A Population-Based Study on Comorbidity in Children with Severe Motor and Intellectual Disabilities:

Focus on Feasibility and Prevalence

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Comorbidity in children with severe motor and intellectual disabilities is a heavy burden symbolized as a large rock. They try to express their problems in many different ways (ropes). The communication however, is difficult which cages them. Medicine tries to lift their burden using research and therapy. Research is the knot that tries to bind all the pieces together. This way we can hopefully improve their communication and take some load of their lives.

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A Population-Based Study on Comorbidity in Children with Severe Motor and Intellectual Disabilities:

Focus on Feasibility and Prevalence

Een populatiestudie naar co-morbiditeit bij kinderen met
ernstige motorische en verstandelijke beperkingen:

Focus op toepasbaarheid en prevalentie

Proefschrift

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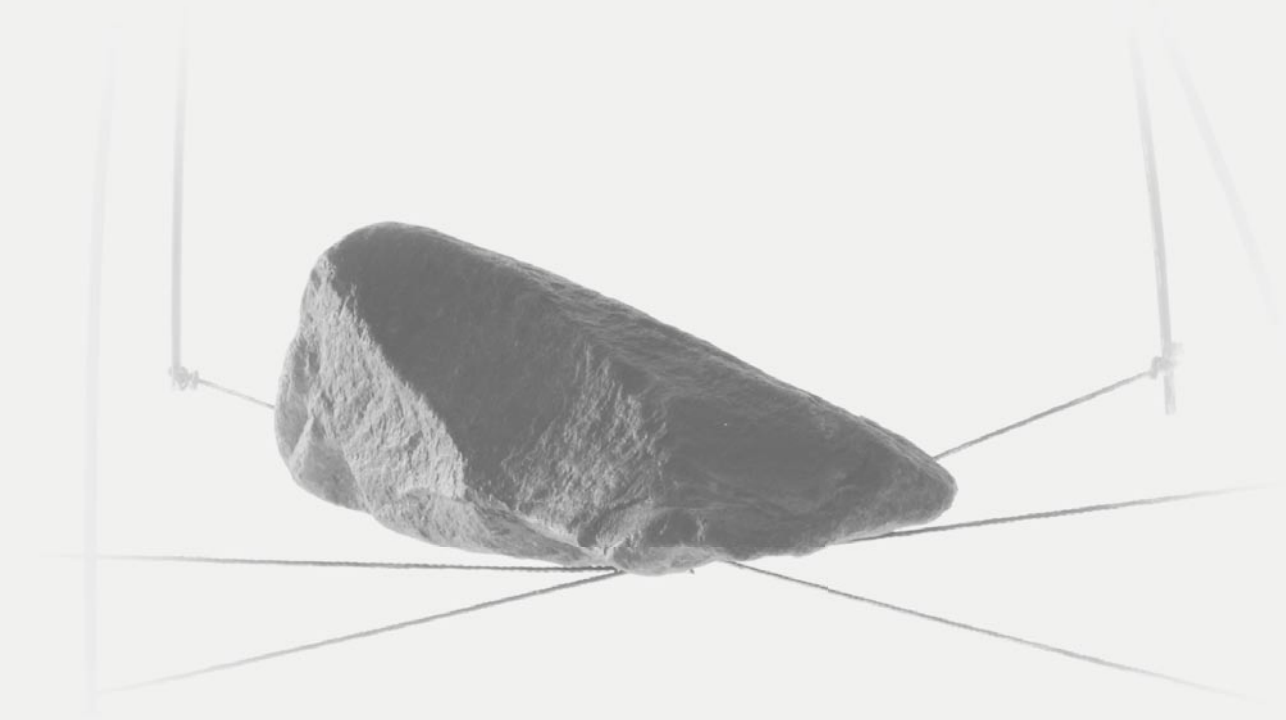
General Introduction



CHILDREN WITH SEVERE MOTOR AND INTELLECTUAL DISABILITIES

In literature and in health care, a wide variety of terms are used to describe children with a combination of Severe Motor and Intellectual Disabilities. The terminology applied by the IASSID (International Association for the Scientific Study of Intellectual Disabilities) for these children is **Profound Intellectual and Multiple Disabilities (PIMD)**. However, since multiple does not necessarily indicate motor and intellectual disabilities, we prefer the term **Severe Motor and Intellectual Disabilities (SMID)**.

In the publications of which this thesis is compiled, we have chosen to apply the term **Severe Generalized Cerebral Palsy** instead. This term does not cover all children with SMID (excluding children with progressive or acquired disabilities), but also includes children with only mild intellectual disabilities. However, we chose to use this term in our manuscripts because it is regularly applied internationally for this population, and therefore enhances recognition of our manuscripts in literature databases.

Cerebral palsy was first studied by the British orthopedist William John Little, who in 1861 held a historical oral presentation on the influence of premature birth and asphyxia neonatorum on the mental and physical condition of the child. He introduced the term cerebral palsy, which definition and characteristics have been revised and discussed often since then. To date, it is most commonly specified as "an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development" [1]. Intellectual disabilities are often associated with cerebral palsy, but intellect may vary between normal and profoundly disabled.

This thesis focuses on health-related problems of children with SMID. Most of them have a severe generalized form of cerebral palsy, resulting from abnormal brain development or brain damage in early development (pre- or peri-natally). Others have acquired brain damage during childhood (for instance due to near drowning accidents or as a result from severe meningitis) or otherwise due to progressive disease such as Rett's syndrome or metabolic disease such as Alpers' syndrome.

Although the etiology of this combination of severe motor and intellectual disabilities can be diverse, comorbidity and clinical characteristics are often similar. Therefore, the inclusion criteria we have used for the population-based cohort

presented in this thesis were based on clinical presentation and severity of the disabilities rather than etiology, and were defined as follows:

Children (2 to 18 years) with a combination of moderate to profound intellectual disabilities and a severe motor disability.

We defined moderate to profound intellectual disability as an IQ value below 55. If IQ was not recorded in the medical files, it was estimated:
IQ = (developmental age / calendar age) * 100.
We defined severe motor disability as hypertonic or hypotonic generalized cerebral palsy or a motor developmental delay to such an extent that a child could at best crawl.

EPIDEMIOLOGY

Since a central registry for people with intellectual disabilities is not available in the Netherlands, prevalence and incidence rates of combined severe motor and intellectual disabilities can only be estimated from scientific studies or national surveys.

The prevalence of cerebral palsy is estimated at approximately 1.5-2.8 per 1000 neonatal survivors in western countries [2-4]. For the Dutch population, the prevalence was estimated at 0.8 per 1000 live births in 1977-1979, and increased to 2.4 in 1986-1988 [3].

The observed increase of the prevalence of cerebral palsy from the mid 1960's till the late 1980's can mainly be ascribed to the increased survival of preterm infants [4-7]. Since the last decade however, the incidence rates are declining, especially due to the reduced prevalence of brain damage in preterm infants [4-6]. This positive trend however was not observed among infants less than 25 weeks estimated gestational age, despite intensive obstetric and neonatal input [8].

Approximately a quarter of the children with cerebral palsy have has moderate to profound intellectual disabilities [9,10]. Therewith the prevalence of children with SMID is estimated at 0.6 per 1000 live births. With an annual total number of approximately 194.000 live births in the Netherlands [11], this implies an incidence of SMID of approximately 117 children per year. According to an evaluation of quality of care for people with multiple disabilities in 2000, approximately 2100

children and adolescents with SMID lived In the Netherlands. Nowadays, most of them live with their parents and visit a day-care centre during weekdays [12].

ETIOLOGY

The etiology of severe generalized cerebral palsy (the majority of children with SMID) remains unclear. Similar to milder forms of cerebral palsy the developing brain is, by definition, injured prenatally, perinatally or postnatally [13,14]. Approximately 24% of children with moderate or severe spastic quadriplegia are thought to have been affected by intrapartum events [13]. The most important risk factor for cerebral palsy seems to be prematurity and low birth weight. Other risk factors include infections, teratogenic exposures, placental complications, multiple births, maternal diseases, intracranial hemorrhage, seizures, hypoglycemia, hyperbilirubinemia, birth asphyxia, ischemic stroke, trauma and coagulopathies. In a large number of cases however, the etiology of the disabilities remains unknown [14].

In contrast, when SMID is acquired during childhood, the etiology is usually known, including (severe) trauma, near-drowning accidents and meningitis. In addition, in SMID children with progressive brain damage, the causal syndrome is usually identified. Finally, etiology can be multi-factorial, including congenital and acquired disorders.

