose and follow up

After inclusion, all children were followed for a period of 18 months. Parents and caregivers were asked to fill in and return a short questionnaire each time their child was ill. The questions were designed to discriminate between lower respiratory tract infections and other diseases, and dealt with body temperature and duration of fever, nature and duration of signs and symptoms such as cough, wheezing, shortness of breath, and the use of medication such as paracetamol, or antibiotics (prophylactic or temporary). If a physician was consulted, parents were asked to hand over a short questionnaire concerning diagnostics (auscultation, chest radiography) and treatment. Every four months, a reminder was sent to the parents to return all questionnaires to the researchers. Also, parents were asked to indicate the number of disease episodes in the past four months. If there was any discrepancy between the indicated number of disease episodes on the reminder form and the number of returned questionnaires, parents were contacted by telephone in order to retrieve missing information. The definition of a lower respiratory tract infection was established by a consensus group of paediatric pulmonologists and is presented in Table 1. A child was considered to have recurrent pulmonary infections if it suffered from at least two infections within one year (i.e. the second infection occurring within one year after the first).

Statistical analysis

The incidence of lower respiratory tract infections was expressed as number of infections per 1000 children per year, and a 95% confidence interval (CI) was calculated using a Poisson distribution. Univariate analysis was performed to evaluate the association between recurrent pulmonary infections and child characteristics: age, gender, GMFCS level, presence of tube feeding, indices of scoliosis and hypothesized risk factors: constipation, dysphagia, and nutritional state (Z-scores of anthropometric measures). The following tests were used: independent t-test, Mann-Whitney test and Pearson chi-square including Fisher's exact test for small expected

Table 1 Definition* of lower respiratory tract infection

Lower respiratory tract infection is defined by the simultaneous presence** of 1, 2 and 3	
1.	The presence of body temperature> 38.5°C, or 1.5°C> basal temperature during more than 24 hours.
2.	The presence of pneumonia is suspected on the basis of - (an increase of) dyspnoea (tachypnoea, use of assistant respiratory muscles, wheezing) during the last 6 hours. - and / or (increase of) hyper secretion of mucus, and / or, tachypnoea and regular coughing. OR - the presence of pneumonia is confirmed on chest X-ray.
3.	No other explanation for fever (such as middle ear infection or a urinary tract infection) is present.

* Established by a consensus group of paediatric pulmonologists

** In case of a hospital admittance due to pneumonia, the presence of a lower respiratory tract infection was recorded without further inquiry on criteria 1, 2 and 3

Ad 1. If a child had used paracetamol, the body temperature criterion did not need to have been met in the presence of criteria 2 and 3

values. A binary logistic regression analysis (backward conditional) was performed in order to further examine the correlation of recurrent pulmonary infections, child characteristics, and risk factors that reached significance in the univariate analysis. The probability of the conditional technique was set as follows: entry 0.05 and removal 0.10. Results were presented in terms of regression coefficient (b), standard error of b (SE), and p-value. For all other tests, significance level was set at $p< 0.05$. Analysis was done using SPSS version 15.0 software.

RESULTS

Out of 194 children originally included in the study, 14 were lost to follow-up (5 deceased, 1 too ill for participation, 8 consent withdrawn). These children did not differ significantly from the 180 remaining children in terms of age, gender and GMFCS level (data not shown). Table 2 presents the general characteristics of the 180 children that completed 18 months of follow-up.

Lower respiratory tract infections

A total of 94 pulmonary infections was observed in 180 children, and the incidence of lower respiratory tract infections was 348 per 1000 children per year (95% CI: 281-426). Fifty-seven (32%) children had suffered from at least one chest infection during the 18 months follow up period, and 19 (11%) children met the criteria of recurrent pulmonary infections. Seventeen children had used antibiotic prophylaxis during two years prior to the follow up period. In children with recurrent pulmonary infections, use of antibiotic prophylaxis was more common (26%, versus 8% in children without recurrent infections, Fisher's exact test: $p= 0.027$). Table 3 presents an overview of doctors consulted, chest radiography performed, antibiotics used, and hospital admissions.

Table 2 General characteristics of the study population (n=180)

Age[a] ; mean (SD) Minimum Maximum		9y, 0mo (4y, 4mo) 2y, 0mo 19y, 8mo
Male gender		97
GMFCS; n (%)	level IV	31 (17%)
	level V	149 (83%)
Aetiology of handicap; n (%)	congenital	62 (35%)
	perinatal	51 (28%)
	acquired	12 (7%)
	combination[b]	15 (8%)
	unknown	40 (22%)

[a] Age at start follow-up

[b] Combination represents all children with congenital and / or perinatal and / or acquired syndromes

Table 3 Disease episodes; diagnostics and treatment

Reported lower respiratory tract infection episodes[1] (n)		94
Doctor visits (n)	general practitioner/ intellectual disability physician	50
	paediatrician	15
	unknown doctor	7
	no doctor was consulted	13
	missing data	9
Chest radiography (n)		11
Antibiotics (treatment) per disease episode (n)	amoxicillin	28
	amoxicillin/clavulanate potassium	17
	azithromycin	10
	clarithromycin	3
	erythrocine	1
	co-trimoxazole	1
	no antibiotics	13
	missing data	21
Antibiotics (prophylaxis) in 180 children (n)	amoxicillin	1
	amoxicillin/clavulanate potassium	1
	co-trimoxazole	11
	antibiotics unknown	4
	no antibiotics	124
	missing data	39
Hospital admittance[2] (n)		15

[1] Fifty-seven children

[2] The use of chest radiography and antibiotics may be presumed, however was not confirmed in ten (radiography) and seven (antibiotics) children

Risk factors of recurrent pulmonary infections

Table 4 presents child characteristics and risk factors in children with recurrent lower respiratory tract infections (rLRTI+) versus children without recurrent lower respiratory tract infections (rLRTI-). Children with rLRTI+ were significantly more often severely disabled (GMFCS level V) and tube fed, more frequently suffered from dysphagia, and were more often currently treated by an orthopaedist because of scoliosis. The following variables were entered in the consecutive