COMORBIDITY

Apart from their cognitive and motor impairments, children with SMID are at risk of developing several additional health problems. Frequently observed health problems are epilepsy, sensory impairment, recurrent pulmonary infections [15-22], poor nutritional state [23-29], growth retardation [30,31], dysphagia [32-37], gastro-oesophageal reflux [32,38-44], constipation [21,42,45], delayed gastric emptying [46], osteoporosis [47], scoliosis, hip displacement [48] and/or contractures. In addition, side-effects of multiple drug use occur often. In these children life expectancy is reduced [49-59], with respiratory disease as one of the leading causes of death. [49-51,56,58,60]

Some disorders are most likely primary results from brain damage, such as epilepsy, dysphagia, gastro-oesophageal reflux [27] and visual and hearing impairment.

These primary problems can be negatively influenced by secondary problems as well. For example the severity of dysphagia, primarily due to motor and sensory impairment, might increase due to epilepsy, medication side-effects, irritated mucosa and due to gastro-oesophageal reflux. Or more indirectly, dysphagia can be worsened due to an altered oesophageal pressure gradient caused by increased abdominal pressure due to constipation.

Due to the above-mentioned concomitant health problems, children with severe generalized cerebral palsy are especially prone to develop two major life-threatening disorders: malnutrition and/or recurrent pulmonary infections. Malnutrition can be the result of dysphagia, prolonged meal times, frequent vomiting (due to gastro-oesophageal reflux), decreased appetite (due to delayed gastric emptying), recurrent periods of illness and increased energy expenditure (due to epilepsy or spasms). In addition, children are prone to develop recurrent pulmonary infections due to aspiration [23,24,27,61,62] (as a result of dysphagia and gastro-oesophageal reflux [63]), poor airway clearance (due to primary slow cilial movement or resulting from previous pulmonary problems), poor or absent cough reflex [15,64] (idem), inefficient cough (due to motor impairment), poor ventilation (due to lack of deep breaths and due to thoracic deformities) but also immunological defence can be compromised due to malnutrition [65]. Although both malnutrition and recurrent lower respiratory tract infections are very commonly observed in these children, the influence of co-morbid disorders on these disorders have not been studied previously.

Due to the increased chance of developing several concomitant health problems, children with SMID are at risk of entering a downward spiral. Dysphagia for example interferes with the ability to ingest food and thus might put children at risk to develop malnutrition. Malnutrition might eventually lead to decreased alertness and fatigue during the meal, which will further deteriorate dysphagia and will increase the risk of choking and aspiration. Aspiration might induce pneumonia, which may result in hospital admissions and even early death. Interventions at the top of the spiral might prevent secondary or tertiary results: it was for example demonstrated that nutritional intervention in children with developmental disabilities significantly reduced the frequency of acute care hospitalization [32].

SCIENTIFIC RESEARCH IN CHILDREN WITH SMID

During the last decades, general care for people with intellectual disabilities (ID) is developing rapidly. In general, the integration of intellectually disabled people into the non-disabled society is promoted. In the Netherlands, it used to be common for people with intellectual disabilities to live in residential facilities. The process of decentralization increased the visibility of intellectually disabled people and their health needs to the non-disabled general population.

The need for better medical resources and for the increase of scientific evidence was for example expressed by the foundation of the Chair for Intellectual Disability Medicine at the Erasmus University in 2000, and the start of specialist education for medical doctors in 2001.

Nowadays, health care professionals are well aware of the serious health problems of children with SMID. However, scientific studies on prevention and treatment of these health problems, and therewith evidence-based guidelines, are still lacking. The need for these guidelines became painfully obvious at the start of the study described in this thesis. We were overwhelmed with questions from healthcare professionals and our hypothesis regarding the possible risk factors of recurrent lower respiratory infections triggered many of them to start diagnostics for the supposed risk factors in their own patients.

Although there is a need for evidence-based guidelines in ID-medicine, prevalence data are usually not available yet. Therefore, population-based studies are the first necessary step.

As a research chair, we take special interest in comorbidity in children and adolescents with SMID, because they suffer from many co-morbidities. We do not focus on adults, since the life expectancy of people with SMID is limited, and the onset of co-morbid disorders is often during childhood. When the major childhood disorders are properly studied, adequate preventive and treatment options can be developed and their use can be extrapolated to adults.

PREVALENCE AND RISK FACTOR STUDY ON RECURRENT PULMONARY INFECTIONS

The main focus of the study presented in this thesis, was studying the prevalence and risk factors of recurrent lower respiratory infections and malnutrition. The

initiation of this study resulted from lack of knowledge in medical practice for these children. A previous inventory in two separate day-care centres for SMID children (n=40) in 2000 had indicated high prevalence rates of epilepsy (80%), gastro-oesophageal reflux (48%), dysphagia (78%), visual impairment (68%), hearing impairment (18%), chronic constipation (68%) and recurrent lower respiratory tract infections (40%). Most of those children visited several medical specialists. Treatment of motor impairment was organized relatively well. Diagnosis and treatment of sensory impairment was less optimal, where diagnostics and treatment of gastro-oesophageal reflux were inadequate (unpublished data of Prof. Dr. H.M. Evenhuis 1999).

An inventory by the Dutch Society of Physicians for Persons with Intellectual Disabilities (NVAVG) among its members indicated that recurrent lower respiratory tract infections were more frequently observed in people with severe intellectual disabilities than in more mildly affected people. They expressed the need for information on the prevalence of comorbidity (such as gastro-oesophageal reflux) for diagnostic and treatment purposes and the need for information on risk factors and prevention options for chronic and recurrent lower respiratory tract infections. To our experience, many children's physicians experience the same issues.

Preceding the study presented in this thesis, a pilot study was performed in a residential facility. In the medical records, diagnosed lower respiratory tract infections were studied retrospectively in 37 children, resulting in an incidence of 43%. An additional conclusion of that study was that it is difficult to study this incidence in retrospect, due to lack of standardization and poor documentation of the diagnostic and treatment methods.

STRUCTURE OF THIS THESIS

This thesis is the first of two, both based on the results of a population-based nested case control study on recurrent lower respiratory infections and malnutrition in children with SMID. In **chapter 2** the design of this study is presented and accompanying ethical considerations are discussed. It also presents an overview of the included study population and its representativeness. In **chapter 3** we describe a pilot study on the feasibility of a nutritional assessment method, Bioelectric Impedance Analysis (BIA), in these children. In **chapter 4** we focus on the development and additive value of objective rejection criteria for interpretation of the results of the interruption technique, a pulmonary function test that measures respiratory resistance. Its feasibility in children with SMID is discussed in **chapter**

5. In this chapter the results are compared to those of a non-disabled population as well. This was the first published study on feasibility of a pulmonary function test in children with SMID. **Chapter 6** focuses on the definition, prevalence and risk factors of constipation. In **Chapter 7** the results of this thesis are discussed. In addition, we will focus on the future implications of the present study for medical scientific research in this population. This thesis ends with a summary in English and in Dutch (**chapter 8**).

REFERENCES

1. Mutch, L., et al., Cerebral palsy epidemiology: where are we now and where are we going? Dev Med Child Neurol, 1992. 34(6): p. 547-51.
2. Parkes, J., et al., Cerebral palsy in Northern Ireland: 1981-93. Paediatr Perinat Epidemiol, 2001. 15(3): p. 278-86.
3. Wichers, M.J., et al., Prevalence of cerebral palsy in The Netherlands (1977-1988). Eur J Epidemiol, 2001. 17(6): p. 527-32.
4. Keogh, J.M. and N. Badawi, The origins of cerebral palsy. Curr Opin Neurol, 2006. 19(2): p. 129-34.
5. Himmelmann, K., et al., The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. Acta Paediatr, 2005. 94(3): p. 287-94.
6. Doyle, L.W. and P.J. Anderson, Improved neurosensory outcome at 8 years of age of extremely low birthweight children born in Victoria over three distinct eras. Arch Dis Child Fetal Neonatal Ed, 2005. 90(6): p. F484-8.
7. Wilson-Costello, D., et al., Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics, 2005. 115(4): p. 997-1003.
8. Hintz, S.R., et al., Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993-1999. Pediatrics, 2005. 115(6): p. 1645-51.
9. Pharoah, P.O., et al., Epidemiology of cerebral palsy in England and Scotland, 1984-9. Arch Dis Child Fetal Neonatal Ed, 1998. 79(1): p. F21-5.
10. Hammal, D., S.N. Jarvis, and A.F. Colver, Participation of children with cerebral palsy is influenced by where they live. Dev Med Child Neurol, 2004. 46(5): p. 292-8.
11. Beets GCN (NIDI) and B.S. (RIVM), Wat is de huidige situatie? Bevolking\ Geboorte. Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid, 2005.
12. IGZ, Ernstig Meervoudig gehandicapt en dán? Een onderzoek naar de kwaliteit van zorg voor mensen met meervoudige complexe handicaps, Inspectie voor de Gezondheidszorg i.s.m. ministerie van VWS. 2000: Den Haag, The Netherlands.
13. MacLennan, A., A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. Bmj, 1999. 319(7216): p. 1054-9.
14. Sankar, C. and N. Mundkur, Cerebral palsy-definition, classification, etiology and early diagnosis. Indian J Pediatr, 2005. 72(10): p. 865-8.
15. Seddon, P.C. and Y. Khan, Respiratory problems in children with neurological impairment. Arch Dis Child, 2003. 88(1): p. 75-8.
16. Couriel, J., Respiratory complications of neurological disease in children. Current Medical Literature: Respiratory Medicine, 1997. 10: p. 70-5.
17. Morton, R.E., R. Wheatley, and J. Minford, Respiratory tract infections due to direct and reflux aspiration in children with severe neurodisability. Dev Med Child Neurol, 1999. 41(5): p. 329-34.
18. Liptak, G.S., et al., Health status of children with moderate to severe cerebral palsy. Dev Med Child Neurol, 2001. 43(6): p. 364-70.
19. Mahon, M. and M.S. Kibirige, Patterns of admissions for children with special needs to the paediatric assessment unit. Arch Dis Child, 2004. 89(2): p. 165-9.

20. Saito, N., et al., Natural history of scoliosis in spastic cerebral palsy. Lancet, 1998. 351(9117): p. 1687-92.

21. Sullivan, P.B., et al., Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. Dev Med Child Neurol, 2000. 42(10): p. 674-80.

22. Fischer-Brandies, H., C. Avalle, and G.J. Limbrock, Therapy of orofacial dysfunctions in cerebral palsy according to Castillo-Morales: first results of a new treatment concept. Eur J Orthod, 1987. 9(2): p. 139-43.

23. Bax, M., Eating is important. Dev Med Child Neurol, 1989. 31(3): p. 285-6.

24. Jones, P.M., Feeding disorders in children with multiple handicaps. Dev Med Child Neurol, 1989. 31(3): p. 404-6.

25. Gisel, E.G. and J. Patrick, Identification of children with cerebral palsy unable to maintain a normal nutritional state. Lancet, 1988. 1(8580): p. 283-6.

26. Patrick, J., et al., Rapid correction of wasting in children with cerebral palsy. Dev Med Child Neurol, 1986. 28(6): p. 734-9.

27. Couriel, J.M., et al., Assessment of feeding problems in neurodevelopmental handicap: a team approach. Arch Dis Child, 1993. 69(5): p. 609-13.

28. Dahl, M., et al., Feeding and nutritional characteristics in children with moderate or severe cerebral palsy. Acta Paediatr, 1996. 85(6): p. 697-701.

29. Gonzalez, L., C.M. Nazario, and M.J. Gonzalez, Nutrition-related problems of pediatric patients with neuromuscular disorders. P R Health Sci J, 2000. 19(1): p. 35-8.

30. Stevenson, R.D., et al., Clinical correlates of linear growth in children with cerebral palsy. Dev Med Child Neurol, 1994. 36(2): p. 135-42.

31. Stallings, V.A., et al., Nutrition-related growth failure of children with quadriplegic cerebral palsy. Dev Med Child Neurol, 1993. 35(2): p. 126-38.

32. Schwarz, S.M., et al., Diagnosis and treatment of feeding disorders in children with developmental disabilities. Pediatrics, 2001. 108(3): p. 671-6.

33. Reilly, S., D. Skuse, and X. Poblete, Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: a community survey. J Pediatr, 1996. 129(6): p. 877-82.

34. Del Giudice, E., et al., Gastrointestinal manifestations in children with cerebral palsy. Brain Dev, 1999. 21(5): p. 307-11.

35. Waterman, E.T., et al., Swallowing disorders in a population of children with cerebral palsy. Int J Pediatr Otorhinolaryngol, 1992. 24(1): p. 63-71.

36. Gangil, A., et al., Feeding problems in children with cerebral palsy. Indian Pediatr, 2001. 38(8): p. 839-46.

37. Mutch, L. and A. Leyland, Growth and nutrition in children with cerebral palsy. Lancet, 1990. 336(8714): p. 569-70.

38. Gangil, A., et al., Gastroesophageal reflux disease in children with cerebral palsy. Indian Pediatr, 2001. 38(7): p. 766-70.

39. Gustafsson, P.M. and L. Tibbling, Gastro-oesophageal reflux and oesophageal dysfunction in children and adolescents with brain damage. Acta Paediatr, 1994. 83(10): p. 1081-5.

40. Sondheimer, J.M. and B.A. Morris, Gastroesophageal reflux among severely retarded children. J Pediatr, 1979. 94(5): p. 710-4.

41. Reyes, A.L., et al., Gastrooesophageal reflux in children with cerebral palsy. Child Care Health Dev, 1993. 19(2): p. 109-18.

42. Staiano, A., et al., Disorders of oesophageal motility in children with psychomotor retardation and gastro-oesophageal reflux. Eur J Pediatr, 1991. 150(9): p. 638-41.

43. Wang, J.H., et al., Epidemiology of gastroesophageal reflux disease: a general population-based study in Xi'an of Northwest China. World J Gastroenterol, 2004. 10(11): p. 1647-51.

44. Booth, I.W., Silent gastro-oesophageal reflux: how much do we miss? Arch Dis Child, 1992. 67(11): p. 1325-7.

45. Frame, P.S., et al., Use of colchicine to treat severe constipation in developmentally disabled patients. J Am Board Fam Pract, 1998. 11(5): p. 341-6.

46. Spiroglou, K., et al., Gastric emptying in children with cerebral palsy and gastroesophageal reflux. Pediatr Neurol, 2004. 31(3): p. 177-82.

47. Henderson, R.C., et al., Predicting low bone density in children and young adults with quadriplegic cerebral palsy. Dev Med Child Neurol, 2004. 46(6): p. 416-9.

48. Soo, B., et al., Hip displacement in cerebral palsy. J Bone Joint Surg Am, 2006. 88(1): p. 121-9.

49. Katz, R.T., Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. NeuroRehabilitation, 2003. 18(3): p. 261-70.

50. Blair, E., et al., Life expectancy among people with cerebral palsy in Western Australia. Dev Med Child Neurol, 2001. 43(8): p. 508-15.

51. Reddihough, D.S., G. Baikie, and J.E. Walstab, Cerebral palsy in Victoria, Australia: mortality and causes of death. J Paediatr Child Health, 2001. 37(2): p. 183-6.

52. Shavelle, R.M., D.J. Straus, and S.M. Day, Comparison of survival in cerebral palsy between countries. Dev Med Child Neurol, 2001. 43(8): p. 574.

53. Strauss, D., W. Cable, and R. Shavelle, Causes of excess mortality in cerebral palsy. Dev Med Child Neurol, 1999. 41(9): p. 580-5.

54. Hutton, J.L., A.F. Colver, and P.C. Mackie, Effect of severity of disability on survival in north east England cerebral palsy cohort. Arch Dis Child, 2000. 83(6): p. 468-74.

55. Singer, R.B., D. Strauss, and R. Shavelle, Comparative mortality in cerebral palsy patients in California, 1980-1996. J Insur Med, 1998. 30(4): p. 240-6.

56. Plioplys, A.V., et al., Survival rates among children with severe neurologic disabilities. South Med J, 1998. 91(2): p. 161-72.

57. Strauss, D.J., R.M. Shavelle, and T.W. Anderson, Life expectancy of children with cerebral palsy. Pediatr Neurol, 1998. 18(2): p. 143-9.

58. Hollins, S., et al., Mortality in people with learning disability: risks, causes, and death certification findings in London. Dev Med Child Neurol, 1998. 40(1): p. 50-6.

59. Strauss, D. and R. Shavelle, Life expectancy of adults with cerebral palsy. Dev Med Child Neurol, 1998. 40(6): p. 369-75.

60. Williams, K. and E. Alberman, Survival in cerebral palsy: the role of severity and diagnostic labels. Dev Med Child Neurol, 1998. 40(6): p. 376-9.

61. Loughlin, G.M., Respiratory consequences of dysfunctional swallowing and aspiration. Dysphagia, 1989. 3(3): p. 126-30.

62. Rogers, B., M. Msall, and D. Shucard, Hypoxemia during oral feedings in adults with dysphagia and severe neurological disabilities. Dysphagia, 1993. 8(1): p. 43-8.

63. Berquist, W.E., et al., Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. Pediatrics, 1981. 68(1): p. 29-35.

64. Toder, D.S., Respiratory problems in the adolescent with developmental delay. Adolesc Med, 2000. 11(3): p. 617-31.

65. Martin, T.R., The relationship between malnutrition and lung infections. Clin Chest Med, 1987. 8(3): p. 359-72.

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

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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 jeopardized. 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 comorbidity 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], get hospitalized for this [18] with a major impact on their quality of life and life expectancy [14], 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].