Table 4 Child characteristics and risk factors; children with recurrent lower respiratory tract infections (rLRTI+) versus children without (rLRTI-)

		rLRTI+ (n=19)	rLRTI- (n=161)	Statistics
Mean age, (SD)		8y, 0mo (4y, 4mo)	9y, 1mo (4y, 4mo)	t^a= 1.043, df 178 p= 0.298
Male gender, n (%)		7 (37%)	90 (56%)	X^2= 2.484[b], df 1 p= 0.115
GMFCS level V, n (%)		19 (100%)	130 (81%)	p^c= 0.048
Tube feeding[1], n (%)		11 (58%)	51 (32%)	X^2= 5.173[b], df 1 p= 0.023
Scoliosis[2], n (%)	yes	9 (47%)	41 (26%)	X^2= 4.641[b], df 1 p= 0.031
	missing data	5 (26%)	43 (27%)	
Constipation, n (%)	yes	3 (16%)	31 (19%)	p^c= 1.000
	missing data	6 (32%)	28 (17%)	
Dysphagia, n (%)	absent	0 (0%)	2 (1%)	U^d= 794.000 p=0.005
	mild	0 (0%)	14 (9%)	
	moderate to severe	10 (53%)	112 (70%)	
	profound[3]	6 (31%)	18 (11%)	
	missing data	3 (16%)	15 (9%)	
Anthropometry, median Z-score (range)	Z-tibia[4]	-1.37 (8.17)	-1.81 (6.63)	U^d= 1123.000 p= 0.296
	Z-biceps[5]	-0.85 (4.02)	-0.90 (10.04)	U^d= 1132.000 p= 0.583
	Z-subscap[6]	0.85 (7.17)	0.23 (8.92)	U^d= 762.000 p= 0.206
	Z-sum[7]	-0.57 (3.97)	-1.27 (5.81)	U^d= 512.000 p= 0.234

[1] Adjuvant or exclusive tube feeding
[2] As reported by parents: scoliosis requiring orthopaedic attention
[3] Exclusively tube fed because of dysphagia
[4] Z-score tibia length for age
[5] Z-score triceps skinfold thickness for age
[6] Z-score subscapular skinfold thickness for age
[7] Z-score sum of four skinfolds for age
[a] Independent samples t-test
[b] Pearson Chi-square
[c] Based on Fisher's exact test (2-sided p-value)
[d] Based on Mann-Whitney test

binary logistic regression analysis: recurrent lower respiratory tract infections (yes / no), GMFCS level (IV / V), tube feeding (yes / no), signs of severe scoliosis (yes / no), and dysphagia (3 categories: the first two categories of dysphagia "no dysphagia" and "mild dysphagia" were collapsed into one, because these categories included a relatively small number of children). Out of all variables entered in the analysis, only dysphagia (b= 1.351, SE= 0.618, p= 0.029), and signs of severe scoliosis (b= 1.247, SE= 0.647, p= 0.054) significantly predicted the presence of recurrent pulmonary infections.

DISCUSSION

The present study is the first to prospectively evaluate lower respiratory tract infections in a population-based sample of children with severe generalized CP and intellectual disability. In the present population the incidence of lower respiratory tract infections was remarkably high (348 per 1000 child-years). Eleven percent of the children met the criteria of recurrent pulmonary infections (at least two infections within one year), and children with dysphagia and indicators of severe scoliosis were particularly affected.

The incidence of lower respiratory tract infections in the present study population was much higher than the incidence rate in the general population attending general practices in the Netherlands (23-78 per 1000 child-years).[16] Children with CP are particularly prone to pulmonary infections due to several conditions that are highly prevalent in this population. In the present study population, children with moderate to profound dysphagia were particularly at risk. Dysphagia is frequently observed in children with CP,[14] and is hypothesized to cause chest infections through (silent) aspiration of foodstuff and saliva.[7,8,17] Moreover, the concurrent presence of dysphagia-based aspiration and gastro-oesophageal reflux (GER) in children with CP proved to increase the risk of chest infections in former research.[8] Although Nissen fundoplication actually reduced the number of pulmonary infections in a population of neurologically impaired and unimpaired children,[18] the cause-effect relation of GER and pulmonary infections has yet to be untangled. Treatment of recurrent dysphagia-associated aspiration consists of the introduction of gastrostomy feeding and the reduction or complete discontinuation of oral feeding. The introduction of enteral tube feeding proved to actually lower the incidence of chest infections in children with CP and dysphagia.[6] In the present study the presence of tube feeding positively correlated with recurrent pulmonary infections, however, when controlled for presence of dysphagia the positive effect of tube feeding on recurrent infections disappeared.

Another interesting finding in the present study was the relation of signs of severe scoliosis and recurrent pulmonary infections. The presence of scoliosis was based on parental report on present treatment by an orthopaedist because of scoliosis. Of course, the most accurate diagnostic tool to evaluate presence and severity of scoliosis is radiography. However, X-rays

had not been performed in many children and we believe that information on consultation of an orthopaedist as part of scoliosis-care offers an acceptable estimation of presence and severity of scoliosis. The association between signs of scoliosis and lower respiratory tract infections has never been established before in this population. Saito et al. evaluated scoliosis and chest infections in children with CP, however, they only reported that the presence of chest infections did not correlate with the final magnitude of the curve.[9] Studies on the consequences of idiopathic scoliosis found a reduction in chest wall compliance and pulmonary function as a result of the spinal deformity.[19,20] Hypothetically, a reduction in pulmonary function leads to underventilation of lung regions and impairs airway clearance, thereby increasing the susceptibility to pulmonary infections, however, more research is needed to determine the explaining mechanisms involved.

In former research in children with CP, treatment of malnutrition was followed by a decrease in number of chest infections.[5] Malnutrition is thought to increase the risk of pulmonary infections by two mechanisms. First, it acts upon systemic immunity and thereby impairs the defence mechanisms of the body against microorganisms,[21] and second, skeletal muscle function is reduced affecting the performance of respiratory muscles.[22] In the present study, however, no significant correlation between anthropometric indices and recurrent pulmonary infections was found. These findings may be explained by the high density of tube feeding due to severe dysphagia, ensuring adequate nutritional intake in those children that often suffer from chest infections.

Although constipation is hypothesized to increase the risk of pulmonary infections by decreasing movement of the diaphragm and thereby impairing respiration, or through lipid aspiration credit to mineral oil treatment,[23] the correlation between constipation and recurrent pulmonary infections had not been studied before in this population. We may presume that the contribution of constipation to the respiratory infection risk profile of children with CP is not large, since our results showed no difference in frequency of constipation between children with and without recurrent infections.

In the present study it was decided to use parents as the principal source of information about presence and characteristics of disease episodes in order to ensure the highest probability of "catching" all lower respiratory tract infections. From a medical point of view it would have been more obvious to use the physician's opinion for the assessment of chest infections, since this would have given more direct access to valuable information on physical examination and chest X-rays. However, as we have seen in the present study, in 14% of the disease episodes, a doctor was not consulted. Furthermore, parents visited a wide range of doctors. For practical reasons it would have been impossible to track down all information on disease episodes. In order to maximize the retrieval of information on pulmonary infections, parents were asked to hand over a questionnaire to their physician. The number of returned physician-questionnaires was, however, disappointing.