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]

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 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 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.

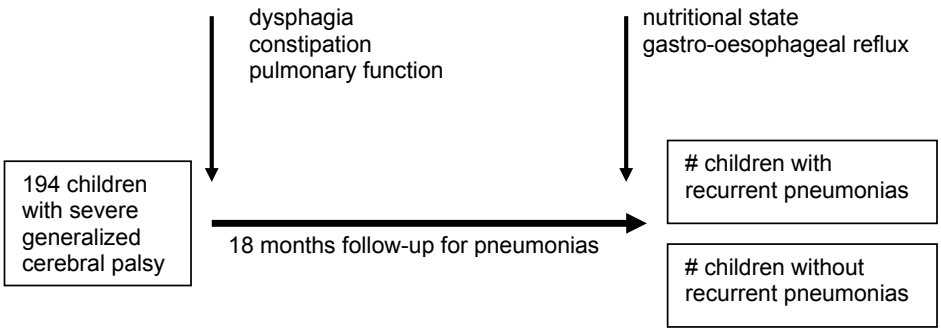

Figure 1 Study design
In this nested case-control study, a cohort of 194 children with severe generalized cerebral palsy is followed up for 18 months in order to record recurrent pneumonias (2 or more episodes per year). Possible risk factors are measured during the follow-up. Dysphagia, constipation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

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 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 dis-

ability. 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) score IV or V [30]. These broad criteria, resulting in a heterogeneous cohort with regard to etiology 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.

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 categorized as severe dysphagic if they received daily tube feeding, with or without additional oral food. Children with dietary restrictions (liquid, solid, ground, pureed) were categorized as having moderate dysphagia. All other children were categorized 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 reasons for not participating were 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

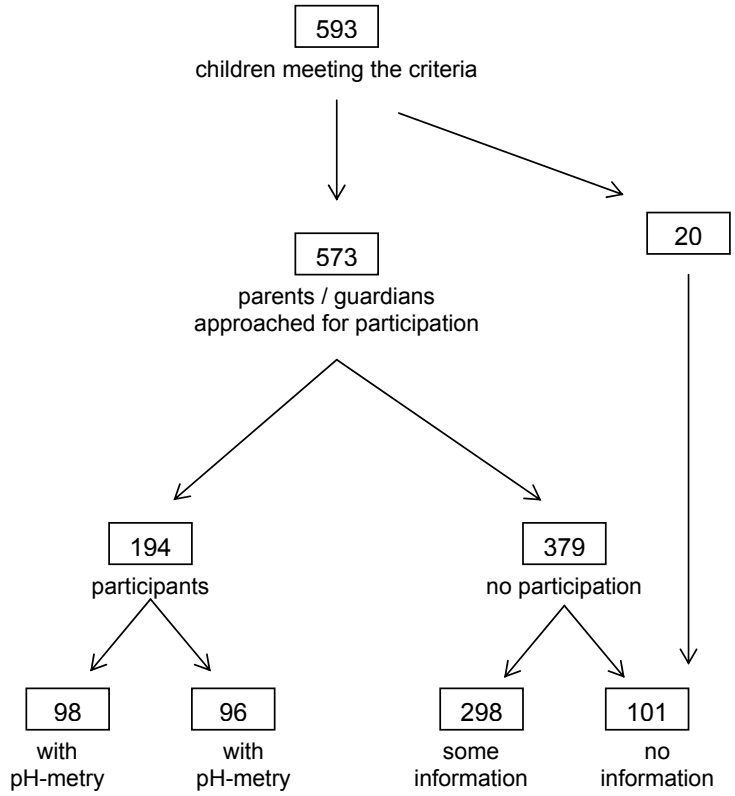

Figure 2 Flow chart of inclusion period
This figure depicts the inclusion of eligible children in the study from a predefined geographical area. 593 children met our inclusion criteria and parents or guardians of 573 children were informed. For several reasons, parents of 20 children were not informed. 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.

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.

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.

Table 2: Etiology 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	12.8
Missing		
	24	12.3
Total	194	children

Table 3: Characteristics of the participants

		%	valid*
GMFCS score 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

GMFCS = Gross Motor Function Classification Scale,
*valid = fraction of the population with known information

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 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.

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

		Non-participants	valid*	Participants	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/m^2)		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, *valid = fraction of the population with known information, ** recurrent = two or more episodes per year, BMI = body mass index.

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 Disorder 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 Analysis (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 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 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 need 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 etiology, 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 than 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 between 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 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 selective 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, 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.

REFERENCES

1. Katz, R.T., Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. NeuroRehabilitation, 2003. 18(3): p. 261-70.
2. Blair, E., et al., Life expectancy among people with cerebral palsy in Western Australia. Dev Med Child Neurol, 2001. 43(8): p. 508-15.
3. Reddihough, D.S., G. Baikie, and J.E. Walstab, Cerebral palsy in Victoria, Australia: mortality and causes of death. J Paediatr Child Health, 2001. 37(2): p. 183-6.
4. Shavelle, R.M., D.J. Straus, and S.M. Day, Comparison of survival in cerebral palsy between countries. Dev Med Child Neurol, 2001. 43(8): p. 574.
5. Strauss, D., W. Cable, and R. Shavelle, Causes of excess mortality in cerebral palsy. Dev Med Child Neurol, 1999. 41(9): p. 580-5.
6. Hutton, J.L., A.F. Colver, and P.C. Mackie, Effect of severity of disability on survival in north east England cerebral palsy cohort. Arch Dis Child, 2000. 83(6): p. 468-74.
7. Singer, R.B., D. Strauss, and R. Shavelle, Comparative mortality in cerebral palsy patients in California, 1980-1996. J Insur Med, 1998. 30(4): p. 240-6.
8. Plioplys, A.V., et al., Survival rates among children with severe neurologic disabilities. South Med J, 1998. 91(2): p. 161-72.
9. Strauss, D.J., R.M. Shavelle, and T.W. Anderson, Life expectancy of children with cerebral palsy. Pediatr Neurol, 1998. 18(2): p. 143-9.
10. Hollins, S., et al., Mortality in people with learning disability: risks, causes, and death certification findings in London. Dev Med Child Neurol, 1998. 40(1): p. 50-6.
11. Strauss, D. and R. Shavelle, Life expectancy of adults with cerebral palsy. Dev Med Child Neurol, 1998. 40(6): p. 369-75.
12. Williams, K. and E. Alberman, Survival in cerebral palsy: the role of severity and diagnostic labels. Dev Med Child Neurol, 1998. 40(6): p. 376-9.
13. Fischer-Brandies, H., C. Avalle, and G.J. Limbrock, Therapy of orofacial dysfunctions in cerebral palsy according to Castillo-Morales: first results of a new treatment concept. Eur J Orthod, 1987. 9(2): p. 139-43.
14. Seddon, P.C. and Y. Khan, Respiratory problems in children with neurological impairment. Arch Dis Child, 2003. 88(1): p. 75-8.
15. Couriel, J., Respiratory complications of neurological disease in children. Current Medical Literature: Respiratory Medicine, 1997. 10: p. 70-5.
16. Morton, R.E., R. Wheatley, and J. Minford, Respiratory tract infections due to direct and reflux aspiration in children with severe neurodisability. Dev Med Child Neurol, 1999. 41(5): p. 329-34.
17. Liptak, G.S., et al., Health status of children with moderate to severe cerebral palsy. Dev Med Child Neurol, 2001. 43(6): p. 364-70.
18. Mahon, M. and M.S. Kibirige, Patterns of admissions for children with special needs to the paediatric assessment unit. Arch Dis Child, 2004. 89(2): p. 165-9.
19. Saito, N., et al., Natural history of scoliosis in spastic cerebral palsy. Lancet, 1998. 351(9117): p. 1687-92.
20. Sullivan, P.B., et al., Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. Dev Med Child Neurol, 2000. 42(10): p. 674-80.

21. Couriel, J.M., et al., Assessment of feeding problems in neurodevelopmental handicap: a team approach. Arch Dis Child, 1993. 69(5): p. 609-13.

22. Fung, C.W., et al., Video-fluoroscopic study of swallowing in children with neurodevelopmental disorders. Pediatr Int, 2004. 46(1): p. 26-30.

23. Berquist, W.E., et al., Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. Pediatrics, 1981. 68(1): p. 29-35.

24. Gangil, A., et al., Gastroesophageal reflux disease in children with cerebral palsy. Indian Pediatr, 2001. 38(7): p. 766-70.

25. Booth, I.W., Silent gastro-oesophageal reflux: how much do we miss? Arch Dis Child, 1992. 67(11): p. 1325-7.

26. Gisel, E.G. and J. Patrick, Identification of children with cerebral palsy unable to maintain a normal nutritional state. Lancet, 1988. 1(8580): p. 283-6.

27. Loughlin, G.M., Respiratory consequences of dysfunctional swallowing and aspiration. Dysphagia, 1989. 3(3): p. 126-30.

28. Toder, D.S., Respiratory problems in the adolescent with developmental delay. Adolesc Med, 2000. 11(3): p. 617-31.

29. Martin, T.R., The relationship between malnutrition and lung infections. Clin Chest Med, 1987. 8(3): p. 359-72.

30. Palisano, R.J., et al., Validation of a model of gross motor function for children with cerebral palsy. Phys Ther, 2000. 80(10): p. 974-85.

31. IGZ, Ernstig Meervoudig gehandicapt en dán? Een onderzoek naar de kwaliteit van zorg voor mensen met meervoudige complexe handicaps, Inspectie voor de Gezondheidszorg i.s.m. ministerie van VWS. 2000: Den Haag, The Netherlands.

32. Bax, M.C., Terminology and Classification of Cerebral Palsy. Dev Med Child Neurol, 1964. 11: p. 295-7.

33. Huisman, S., Een pilotonderzoek naar luchtweginfecties bij mensen met mcg problematiek. TVAZ, tijdschrift van de vereniging van artsen in de zorg voor mensen met een verstandelijke handicap, 2001. nr. 4: p. 9-11.

34. Merkus, P.J., et al., Interrupter resistance in preschool children: measurement characteristics and reference values. Am J Respir Crit Care Med, 2001. 163(6): p. 1350-5.

35. Arets, H.G., H.J. Brackel, and C.K. van der Ent, Applicability of interrupter resistance measurements using the MicroRint in daily practice. Respir Med, 2003. 97(4): p. 366-74.

36. Beelen, R.M., et al., Short and long term variability of the interrupter technique under field and standardized conditions in 3-6 year old children. Thorax, 2003. 58(9): p. 761-4.

37. Bridge, P.D., S. Ranganathan, and S.A. McKenzie, Measurement of airway resistance using the interrupter technique in preschool children in the ambulatory setting. Eur Respir J, 1999. 13(4): p. 792-6.

38. Child, F., et al., How should airways resistance be measured in young children: mask or mouthpiece? Eur Respir J, 2001. 17(6): p. 1244-9.

39. Hadjikoumi, I., A. Hassan, and A.D. Milner, Effects of respiratory timing and cheek support on resistance measurements, before and after bronchodilation in asthmatic children using the interrupter technique. Pediatr Pulmonol, 2003. 36(6): p. 495-501.

40. Phagoo, S.B., N.M. Wilson, and M. Silverman, Evaluation of the interrupter technique for measuring change in airway resistance in 5-year-old asthmatic children. Pediatr Pulmonol, 1995. 20(6): p. 387-95.

41. Beydon, N., et al., Pre/postbronchodilator interrupter resistance values in healthy young children. Am J Respir Crit Care Med, 2002. 165(10): p. 1388-94.

42. Merkus, P.J., et al., Measurements of interrupter resistance: reference values for children 3-13 yrs of age. Eur Respir J, 2002. 20(4): p. 907-11.

43. Lombardi, E., et al., Reference values of interrupter respiratory resistance in healthy preschool white children. Thorax, 2001. 56(9): p. 691-5.

44. McKenzie, S.A., et al., Airway resistance measured by the interrupter technique: normative data for 2-10 year olds of three ethnicities. Arch Dis Child, 2002. 87(3): p. 248-51.

45. Sheppard, J.J. and R. Hochman, Dysphagic disorders in a large residential setting. 1988, Washington, D.C.: Paper presented at the 112th Annual Meeting of the American Association on Mental Retardation.

46. Benninga, M.A., W.P. Voskuijl, and J.A. Taminiau, Childhood constipation: is there new light in the tunnel? J Pediatr Gastroenterol Nutr, 2004. 39(5): p. 448-64.

47. Gerver, W.J. and R. de Bruin, Body composition in children based on anthropometric data. A presentation of normal values. Eur J Pediatr, 1996. 155(10): p. 870-6.

48. NIH Consensus statement. Bioelectrical impedance analysis in body composition measurement. National Institutes of Health Technology Assessment Conference Statement. December 12-14, 1994. Nutrition, 1996. 12(11-12): p. 749-62.

49. A standardized protocol for the methodology of esophageal pH monitoring and interpretation of the data for the diagnosis of gastroesophageal reflux. Working Group of the European Society of Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr, 1992. 14(4): p. 467-71.

50. Pehl, C., et al., pH probe positioning for 24-hour pH-metry by manometry or pH step-up. Eur J Gastroenterol Hepatol, 2004. 16(4): p. 375-82.

51. Klauser, A.G., N.E. Schindlbeck, and S.A. Muller-Lissner, Esophageal 24-h pH monitoring: is prior manometry necessary for correct positioning of the electrode? Am J Gastroenterol, 1990. 85(11): p. 1463-7.

52. Evenhuis, H., et al., Obstacles in large-scale epidemiological assessment of sensory impairments in a Dutch population with intellectual disabilities. J Intellect Disabil Res, 2004. 48(Pt 8): p. 708-18.

53. Loughlin, G.M. and M.A. Lefton-Greif, Dysfunctional swallowing and respiratory disease in children. Adv Pediatr, 1994. 41: p. 135-62.

54. Sheikh, S., et al., Chronic aspiration without gastroesophageal reflux as a cause of chronic respiratory symptoms in neurologically normal infants. Chest, 2001. 120(4): p. 1190-5.

55. Evans, P.M. and E. Alberman, Certified cause of death in children and young adults with cerebral palsy. Arch Dis Child, 1991. 66(3): p. 325-9.

56. Maudsley, G., J.L. Hutton, and P.O. Pharoah, Cause of death in cerebral palsy: a descriptive study. Arch Dis Child, 1999. 81(5): p. 390-4.

Chapter 3

Feasibility of Bioelectrical Impedance Analysis in Children with Severe Generalized Cerebral Palsy

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ABSTRACT

Objective The need is high for an accurate and easy to perform test to evaluate the nutritional state of children with a severe generalized cerebral palsy, defined as both a severe motor handicap and intellectual disability. For that purpose, we determined the feasibility of bioelectrical impedance analysis (BIA) in these children and evaluated their nutritional state.

Methods BIA recordings were done in 35 children with a severe generalized cerebral palsy using a single-frequency BIA device. In addition, arm span and body weight were determined. Components of feasibility were whether the children tolerated the recording, felt comfortable and whether the recording could be performed in a reproducible way (prescribed body position, stable Rz and Xc values). All recordings were performed at specialized children's daycare centres or schools.

Results One child (3%) did not tolerate the recording, while most (71%) of the 34 remaining children felt comfortable. The majority of the children (74%) could be placed in the prescribed position, but stability of Rz values was low. Stability of Rz values was positively influenced by older age, a quiet location for the recording, feeling comfortable and a low number of people in the room. For 29 children, we were able to calculate values for total body water and fat-free mass. Compared to age-matched reference values, these values were significantly reduced in all age groups.

Conclusions The present pilot study has demonstrated that the BIA recording is a feasible nutritional assessment method in children with severe generalized cerebral palsy. Since the test procedure was well tolerated by most children, its value for use in this specific population deserves further investigation.

INTRODUCTION

In children with a severe generalized cerebral palsy and intellectual disability (CP) comorbidity is high. The etiology of CP may differ considerably: underlying disorders are for example chromosomal defects, cerebral hemorrhage, infantile encephalopathy or metabolic disorders. In these children, feeding difficulties, such as gastro-oesophageal reflux (GER) and dysphagia, are frequently observed. The prevalence of gastro-ooesophageal reflux (GER), a disorder associated with vomiting and food refusal [1], varies from 61 to 96 percent [2-5], while dysphagia, a disorder of neurological origin that limits food intake, has been observed in 19 to 38 percent [6,7] of these children. Other disorders limiting food intake are hypersensitivity of the oropharynx [8] and poor appetite [9], which might be enhanced by chronic constipation [10,11]. These feeding difficulties, in combination with an altered energy metabolism, might lead to problems with the nutritional state. Indeed, the prevalence of malnutrition in these children is high: when comparing their results of nutritional assessment tests to reference values for school children or values obtained from a control group of non-handicapped children, approximately 40% of children with severe generalized CP are undernourished [12-15]. Since malnutrition has a profound negative effect on health and quality of life, early diagnosis of malnutrition in these children is desirable.