The presence of a pulmonary infection was based on information on the nature and duration of signs and symptoms such as fever, tachypnoea and use of assistant respiratory muscles. Only if available, auscultation findings and chest radiographic data were taken into account. From our results we may conclude that relying on radiographic data alone, as has been done in some retrospective studies on pulmonary infections in children with CP,[6,9] would have produced a substantial underestimation of the number of infections in this population. Chest radiography had been performed in 11 out of 94 disease episodes only.

Clinical features of pneumonia such as tachypnoea and fever, as defined by the World Health Organization (WHO), are considered to be highly useful signs in diagnosing pneumonia in children, according to paediatric guidelines.[24,25] The added value of both auscultation and chest radiography, however, has been questioned. So far, guidelines on diagnosis and treatment of lower respiratory tract infections in children with CP are lacking.

In everyday practice, the urgency of preventing pulmonary infections in children with severe generalized CP and intellectual disability has already been acknowledged. Antibiotic prophylaxis is offered to children with persistent infections. In the present study population ten percent of the children used prophylaxis. Five children still met the criteria of recurrent pulmonary infections, which demonstrates that prophylaxis does not necessarily eradicate all infections. Another strategy used in the prevention of lower respiratory tract infections has already been discussed: the elimination of dysphagia-related aspiration through gastrostomy feeding. Still, more research is needed to evaluate the preventive effects of treatment of hypothesized risk factors, such as GER (anti-reflux medication or surgery), malnutrition (nutritional rehabilitation), and scoliosis (surgery) on the incidence of pulmonary infections in this population.

CONCLUSION

The incidence of lower respiratory tract infections is much higher in children with severe generalized CP and intellectual disability than in the general paediatric population. In the present study population, children with dysphagia and signs of severe scoliosis were particularly at risk. Although antibiotic prophylaxis is likely to reduce the number of infections in some children, in others pneumonias proved to be refractory even in the presence of prophylaxis. More research is needed on treatment of risk factors, such as GER, malnutrition, and scoliosis to find more strategies in the prevention of recurrent pulmonary infections in this fragile population.

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Chapter 7

General Discussion

This dissertation describes the results of a cohort study on the incidence and risk factors of lower respiratory tract infections in 194 children with severe generalized cerebral palsy and intellectual disability. Within the context of the cohort study, the prevalence and clinical presentation of several major comorbid disorders in the studied population have been evaluated as well.

MAIN RESULTS

This study shows that the incidence of lower respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability is tenfold higher (348 / 1000 child-years) than the incidence in children in general (23-78 / 1000 child-years).[1] Furthermore, 11% of the studied children had recurrent lower respiratory tract infections (≥2 / year). Children suffering from dysphagia and children that visited an orthopaedist because of scoliosis were particularly at risk.

Moderate to profound dysphagia was observed in 91% of the children, although only one third of the parents reported experiencing feeding problems in their child on a regular basis. Poor motor ability, as defined by a Gross Motor Function Classification System (GMFCS)[2] level V, as well as the presence of tube feeding correlated with more severe dysphagia.

In the studied population mean Z-scores of the majority of anthropometric measures fell below zero, and as much as 14% of the children had Z-scores of the sum of four skinfolds ≤2, suggesting a poor nutritional state. Lower anthropometric Z-scores were associated with older age, female gender, the ability to move voluntarily and the absence of tube feeding. Although median energy intake was 62% of the recommended average requirement for healthy children, no correlation was found between energy intake and anthropometric measures, suggesting the presence of considerable differences in energy expenditure between children. Due to a very low consent rate for 24-hr pH-monitoring, the prevalence of gastro-oesophageal reflux could not be evaluated in the present study. In 25 children, however, 24-hr pH-monitoring was performed, and 14 children proved to suffer from pathological gastro-oesophageal reflux. No correlation was found between the presence of pathological gastro-oesophageal reflux and symptoms, such as frequent emesis, rumination, and food refusal.

FROM DESIGN TO RESULTS

In chapter 2 of this dissertation, the design of the present study, including study goals, diagnostic measurements and statistical analysis, has been described in detail. During the implementation of the study, the main structure of the design has been adhered to. However, a few changes have been made, which will be discussed here.

Risk factors

In the design of the study, five comorbid disorders had been identified as possible risk factors for the development of recurrent lower respiratory tract infections in the studied population. These are dysphagia, gastro-oesophageal reflux, poor nutritional state, constipation, and impaired respiratory function. The presence and clinical presentation of dysphagia, gastro-oesophageal reflux, and poor nutritional state have been described in the present dissertation (chapters 3-5). Constipation and respiratory function have been described in a preceding dissertation on this cohort study by Rebekka Veugelers.[3,4] However, two hypothesized risk factors: gastro-oesophageal reflux and respiratory function have not been entered in the analysis of correlates of recurrent lower respiratory tract infections. Gastro-oesophageal reflux was left out because of the low number of measurements (chapter 4), and respiratory function was not included since reproducibility of the measurement, using the interrupter technique (MicroRint),[5] proved to be poor, mainly due to large within-measurement variation.[4]

Diagnostic methods

Most of the diagnostic methods have been performed as planned in the study protocol (chapter 2). However, some adaptations have been introduced during the research process. The main changes are described here.

Dysphagia

The evaluation of the presence and severity of dysphagia was done using the Dysphagia Disorders Survey,[6] combined with cervical auscultation and measurements of oxygen saturation, as has been described in chapter 2. Measurement of oxygen saturation, however, was discontinued after having completed 60 measurements, because it did not add to the accurateness of the observation of feeding performance as expected. Oxygen de-saturation was defined as a decrease in oxygen saturation ≥4%, during ≥5 minutes. During the evaluation of these 60 children, oxygen saturation never dropped significantly, even when a child was evidently choking on food or drinks.

Nutritional status

The evaluation of nutritional status was done using anthropometric measurements and single frequency Bioelectric Impedance Assessment (BIA),[7] as has been described in the study design. The results of the BIA measurements, however, have not been used in the description of nutritional state, nor have they been used in the analysis of risk factors of recurrent pulmonary infections. At the onset of this research project, BIA was considered to be a promising diagnostic tool for the estimation of percentage of body fat through measurement of total body water. In non-neurologically affected children it actually has proven to be a valuable and valid tool.[8] However, the validity of BIA measurements in children with severe generalized cerebral palsy and intellectual disability remained questionable. After all, the interpretation of

BIA measurements is done by transformation of resistance (Rz) into total body water through a prediction equation that has been developed in non-neurologically affected children.[9] In a review article by our group on the validity of BIA measurements using Pencharz's prediction equation[9] in children with severe cerebral palsy, it was concluded that evidence in favour of BIA measurements in this population is poor.[10] In the present study it was therefore decided that the results of the BIA measurements would be omitted from the analyses. Although the estimation of percentage of body fat from skinfold measurements is equally hazardous in this population because of the use of prediction equations that have been developed in healthy children,[10] the results of the skinfold measurements have nevertheless been used in the present study. Skinfold measurements have not been transformed into percentage of body fat, but were compared to skinfold thickness of age and gender-matched children in the general population, and as such have been described as Z-scores.