Several methods are available for evaluation of the nutritional state. However, sophisticated methods such as the deuterium dilution technique or dual energy x-ray absorptiometry (DEXA) are not applicable for routine evaluation of the nutritional state, since such methods are very expensive or only available in specialized hospitals. In addition, the value of methods that are commonly applied by pediatricians or outside the hospital, such as anthropometry, remains unclear and the results have to be interpreted with caution. Due to contractures and scoliosis for example, standing height can often not be measured in a reliable way and therefore the use of alternative measures, such as lower leg length, has been recommended for this population [16]. In addition, most children with CP suffer from growth retardation [17,18], thereby limiting the use of growth charts that include weight or height for age. Furthermore, the value of skin fold measurements might be limited in these children, due to a different distribution of subcutaneous fat [19,20]. As a result, professionals involved in the medical care for these children, such as intellectual disability physicians, pediatricians, pediatric surgeons and dietitians, are in need of an easy to perform and accurate technique to monitor the nutritional state and evaluate the effect of surgical procedures such as gastrostomy or antireflux surgery.

Compared to the deuterium dilution technique, bioelectrical impedance analysis (BIA) is a valid [21,22] method to determine the nutritional state in non-handicapped children. This inexpensive, quick and non-invasive method determines aspects of body composition, such as fat-free mass and total body water, by measuring its reactance and resistance [23]. In clinical practice, the determination of body composition is an accepted measure for theinvestigation of growth in children and adolescents irrespective of their standing height and is an alternative for the use of growth charts [24]. The BIA equipment is portable and can easily be connected to the body. Furthermore, BIA has a low intra- and interobserver variability [25]. The value of BIA in children with severe generalized CP has not been investigated in detail yet: a previous study suggested that BIA is a useful technique in this population [26], but the number of children in that study was limited (n=13) and feasibility data had not been recorded. During a BIA recording, patients should be in a supine position with their arms and legs abducted from the body. Since these children cannot be instructed, often have contractures of the limbs and some are very uncomfortable when lying on their back, a study of the technical feasibility of BIA in these children would be useful.

Thus, the main objective of the present pilot study was to investigate the feasibility of BIA in a representative subset of children with severe generalized CP and also, if possible, to evaluate their nutritional state.

MATERIALS AND METHODS

Subjects

This study is a part of a large-scale epidemiological study investigating the prevalence and risk factors of recurrent lower respiratory tract infections and malnutrition in 200 children with severe generalized CP. Inclusion criteria for that study were a moderate to profound intellectual disability (IQ < 55), a severe motor handicap (hyper- or hypotonic generalized cerebral palsy or a severe motor developmental delay), corresponding with the functional levels 4 or 5 on theGross Motor Functional Classification Scale (GMFCS) [27], and age between 2-18 years. There were no specific exclusion criteria. Verbal communication with these children is very limited due to their disabilities. In order to obtain a representative study population, children were not selected through hospitals. Instead, since 95% of these children visit a specialized children's daycare centre or school, we selected the cohort through 54 participating daycare centres and schools in the western and middle part of the Netherlands. Informed consent was obtained from the parents of each child. The first 35 children for whom informed consent was obtained, par-

ticipated in the present feasibility pilot. This sample was a representative subset of the cohort, since general characteristics such as mean age, gender, standing height and weight were similar between these children and the total cohort (data not shown). The Dutch Central Committee on Research Involving Human Subjects had approved the study protocol.

BIA

All BIA recordings [28] were performed once in each child at the daycare centres or schools. First, body temperature was recorded using an ear thermometer (IRT 3020, Braun GmbH, Kronberg, Germany) in order to exclude children with fever, since fever influences the impedance of the body [29]. Then, we determined body weight and a measure for standing height. Kyphosis and scoliosis are common in children with severe generalized CP [30] and therefore we decided to measure arm span instead of standing height. While sitting, the child's arms were gently stretched and positioned so that the arms had a 90º angle to the trunk. Then the distance between the tips of both middle fingers was determined using a flexible tape measure. Body weight was determined using a portable digital weight plateau (096200, Lopital Nederland B.V., Oisterwijk, The Netherlands), suitable for wheelchair placement.

While in the supine position, the child's shoes and socks and, if present, supportive calf or ankle braces were removed. According to the BIA manual, we aimed to keep the children in a resting supine position for 10 minutes before starting the recording. During that period, four electrodes (LecTec resting electrodes, LecTec corporation, Minnetonka, USA) were attached to the child's wrist and ankle on one side of the body and connected to a tetrapolar single-frequency BIA-device with a three-digit display (STA/BIA Soft Tissue Analyzer, Akern Bioresearch, Florence, Italy) and a maximum measurable value for Rz (resistance) of 999 Ω. The child was then gently put into the prescribed position, with its arms and legs stretched and 30º abducted from the trunk [31]. If necessary, the investigator fixed the limbs during the recording using a flannel blanket.

Components of feasibility were: 1) whether the children tolerated the recording and felt comfortable, 2) accuracy and effects of the child's body position during the recording, and 3) stability of the Rz and Xc values.

The number of people in the room during the measurement and the location (classroom or separate room) were logged. Since these children are unable to communicate verbally, the investigator carefully observed the children during the

recording for signs of emotional stress, such as protest behavior, fear or crying, to estimate whether they felt comfortable. A child was supposedly uncomfortable if it showed signs of emotional stress, such as protest behavior, fear or crying. In order to prevent interobserver variability of the subjective feasibility data, all children were observed by the same person. In addition, we recorded whether the children were in the correct position during the recording.

During the recording, the most stable values for Rz and Xc (reactance) were logged. Since a previous study had reported fluctuating Rz and Xc values in this population [26], we measured the duration of stability of Rz and Xc values and subdivided them into 3 categories: stable for over 5 sec, 2-5 sec or less than 2 sec. Since fluctuations of Rz and Xc influence the outcome of the recording, we considered this a relatively important aspect of feasibility.

Demographic factors and comorbidity (presence of spasticity and/or hypotonia, age and sex) were logged from the medical records, in order to determine their influence on feasibility.

Analysis and statistics

Arm span was converted to standing height according to the graph "arm span for standing height" for Dutch children [32]. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Total body water (TBW) and fat-free mass (FFM) were calculated according to the cross-validated equations of Horlick [33]:

$$TBW = 0.725 + 0.475\ H^2/\ Rz + 0.140\ W$$
$$FFM = (3.474 + 0.459\ H^2/\ Rz + 0.064\ W) / (0.769 - 0.009\ A - 0.016\ S)$$

Whereas H is standing height (cm), Rz is resistance (Ω), W is weight (kg), A is age (years) and S is sex (1 for males, 0 for females). Children were subdivided into age groups 4-8 (n=16), 9-12 (n=12), 13-15 (n=3) and 16-18 years (n=3), so that group means of TBW and FFM could be statistically compared to age-matched reference values obtained from non-handicapped American children [33] using Student's unpaired *t*-test.

In addition, we calculated percentage of body fat contributing to body weight according to the following formula:

$$\text{Body fat (\%)} = ((\text{weight} - FFM) / \text{weight}) * 100$$

Feasibility parameters were statistically compared between the children using Pearson's chi-square test or Student's unpaired *t*-test where appropriate. The influ-

ence of age on feasibility and the relationship between BMI and body fat percentage were determined using linear regression analysis. Results are expressed as mean ± SD (standard deviation). A p-value below 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the children are listed in Table 1.

Table 1: Clinical characteristics

General		Etiology		Motor handicap	
Total number	n = 35	Syndromes	10 (29%)	Hypertonia	11 (31%)
Mean age (years)	8.7 ± 4.0	Brain anomalies	4 (11%)	Hypertonia + hypotonia	8 (23%)
Gender	19 m, 16 f	Perinatal problems	12 (34%)		12 (34%)
Mean height (cm)	127 ± 20		5 (14%)	Hypotonia	4 (12%)
Mean weight (kg)	26 ± 10	Metabolic diseases	1 (3%)	Unknown	
Mean BMI (kg/m2)	16.2 ± 3.1	Meningitis	3 (9%		
		Unknown			

Data are represented as mean ± SD. BMI = body mass index. The percentage of children is between parentheses.

Feasibility

None of the children had a body temperature ≥ 38°C. Due to motor activity, 11 children (31%) were unable to maintain a supine resting position for at least 10 minutes preceding the BIA-recording. We aimed to keep these children as long as possible in the supine position before starting the BIA-recording. After the rest period, the children were gently put into the prescribed position. Due to protest behavior during positioning, the recording in one child was aborted. Nine of the 34 remaining children (26%) were in an incorrect position during the recording due to one or more contractures of the limbs. In these children, the limbs were gently stretched as far as possible.

We observed considerable fluctuation of the Rz and Xc values: in 16 / 34 (47%) children values were stable for less than 2 sec, in 8 / 34 (24%) they were stable from 2 – 5 sec and in 10 / 34 (29%) they were stable for over 5 sec. Rz showed significantly less fluctuation if the recording was performed in a separate room instead of in the classroom: in 73% of the recordings performed in the classroom,

Rz-values were stable for less than 2 sec, compared to 37% of the recordings performed in a separate room (p=0.017). In addition, Rz was significantly (p<0.05) longer stable in children of older age and during recordings with a lower number of people in the room (Table 2). However, no significant association was observed between duration of stability of Rz-values and body position during the recording and duration of the rest period (data not shown). We observed that 24 / 34 (71%) children felt comfortable during the recording, 6 children felt clearly uncomfortable and for 4 children it remained unclear. All children that felt uncomfortable had unstable Rz-values (less than 2 sec stable), and stability of Rz was significantly (p<0.05) higher in children feeling comfortable (Table 2). Feeling comfortable was not associated with the duration of the rest period, the location of the recording, the number of people in the room, the child's position or other parameters (data not shown).

Table 2: Parameters influencing stability of Rz-values

Duration of stability of Rz	< 2 sec	2 – 5 sec	> 5 sec
Mean age (years)	6.8 ± 2.7 (16)	9.5 ± 4.5 * (8)	10.4 ± 3.8 * (10)
Number of people in the room	5.3 ± 2.5 (16)	2.9 ± 1.0 * (8)	3.0 ± 2.0 * (10)
Number of children feeling uncomfortable	4 / 14 [29%]	0 / 6 [0%] *	0 / 8 [0%] *

Rz = resistance. The number of children per category is between parentheses, the percentage of children is between square brackets. * = p<0,05 vs. "< 2 sec".

BIA

The results of 5 of the 34 completed BIA recordings were not interpretable because Rz reached a stable value of 999 Ω. As this is the highest value that can be recorded with a three-digit BIA device, it is unknown whether the true Rz-value was 999 Ω or more. No association between an Rz-value of 999 Ω and body position during the recording, demographic factors or comorbidity was observed (data not shown).

Therefore, the data from 29 / 35 recordings (83%) could be used for the calculation of TBW and FFM. Mean values for TBW and FFM were 13.4 ± 0.8 l and 20.6 ± 1.1 kg respectively. Figure 1 and 2 display mean values by age group of TBW and FFM respectively. In all age groups, mean TBW and FFM were lower in children with severe generalized CP compared to the age-matched non-handicapped controls from literature [33]. These differences were statistically significant in children aged 4-8 and 9-12 years (both: p<0.000). Due to a low number of children in the older age groups, statistical comparisons were not possible.

The correlation between BMI and percentage body fat is displayed in figure 3. In four children, fat mass had a negative value. In figure 3, these children are indicated by a body fat percentage of 0%. A significant correlation (r=0.776, $p<0.05$) between BMI and fat percentage was observed.

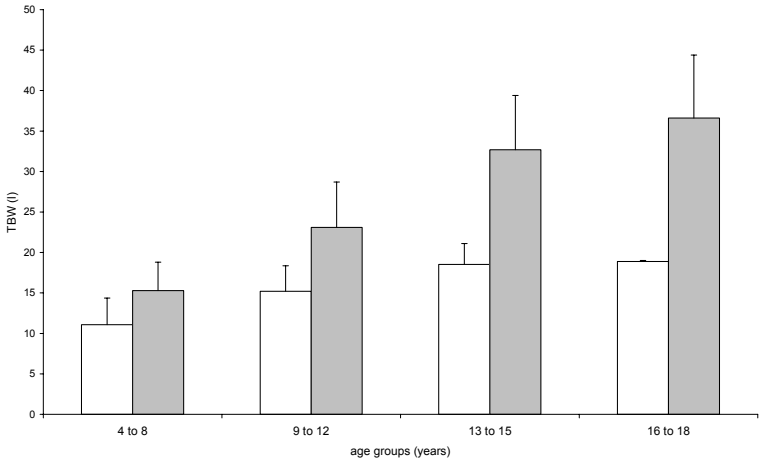

Figure 1. Total body water (TBW; mean ± SD) in different age groups of children with severe generalized cerebral palsy (white bars) and non-handicapped children (grey bars).

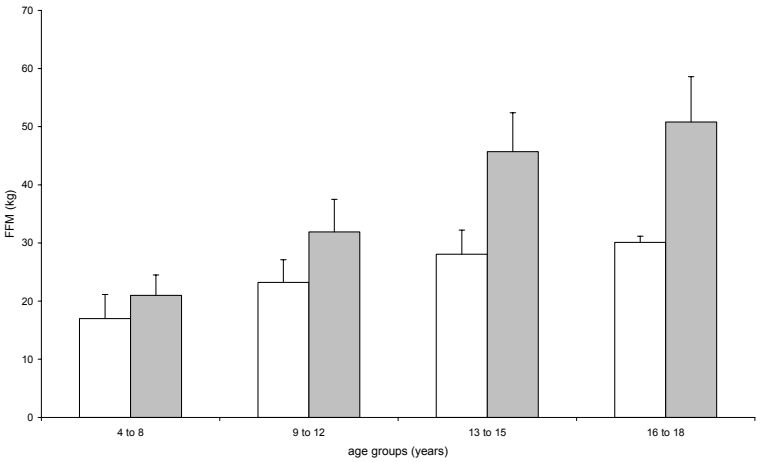

Figure 2. Fat-free mass (FFM; mean ± SD) in different age groups of children with severe generalized cerebral palsy (white bars) and non-handicapped children (grey bars).

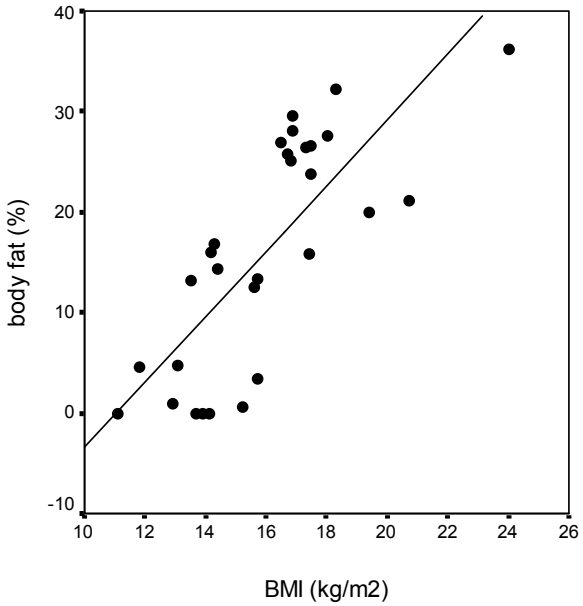

Figure 3. Significant correlation (r=0.776, p<0.05) between Body Mass Index (BMI) and calculated body fat percentage according to the BIA results in 29 children with severe generalized cerebral palsy.

DISCUSSION

Among specialists involved in health care for children with severe generalized CP, the need for an accurate, easy to perform method for monitoring the nutritional state is high. For that purpose, we have evaluated whether BIA might be a feasible method in these children. The present study has demonstrated that the feasibility of BIA in children with severe generalized CP is good. The majority of the children (34 / 35) completed the recording and most children (71%) felt comfortable during the recordings. However, we observed considerable fluctuation of Rz and Xc values. The most stable Rz values were obtained in children of older age, children that felt comfortable during the recording, during recordings in a quiet place and with a lower number of people in the room. Although 26% of the children was not in the prescribed body position during the recording, this did not influence the stability of the recorded values. We demonstrated that for all age groups, fat-free mass and total body water were significantly lower in these children as compared to non-handicapped controls. In addition, a significant correlation was observed between body fat percentage and body mass index.