Because from earlier studies,[11,12] and the present research project (chapter 5) we learned that children with (severe) cerebral palsy are smaller and lighter, and have thinner skinfold thicknesses than their age and gender-matched healthy peers, growth charts derived from healthy children are probably unsuitable to serve as a reference for normal growth in children with cerebral palsy. A prevalence rate of malnutrition was therefore not presented in the present dissertation (chapter 5).

Analysis

The present study was designed as an observational cohort study. In chapter 2, the analysis of the association between hypothesized risk factors and recurrent lower respiratory tract infections was described in terms of a nested case-control design. This design had been chosen because of practical reasons. The measurement of respiratory function and gastro-oesophageal reflux was limited to a relatively small number of children in the cohort. A nested case analysis would have potentiated the evaluation of correlates of recurrent pulmonary infections, including gastro-oesophageal reflux and respiratory function, in a smaller sample of children. However, respiratory function and gastro-oesophageal reflux have been omitted from the final analysis for reasons earlier explained, and eventually, a full-cohort analysis has been performed.

IS EPIDEMIOLOGICAL RESEARCH IN THIS POPULATION A SISYPHEAN TASK?

The present study was conceived in the year 2001, and in 2003 the first measurements were done. At that time, many hurdles regarding the inclusion of 56 care centres and an equal amount of consent procedures had already been overcome. The envisioned number of 300 participating children proved to be impossible to attain within reasonable time limits and 194 children were eventually included in the study. In chapter 2 the problems dealt with in the preparatory phase of this epidemiological study have been elaborately described. In the period

of 2003 to 2006, measurements were done and more obstacles were encountered, in particular the low consent rate for the 24-hr pH-measurements, which has been described in chapter 4. Also, growing insight into the validity of diagnostic tools used in the studied population (interrupter technique[5], and BIA[7]) as discussed in the above paragraph, resulted in an inevitable rejection of carefully obtained data. Last, the lack of valid reference values for children with severe generalized cerebral palsy and intellectual disability, especially for growth and nutritional state, complicated the accurate interpretation of the results.

Still, the epidemiological research described in this dissertation by no means resembles a Sisyphean task, for the results of this study make up an important step towards the development of a guideline for the prevention of pulmonary infections in the studied population. Also, the outcomes offer a valuable overview of the highly prevalent major comorbid disorders, which is bound to induce increased awareness among healthcare workers. Already, during the executory phase of the study, understanding of important comorbidity in these children, such as dysphagia, gastro-oesophageal reflux and poor nutritional status, and their possible effects on the development of pulmonary infections, increased among paediatricians and intellectual disability physicians in the Netherlands, in part as a result of this study. Nowadays, diagnosis and treatment of gastro-oesophageal reflux seems to have taken up a more substantial part of diagnostic procedures in these children. However, almost half of the children diagnosed with pathological gastro-oesophageal reflux in the present study had not been treated with anti-reflux medication (chapter 4), which indicates the presence of room for improvement.

Several groups of Dutch speech and hearing specialists, working in intellectual disability care, have participated in courses on dysphagia screening by Prof. Joan Sheppard (Columbia University, New York), organised by our group in collaboration with the NGBZ (vereniging voor deskundigheidsbevordering in de zorg voor mensen met een verstandelijke handicap). However, in many day-care centres and general hospitals, such experts are not yet available.

Thus, although in clinical practice awareness of the presence and impact of comorbid disorders in these children has grown, guidelines are needed for the detection and treatment of such common comorbid disorders, in order to ensure the same pro-active care in each child. In the following paragraph, recommendations for clinical practice are made, which may serve as a first step towards the development of clinical guidelines.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Although the present study was designed to evaluate the incidence and risk factors of recurrent lower respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability, the main recommendations for clinical practice that are made here concern dysphagia, gastro-oesophageal reflux and poor nutritional state, including energy intake. A summary of the principal recommendations is presented in Table 1.

Table 1 Recommendations for clinical practice in children with severe generalized cerebral palsy and intellectual disability

Recommendations for clinical practice	
Dysphagia	• Standard screening for dysphagia in all children • Suggested screening instrument: Dysphagia Disorders Survey (DDS) (more information on DDS: *www.nutritionalmanagement.org*) • In case of pharyngeal phase problems: refer for further evaluation and diagnostic workup
Gastro-oesophageal reflux	From guideline of the Dutch Association of Physicians in Care of Intellectually Disabled:[13] • Oesophageal endoscopy in any intellectually disabled person in case of (alarming) symptoms; - hematemesis - frequent vomiting - unexplained anaemia - recurrent respiratory tract infections - nutritional problems - rumination - regurgitation - dental erosions • Standard 24-hr pH-monitoring in children / adults with an IQ<35, or with spasticity of at least two limbs, even in the absence of symptoms
Nutritional assessment	• Regular nutritional assessment in all children • Anthropometry, if possible combined with BIA (use Rieken equations[19]) • Segmental measures (tibia length, knee height, upper arm length) should be used in stead of body height. • Growth charts for healthy children, and children with cerebral palsy should be used with caution. • Calculation of adequate energy intake based on formulas of Rieken et al.,[19] if necessary supplemented with indirect calorimetry

Dysphagia

Since the prevalence of (severe) dysphagia in these children is high, and its consequences are serious, screening for presence and severity of dysphagia in each child is justified. The DDS is suitable for this purpose. Speech-language pathologists, occupational therapists, physical therapists, dieticians, nurses, and other licensed professionals who have attended a DDS certification workshop can administer the DDS. Additional information on the DDS or the certification workshop can be found at *www.nutritionalmanagement.org*.

Once apparent swallowing difficulties are established by the DDS or other screening instruments, referral should be considered to evaluate specific causes of the dysphagia and to determine appropriate management strategies. In particular, when problems in the pharyngeal or oesophageal phases of swallowing are suspected, imaging diagnostic techniques should be used to assess the risk of aspiration. If no signs of dysphagia are detected during screening, we recommend a repetition of dysphagia screening once a year. Although the natural course of dysphagia has never been evaluated in this population, a deterioration of swallowing function is regularly seen in clinical practice.

Gastro-oesophageal reflux

A guideline for the diagnosis and treatment of pathological gastro-oesophageal reflux in intellectually disabled persons already exists.[13] In this guideline it is recommended to perform oesophageal endoscopy in any intellectually disabled person in case of alarming symptoms, such as hematemesis, frequent vomiting, or unexplained anaemia, and in case of symptoms such as recurrent respiratory tract infections, nutritional problems, rumination, regurgitation and dental erosions. In adults or children with an IQ<35, or with spasticity of at least two limbs, routine 24-hr pH-monitoring is recommended, even in the absence of symptoms. The results of the present study support the latter recommendations, since the presence of pathological gastro-oesophageal reflux could not be predicted by symptoms in a limited sample of the studied population (chapter 4).

In the above mentioned guideline, no recommendations were made for the repetition of 24-hr pH-monitoring if the first measurement did not show signs of pathological gastro-oesophageal reflux. Guidelines for the detection and treatment of pathological gastro-oesophageal reflux in the general paediatric population, developed by the North American and the European Society for Pediatric Gastroenterology and Nutrition (NASPGAN / ESPGAN)[14,15] offer little directions for these neurologically affected children. Until more research is done into the natural history of the development of pathological gastro-oesophageal reflux in this population, we recommend healthcare workers to repeat a 24-hr pH-measurement in a child after 3 to 5 years, and not to postpone 24-hr pH-measurements until symptoms become apparent, because at that time, oesophagitis may already have developed.

Nutritional assessment

Children with severe generalized cerebral palsy and intellectual disability are smaller, lighter and have thinner skinfold thicknesses than otherwise healthy children, which in part is considered to be inherent to their neurological disability, and in part may be attributed to malnutrition. Because poor nutritional state is common among these children, we recommend regular evaluation of nutritional state and growth. Diagnostic method of choice is anthropometry, for reasons of easy applicability in non-clinical settings. The observation must be made that the measurement of body height for the evaluation of growth is advised against in children with cerebral palsy, because scoliosis and fixed joint contractions compromise the accuracy of this measurement. Segmental measures such as tibia length and knee height are useful and accurate measures. They may be converted into body height, using prediction equations that were developed in children with cerebral palsy without scoliosis,[16] however, they are preferably used without the conversion into body height. The interpretation of anthropometry measures needs to be done with great caution. Since growth characteristics of these children are different from those of their non-neurologically affected peers, national growth curves, based on growth data of healthy children, should not be used as a compelling guide of 'ideal growth' in this population. Even growth charts[17,18] based on characteristics of large populations of

children with cerebral palsy should be used with caution. The nutritional state of many of these children is considered to be suboptimal and the authors of the cerebral palsy-growth charts make the pertinent remark that taking these curves as a reference of 'healthy growth' would be a mistake. Still, an interpretation of anthropometric measurements needs to be done in order to manage nutritional problems. We suggest that growth and nutritional state are monitored using repeated anthropometric measurements in time. Z-scores may then be calculated based on reference data of healthy children or, if available, cerebral palsy-specific reference data, and attention should be paid to the abovementioned drawbacks in the use of growth curves in this population. A negative change in Z-scores in time should alarm healthcare workers, so that nutritional intervention can be commenced in time. Recently, in his dissertation, Rob Rieken described the development of new equations for the prediction of body composition from BIA and skinfold measurements in children with severe generalized cerebral palsy and intellectual disability, based on a validation study that compared BIA and skinfold measurements with the doubly labelled water technique.[19] Although BIA is not yet readily available in all care centres and clinical settings, it is easily applicable and, when combined with the newly developed equations of Rieken et al.,[19] the method offers a valuable contribution to the assessment of nutritional state in these children.

Besides growth charts, reference values[20] for the estimation of adequate energy intake in children should not be applied straightforwardly in this population. First, these reference values have been derived from populations of healthy children, and may not be easily translated to children with severe generalized cerebral palsy and intellectual disability. Second, from the present results we learned that, in this population, energy intake does not correlate with nutritional state as measured by anthropometry, which suggests the presence of a large variation in energy expenditure between children, irrespective of age and gender. Recently, Rob Rieken adapted Schofield's equations[20] for the prediction of total energy expenditure in healthy individuals for use in children with severe neurological impairment and intellectual disability. Adjustments for movement and severity of motor impairment were added to the existing equations. In his dissertation, he describes the validation of these prediction equations, with the doubly labelled water method as the reference method, in 61 severely neurologically impaired children with intellectual disability.[19] Rieken concludes that, although these newly developed prediction equations need to be evaluated in larger populations, their agreement with the reference method was reasonable. In clinical practice, these prediction equations may very well be used to estimate daily requirements of energy intake in a child. Of course, the regular assessment of nutritional state needs to continue, in order to evaluate the accuracy of the energy requirements proposed. If available, indirect calorimetry for the measurement of resting energy expenditure, may offer valuable additional information when doubts on adequate energy intake in a child continue to exist.

Lower respiratory tract infections

The identification of children at risk of recurrent lower respiratory tract infections is the first step towards the development of a guideline for the prevention of pulmonary infections in children with severe generalized cerebral palsy and intellectual disability. In the present study severe dysphagia showed to be related to the presence of recurrent lower respiratory tract infections. The association between dysphagia-related aspiration and pulmonary infections had already been described in literature and offers the main justification for the discontinuation of oral feeding in everyday medical practice. The added value of the present results lies within the notion of dysphagia as a widespread comorbid disorder in this population. Nearly all the participating children suffered from feeding problems to some extent, and in as much as 91%, pharyngeal phase problems were highly suspected, indicating an increased risk of aspiration. In 24 children, oral feeding had already been discontinued, however, the remaining 126 children were still orally fed (sometimes in the presence of supportive enteral feeding). In future practice the presence of pharyngeal phase problems with an increased risk of aspiration should be suspected in each child with severe generalized cerebral palsy and intellectual disability. Therefore, routine screening and management of dysphagia, as has already been suggested in the above paragraph on dysphagia, is highly recommended as a means to prevent respiratory tract infections.

In the present study, children that visited an orthopaedist because of their scoliosis were significantly at risk of developing recurrent pulmonary infections. The hypothesis of reduced pulmonary function as an explanation of the correlation between scoliosis and pulmonary infections has been discussed in chapter 6, however, this correlation has never been evaluated in clinical research. Whether surgical correction of scoliosis will reduce the number of pulmonary infections remains the question. From the results of present study, no recommendations for clinical scoliosis-care can be made, although clinicians should be aware of the increased risk of recurrent pulmonary infections in children with severe scoliosis.

DIRECTIONS FOR FUTURE RESEARCH

The first step towards the development of a guideline for the prevention of lower respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability has been taken. The incidence of recurrent pulmonary infections in this population is high, and from earlier research we know that pulmonary infections are the primary cause of death in these children.[21-23] This knowledge justifies vigorous attempts to reduce the number of pulmonary infections in children.

Although the present study convincingly showed a correlation between the presence of recurrent lower respiratory tract infections and dysphagia and indices of scoliosis, the association of some other hypothesized risk factors with recurrent pulmonary infections could not be evaluated, mainly due to practical hurdles. Of course, in future research such hurdles may be

overcome and more knowledge on pulmonary infections and its correlates in this population will then be available. Most interesting, however, is the evaluation of prevalence of gastro-oesophageal reflux and its association with lower respiratory tract infections in this population. In a longitudinal design, the natural course of gastro-oesophageal reflux in this population could be evaluated, together with the effect of treatment and the incidence of 'new' pathological gastro-oesophageal reflux in children, whose 24-hr pH-measurement was negative before. With the latter information, new recommendations can be done for the frequency of 24-hr pH-measurements in children with a negative pH-metry.

Although since 40 years, knowledge on nutritional assessment and nutritional care in children with severe generalized cerebral palsy and intellectual disability has increased exponentially, the key-questions have not yet been answered. We still have no notion of 'normal' growth and body composition in these children. These severely impaired children suffer from many comorbid disorders that may or may not be inherent to their neurological deficit. Many of those disorders act upon growth and nutritional status. Also, the heterogeneity of aetiologies that caused the intellectual and motor disabilities is likely to have a significant effect on differences in growth potential in this population. Cerebral palsy-specific growth curves have been developed and offer an important description of 'how children with cerebral palsy grew'.[17,18] The authors Stevenson and Conaway propose "working toward the development of standards of growth for children with cerebral palsy associated with health and well-being".[18] Indeed, health-related nutritional state standards would offer a great opportunity to develop sensible nutritional policy in children with cerebral palsy. However, a long road is still ahead and several hurdles still need to be taken. Questions like "what is health in children with cerebral palsy" are not easily answered.

CONCLUDING REMARKS

The present study was designed to evaluate the incidence and risk factors of recurrent respiratory tract infections in children with severe generalized cerebral palsy and intellectual disability. The identification of dysphagia and indicators of severe scoliosis as risk factors of pulmonary infections may be considered a modest, but significant step towards the reduction of pulmonary infections in the population.

The description of presence and clinical presentation of gastro-oesophageal reflux, dysphagia and nutritional state (including energy intake), however, attributes most to the clinical significance of the present study. Clinicians are made aware of the comprehensiveness of the disorders among these children. Furthermore, practical recommendations for the detection and interventions are made, based on present study results and former research. Foremost, the present study shows that, although research in children with severe generalized cerebral palsy and intellectual disability takes prudence, flexibility, and a long breath, it needs to be done, since basic knowledge on health in this population is still limited.

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Summary

Children with severe generalized cerebral palsy and intellectual disability are at high risk of a range of comorbid disorders, such as dysphagia, gastro-oesophageal reflux, delayed gastric emptying, constipation, poor nutritional state and osteoporosis. Lower respiratory tract infections are particularly disrupting, since they cause much morbidity and distress, and are the primary cause of death in this population. Prevention of pulmonary infections may induce an important improvement of general health and quality of life. In order to gain insight into preventive measures, more knowledge was needed of the incidence of pulmonary infections and the risk factors in this population.

In the cohort study that is described in this dissertation, the incidence of lower respiratory tract infections has been assessed in a population-based sample of 194 children with severe generalized cerebral palsy and intellectual disability. Also, the correlation of recurrent pulmonary infections with general child characteristics and important comorbid disorders, that have been hypothesized to be risk factors, has been evaluated. The main comorbid disorders selected for this purpose were dysphagia, gastro-oesophageal reflux, constipation and poor nutritional state. Because the prevalence of these disorders has never been evaluated in a representative, population-based sample of these children, the presence and characteristics of all cited comorbid disorders, except for constipation, which has been discussed in a previous dissertation, have been evaluated as well.

Chapter 2 describes the study design and the inclusion procedure of this epidemiological research in detail. In particular, the ethical issues concerning the use of diagnostic instruments and the consequences for the study design are discussed. Furthermore, an overview is given of the hurdles that have been encountered in the preparatory phase and the inclusion of 194 participants through 56 specialized day-care centres, special schools, and residential facilities. At the start of the study, the mean age of the participating children was 8.9 years (SD 4.4 years). Furthermore, 53% was male, 83% had a Gross Motor Function Classification System level V, whereas the remaining children had a level IV. All children had an IQ below 55. The basic characteristics of participating children were compared with those of the 379 eligible children that did not participate in the study. We found that the participating children were slightly younger, and that their parents reported slightly more comorbidity. Nevertheless, we consider the representativeness of the studied population to be of maximum attainable quality.

Chapter 3 discusses the presence and severity of dysphagia in the studied population as assessed with the Dysphagia Disorders Survey, a mealtime-observational tool. As much as 99% of the study population was to some extent affected by dysphagia, and 91% had signs of pharyngeal-phase involvement or were exclusively fed by tube. Dysphagia positively related to severity of motor impairment, and to a higher weight for height, which may be explained by the presence of gastro-enteral feeding in severely dysphagic children. Furthermore, actual severity of dysphagia tended to be underestimated by parents. We recommend screening for dysphagia by means of a structured mealtime observation by trained professionals in all children with severe generalized cerebral palsy and intellectual disability, with subsequent

referral for clinical evaluation of specific causes of the dysphagia and to determine appropriate management strategies.

In **chapter 4** the evaluation of the presence of pathological gastro-oesophageal reflux is described in a subset of 25 children, whose parents gave additional informed consent for a 24-hr pH-measurement. Because of the small number of measurements, a prevalence rate of gastro-oesophageal reflux is not presented. Pathological gastro-oesophageal reflux was observed in 14 out of 25 children. Surprisingly, the use of anti-reflux medication was equally distributed among children with and without pathological gastro-oesophageal reflux. Furthermore, in this subset, the presence of pathological gastro-oesophageal reflux did not correlate with symptoms.

Chapter 5 presents the evaluation of the correlation between daily energy intake and nutritional state in the studied population. The nutritional state was measured with anthropometry, and is described in terms of Z-scores. Fourteen percent of the children had a Z-score of the sum of four skinfolds below –2, which suggests the presence of a large group of children with a poor nutritional state. Higher age, female gender, mobility, and to a lesser extent the absence of tube feeding, predicted lower anthropometric Z-scores. Dietary intake, based on a 7-day food diary, is described as well. Median daily energy intake was 62% of the recommended quantity for healthy children. No correlation was found between daily energy intake and anthropometric Z-scores, which suggests a large variation in energy expenditure between these children, irrespective of age and gender.

In **chapter 6** the main study questions are discussed: the incidence and risk factors of lower respiratory tract infections. The occurrence of lower respiratory tract infections was recorded during an 18-months follow-up period. Parents were asked to fill in a questionnaire each time their child fell ill. The questions were designed to discriminate between lower respiratory tract infections and other diseases. The definition of a pulmonary infection was established by a consensus group of paediatric pulmonologists. The incidence of lower respiratory tract infections in the studied population was 348 per 1000 children per year (95% CI: 281-426), which is tenfold higher than the incidence in the general paediatric population (23-78 / 1000 child-years). Eleven percent of the children suffered from a pulmonary infection at least twice a year, and children with dysphagia and scoliosis were particularly at risk.

In **chapter 7** the most important findings of the present dissertation on incidence and risk factors of lower respiratory tract infections, as well as the results on presence and correlates of dysphagia, gastro-oesophageal reflux and nutritional state and energy intake are summarized and discussed in a broader perspective. Also, some adaptations in the study design and methods that have been made throughout the implementation of the study are elucidated and accounted for. Finally, recommendations for clinical practice are given, as well as directions for future research.

Samenvatting

Kinderen met ernstige meervoudige beperkingen hebben een verhoogd risico op een aantal comorbide stoornissen, zoals dysfagie, gastro-oesofageale reflux, vertraagde maagontlediging, obstipatie, een slechte voedingstoestand en osteoporose. Vooral lage luchtweginfecties, die de belangrijkste doodsoorzaak in deze populatie zijn, veroorzaken veel morbiditeit en leed. De preventie van longinfecties zou de algemene gezondheid en kwaliteit van leven van deze kinderen voor een belangrijk deel kunnen verbeteren. Om inzicht te krijgen in mogelijke preventieve maatregelen is er meer kennis nodig over de incidentie van longinfecties en de risicofactoren in deze populatie.

In de cohortstudie die wordt beschreven in dit proefschrift werd de incidentie van lage luchtweginfecties onderzocht in een niet-klinische populatie van 194 kinderen met ernstige meervoudige beperkingen. Verder werd de correlatie onderzocht tussen recidiverende longinfecties en algemene kind karakteristieken en belangrijke comorbide stoornissen die aangemerkt konden worden als risicofactoren. Dysfagie, gastro-oesofageale reflux, obstipatie en een slechte voedingstoestand werden aangewezen als de belangrijkste comorbide stoornissen. Omdat de prevalentie van bovengenoemde stoornissen niet eerder is onderzocht in een representatieve, niet-klinische populatie van deze kinderen werden de aanwezigheid en de karakteristieken van deze comorbide stoornissen eveneens onderzocht. Echter, de prevalentie en kenmerken van obstipatie in deze populatie werden in een eerder proefschrift al besproken en werden hier niet opnieuw behandeld.

Hoofdstuk 2 beschrijft het studie design en de inclusie procedure van dit epidemiologische onderzoek in detail. In het bijzonder worden de ethische problemen die ontstaan bij het gebruik van diagnostische instrumenten en de consequenties daarvan voor het studie design besproken. Verder wordt een overzicht gegeven van de hindernissen die werden genomen in de voorbereidende fase en de inclusie van 194 deelnemers via 56 gespecialiseerde kinderdagverblijven, speciale scholen en woonvoorzieningen. Bij het begin van de studie was de gemiddelde leeftijd van de deelnemende kinderen 8.9 jaar (SD 4.4 jaar). Verder was 53% man en had 83% een Gross Motor Function Classification System niveau 5, terwijl de resterende kinderen niveau 4 hadden. Alle kinderen hadden een IQ lager dan 55. De algemene kenmerken van de deelnemende kinderen werden vergeleken met de 379 kinderen die wel in aanmerking kwamen voor het participeren in de studie, maar die uiteindelijk niet deelnamen. We stelden vast dat de deelnemende kinderen iets jonger waren en dat hun ouders iets vaker de aanwezigheid van comorbiditeit rapporteerden. Toch beschouwen wij de representativiteit van de studiepopulatie zo hoog als verwacht mag worden bij een populatiestudie.

Hoofdstuk 3 bespreekt de aanwezigheid en de ernst van dysfagie in de onderzochte populatie, hetgeen werd gedaan middels een observatie van een gewone maaltijd. Het instrument dat daarvoor werd gebruikt is de 'Dysphagia Disorders Survey'. Negenennegentig procent van de onderzochte kinderen had een vorm van dysfagie en 91% had problemen in de faryngeale fase of werd uitsluitend gevoed middels sondevoeding. Dysfagie was positief gerelateerd aan de ernst van de motorische beperking en aan een hoger gewicht naar lengte, hetgeen verklaard

kan worden door het gebruik van enterale voeding bij kinderen met ernstige dysfagie. Verder bleek dat ouders de ernst van de dysfagie bij hun kind doorgaans onderschatten. Wij bevelen dan ook een screening naar dysfagie middels een door getrainde professionals uitgevoerde gestructureerde maaltijdobservatie aan bij alle kinderen met ernstige meervoudige beperkingen. Indien nodig zal een kind daarna verwezen moeten worden voor verdere diagnostiek naar specifieke oorzaken van de dysfagie en voor het bepalen van het juiste behandelbeleid.

In **hoofdstuk 4** wordt de aanwezigheid van pathologische gastro-oesofageale reflux beschreven bij 25 kinderen uit de onderzoekspopulatie, wiens ouders toestemming gaven voor een 24 uurs pH meting. Omdat het aantal pH metingen klein was kon de prevalentie van gastro-oesofageale reflux niet worden berekend. Pathologische gastro-oesofageale reflux werd vastgesteld bij 14 van de 25 kinderen. Verassend genoeg was het gebruik van anti-reflux medicatie gelijk verdeeld over kinderen met pathologische gastro-oesofageale reflux en kinderen zonder. Verder bleek bij deze 25 kinderen de aanwezigheid van gastro-oesofageale reflux niet te correleren met symptomen.

Hoofdstuk 5 presenteert de evaluatie van de correlatie tussen dagelijkse energie inname en de voedingstoestand in de onderzochte populatie. De voedingstoestand werd gemeten met behulp van antropometrie en werd beschreven in termen van Z-scores. Bij 14% van de kinderen was de Z-score van de som der vier huidplooien lager dan -2, hetgeen doet vermoeden dat er een grote groep kinderen is met een slechte voedingstoestand. Lage antropometrische Z-scores werden voorspeld door een hogere leeftijd, vrouwelijk geslacht, mobiliteit en in mindere mate de afwezigheid van sondevoeding. Middels een voedingsdagboekje dat gedurende 7 dagen werd bijgehouden werd de voedings inname beschreven. De mediane dagelijkse energie inname was 62% van de aanbevolen hoeveelheid voor gezonde kinderen. Er werd geen correlatie gevonden tussen dagelijkse energie inname en antropometrische Z-scores. Dit doet vermoeden dat er binnen deze groep kinderen een grote variatie is in energie verbruik die losstaat van de variatie veroorzaakt door leeftijd en geslacht.

In **hoofdstuk 6** wordt het hoofdonderwerp van de studie behandeld, namelijk de incidentie en risicofactoren van lage luchtweginfecties. Gedurende een 18 maanden lange follow-up periode werd het aantal lage luchtweginfecties vastgelegd. Aan de ouders werd gevraagd om, steeds als hun kind ziek werd, een vragenlijst in te vullen. De vragenlijst was zo ontworpen dat lage luchtweginfecties en andere ziektes van elkaar onderscheiden konden worden. De definitie van een lage luchtweginfectie werd geformuleerd door een consensus groep van kinder-longspecialisten. De incidentie van lage luchtweginfecties in de onderzochte populatie was 348 per 1000 kinderen per jaar (95% CI: 281-426), hetgeen het tienvoudige is van de incidentie bij kinderen in de algemene bevolking (23-78 / 1000 kinderen per jaar). Elf procent van de kinderen had minstens twee keer per jaar een longinfectie, waarbij kinderen met dysfagie en scoliose een verhoogd risico hadden op recidiverende lage luchtweginfecties.

In **hoofdstuk 7** worden de belangrijkste resultaten van dit proefschrift over de incidentie en risicofactoren van lage luchtweginfecties en over dysfagie, gastro-oesofageale reflux,

voedingstoestand en energie inname samengevat en in een breder perspectief geplaatst. Daarnaast worden enkele aanpassingen in het studie design en de methoden die tijdens de implementatie van de studie zijn gemaakt verhelderd en verklaard. Ten laatste worden aanbevelingen gedaan voor de klinische praktijk en voor toekomstig onderzoek.

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Curriculum Vitae

Elsbeth Anne Céline Calis werd op 13 mei 1975 geboren te Heesch. In 1993 behaalde zij het gymnasiumdiploma aan het Titus Brandsma Lyceum te Oss. Aansluitend reisde zij voor één jaar af naar Frankrijk om te werken in gezinsvervangende tehuizen voor verstandelijk gehandicapten (Fondation Sonnenhof te Bischwiller en L'Arche te Compiègne). Na voor een tweede keer te zijn uitgeloot voor geneeskunde in Nederland besloot ze in 1994 de studie geneeskunde te volgen aan de Vrije Universiteit Brussel, België, alwaar zij in 1995 het eerste jaar Kandidaat-arts succesvol afrondde. Nadat zij in 1995 alsnog werd ingeloot voor de studie geneeskunde in Nederland, maakte zij de overstap naar de Universiteit van Amsterdam, waar zij naast geneeskunde twee vakken aan de faculteit Wijsbegeerte volgde en succesvol afrondde. Na haar afstudeeronderzoek naar malariabehandeling in Migori, Kenia, behaalde zij in 2002 haar artsexamen, waarna zij gedurende één jaar werkzaam was als artsassistent interne geneeskunde in Ziekenhuis Amstelveen.

In 2003 trad Elsbeth in dienst van de Leerstoel Geneeskunde voor Verstandelijk Gehandicapten, afdeling Huisartsgeneeskunde, van het ErasmusMC te Rotterdam. In samenwerking met de vakgroep Kinderchirurgie van het ErasmusMC-Sophia hield zij zich bezig met het opzetten en uitvoeren van een onderzoek naar de incidentie en risicofactoren van lage luchtweginfecties bij kinderen met ernstige meervoudige beperkingen, hetgeen resulteerde in meerdere wetenschappelijke publicaties en dit proefschrift. In 2007 behaalde zij haar Master of Science diploma in de Klinische Epidemiologie aan het Netherlands Institute for Health Sciences (NIHES) te Rotterdam. Sinds 2007 is zij werkzaam als psychiater-in-opleiding bij de Parnassia Bavo Groep te Den Haag. Zij verwacht in 2013 haar opleiding tot psychiater af te ronden.

Elsbeth is in 2004 getrouwd met Martijn Vastenburg en samen hebben ze 3 kinderen: Margot, Oscar en Jonathan.

PhD Portfolio

COURSES

Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences (NIHES), 2003-2007, certificate June 2007:

Erasmus Summer Programme

Principles of Research in Medicine	0.7 ECTS
Clinical Decision Analysis	0.7 ECTS
Methods of Public Health Research	0.7 ECTS
Topics in Evidence-based Medicine	0.7 ECTS
Methods of Health Services Research	0.7 ECTS
Prevention Research	0.7 ECTS

Core Curriculum

Study Design	4.3 ECTS
Classical Methods for Data-analysis	5.7 ECTS
Clinical Epidemiology	5.7 ECTS
Methodologic Topics in Epidemiologic Research	1.4 ECTS
Modern Statistical Methods	4.3 ECTS

Advanced Short Courses

Advanced Diagnostic Research	1.4 ECTS
Psychiatric Epidemiology	1.1 ECTS
Health Status Measurement	0.9 ECTS
Ethnicity, Health and Health Care	1.1 ECTS

Skills Courses

English Language	1.4 ECTS
Introduction to Medical Writing	1.1 ECTS
Working with SPSS for Windows	0.15 ECTS
A first glance at SPSS for Windows	0.15 ECTS

CONFERENCES / PRESENTATIONS

Annual conference of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) 2006, Boston (poster presentation)	16 hours

Annual conference of the International Association for the Scientific Study of Intellectual Disabilities (IASSID) 2006, Maastricht (oral and poster presentation)	36 hours
Seminar of the National Network Research Youth & Health 2005, Soesterberg (oral presentation)	8 hours
Paediatrics Seminar 2005, Rotterdam (oral presentation)	8 hours
Seminar of Intellectual Disability Physicians 2006, Utrecht (oral presentation)	8 hours
Dutch conference on Nutrition 2008, Ede (oral presentation)	8 hours
Departmental presentations 2004, 2005, 2006	12 hours

TEACHING ACTIVITIES

Guest lecturer Intellectual Disability Physicians training, 2005	8 hours
Supervising student research, 2005	80 hours