Although we were able to calculate values for fat-free mass (FFM) and total body water (TBW) for 83% of the participating children, we have to take into account that several aspects of the present test conditions might have had a negative influence on the reliability of these values. For example, food intake prior to the recording might influence the recorded values of Rz and Xc [34,35]. However, for logistical purposes it was not possible in the present study to keep the children in the fasting state. For future studies it is therefore recommended to record the time of meal intake or, if possible, to perform the recordings under fasting conditions. In addition, a correct body position for BIA recordings was not obtained in 26% of the children due to contractures of the limbs. However, the influence of an incorrect position on the outcome of the recording seems to be less pronounced, since a previous study in these children has reported a good correlation between BIA and the deuterium dilution technique regardless the presence of fixed contractures [26]. In that study, the interpretation of BIA recordings in children with generalized CP was severely limited by the children's continuous motor activity and involuntary movements. As a result, fluctuation of Rz and Xc was prominent, resulting in a high coefficient of variation in these children [26]. This was confirmed by the findings of the present study, as only in 29% of all children Rz values were stable for over 5 sec. Rz values were most stable in children of older age and in children feeling comfortable. In order to increase stability of these values, performing the test in a quiet room with a low number of people in the room should be considered. Due to the lack of a validated prediction equation for this specific population, it is not yet possible to determine the clinical implications of fluctuating Rz and Xc values. However, it has been reported that the reproducibility of BIA recordings can be augmented by performing repeated measurements of Rz and Xc during a period of 10 minutes [36-38]. Therefore we advise to measure Rz and Xc for at least three times in order to reduce the negative influence of instable values in this population. In addition, we recommend the use of a 4-digit BIA device for this group, since in 12% of the recordings Rz reached a stable value of 999 Ω. Thus, with the present equipment it was unsure whether Rz had a real value of 999 Ω or higher. Increased resistance values have also been observed in patients with myotonic dystrophy [39], in dehydrated patients and in patients with a reduced lean body mass [40]. The clinical significance of the high resistance values in children with generalized CP has to be investigated in more detail. Finally, since we demonstrated that a supine period shorter than the 10 minutes recommended by the manual did not influence the outcome of the recordings, this rest period might be omitted in future studies since for some of these children an obliged supine period is uncomfortable. The additional value of the supine period preceding the recording has also been questioned by others [41].

Thus, BIA recordings in children with generalized CP should be performed in a quiet place with a low number of people in the room, while efforts should be made to make the child feel comfortable. In addition, it should be considered to perform the recording under fasting conditions if possible. Furthermore, we recommend repeated measurements of Rz and Xc and also the use of a 4-digit device.

We are well aware that a feasibility study is only the first step in the evaluation process of applicability of BIA in this handicapped population. In order to determine the nutritional status of children with generalized CP using BIA, several additional aspects, apart from test validity, have to be determined. It is well known that the growth pattern of children with generalized CP is often disturbed [42]: in combination with long-term immobility this might be the cause of a different body composition. A previous study reported an increased internal fat deposit and a different distribution of subcutaneous fat in these children [20]. In addition, resting energy expenditure seems to be reduced [26,43]. As a consequence, the available prediction equations [44] and reference values for non-handicapped children may not apply to this special group. This is illustrated by the finding of negative values of percentage body fat in 4 children. The present study has demonstrated reduced values for TBW and FFM in children with generalized CP compared to non-handicapped children, but there is no clinical implication to this finding yet, since these values might even be normal for these children. First, objective criteria for malnutrition in these children have to be established by performing a large-scale comparative study comparing several methods for nutritional assessment, including the deuterium dilution technique [45]. When comparing the outcome of the BIA recordings to those of the deuterium dilution technique, a specific, validated BIA prediction equation may be developed for these children. After that, test reproducibility should be evaluated with the help of precision studies to determine whether in this population, BIA can be used at the individual or at the group level. Since the BIA recording was well tolerated by the majority of the studied children, further research into its clinical value in this special group is justified.

REFERENCES

1. Field D, Garland M, Williams K. Correlates of specific childhood feeding problems. J Paediatr Child Health 2003;39:299-304.
2. Böhmer CJ, Niezen-de Boer MC, Klinkenberg-Knol EC, et al. The prevalence of gastroesophageal reflux disease in institutionalized intellectually disabled individuals. Am J Gastroenterol 1999;94:804-10.
3. Gustafsson PM, Tibbling L. Gastro-oesophageal reflux and oesophageal dysfunction in children and adolescents with brain damage. Acta Paediatr 1994;83:1081-5.
4. Reyes AL, Cash AJ, Green SH, Booth IW. Gastro-oesophageal reflux in children with cerebral palsy. Child Care Health Dev 1993;19:109-18.
5. Gangil A, Patwari AK, Bajaj P, Kashyap R, Anand VK. Gastroesophageal reflux disease in children with cerebral palsy. Indian Pediatr 2001;38:766-70.
6. Waterman ET, Koltai PJ, Downey JC, Cacace AT. Swallowing disorders in a population of children with cerebral palsy. Int J Pediatr Otorhinolaryngol 1992;24:63-71.
7. Reilly S, Skuse D, Poblete X. Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: a community survey. J Pediatr 1996;129:877-82.
8. Reid JA, King PL, Kilpatrick NM. Desensitization of the gag reflex in an adult with cerebral palsy: a case report. Spec Care Dentist 2000;20:56-60.
9. Thommessen M, Heiberg A, Kase BF, Larsen S, Riis G. Feeding problems, height and weight in different groups of disabled children. Acta Paediatr Scand 1991;80:527-33.
10. Böhmer CJM, Taminiau JA, Klinkenberg-Knol EC, Meuwissen SG. The prevalence of constipation in institutionalized people with intellectual disability. J Intellect Disabil Res 2001;45:212-8.
11. Sullivan PB. Gastrointestinal problems in the neurologically impaired child. Baillieres Clin Gastroenterol 1997;11:529-46.
12. Sanchez-Lastres J, Eiris-Punal J, Otero-Cepeda JL, Pavon-Belinchon P, Castro-Gago M. Nutritional status of mentally retarded children in north-west Spain. I. Anthropometric indicators. Acta Paediatr 2003;92:747-53.
13. Sanchez-Lastres J, Eiris-Punal J, Otero-Cepeda JL, Pavon-Belinchon P, Castro-Gago M. Nutritional status of mentally retarded children in northwest spain: II. Biochemical indicators. Acta Paediatr 2003;92:928-34.
14. Sullivan PB, Lambert B, Rose M, et al. Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. Dev Med Child Neurol 2000;42:674-80.
15. Dahl M, Thommessen M, Rasmussen M, Selberg T. Feeding and nutritional characteristics in children with moderate or severe cerebral palsy. Acta Paediatr 1996;85:697-701.
16. Spender QW, Cronk CE, Charney EB, Stallings VA. Assessment of linear growth of children with cerebral palsy: use of alternative measures to height or length. Dev Med Child Neurol 1989;31:206-14.
17. Samson-Fang L, Stevenson RD. Linear growth velocity in children with cerebral palsy. Dev Med Child Neurol 1998;40:689-92.
18. Stevenson RD, Hayes RP, Cater LV, Blackman JA. Clinical correlates of linear growth in children with cerebral palsy. Dev Med Child Neurol 1994;36:135-42.
19. Spender QW, Cronk CE, Stallings VA, Hediger ML. Fat distribution in children with cerebral palsy. Ann Hum Biol 1988;15:191-6.

20. Berg-Emons RJvd, Baak MAv, Westerterp KR. Are skinfold measurements suitable to compare body fat between children with spastic cerebral palsy and healthy controls? Dev Med Child Neurol 1998;40:335-9.

21. Leman CR, Adeyemo AA, Schoeller DA, Cooper RS, Luke A. Body composition of children in south-western Nigeria: validation of bio-electrical impedance analysis. Ann Trop Paediatr 2003;23:61-7.

22. Wabitsch M, Braun U, Heinze E, et al. Body composition in 5-18-y-old obese children and adolescents before and after weight reduction as assessed by deuterium dilution and bioelectrical impedance analysis. Am J Clin Nutr 1996;64:1-6.

23. Kyle UG, Piccoli A, Pichard C. Body composition measurements: interpretation finally made easy for clinical use. Curr Opin Clin Nutr Metab Care 2003;6:387-93.

24. Sakate T. Relationship between body composition of school children and their growth. Ann Physiol Anthropol 1984;3:142-3.

25. Gregory JW, Greene SA, Scrimgeour CM, Rennie MJ. Body water measurement in growth disorders: a comparison of bioelectrical impedance and skinfold thickness techniques with isotope dilution. Arch Dis Child 1991;66:220-2.

26. Azcue MP, Zello GA, Levy LD, Pencharz PB. Energy expenditure and body composition in children with spastic quadriplegic cerebral palsy. J Pediatr 1996;129:870-6.

27. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.

28. Bioelectrical impedance analysis in body composition measurement. NIH Technol Assess Statement 1994 Dec 12-14; 1-35. Nutrition 1996;12:749-62.

29. Di Iorio BR, Terracciano V, Bellizzi V. Bioelectrical impedance measurement: errors and artifacts. J Ren Nutr 1999;9:192-7.

30. Saito N, Ebara S, Ohotsuka K, Kumeta H, Takaoka K. Natural history of scoliosis in spastic cerebral palsy. Lancet 1998;351:1687-92.

31. Nakadomo F, Watanabe K, Nakajima T, Shinya H, Tanaka K. Factors affecting the measurement of bioelectrical impedance - with special reference to limb position. Bull Osaka Pref Coll of Nurs 1993;15:9-13.

32. Gerver WJM, de Bruin R. Paediatric Morphometrics. Utrecht: Wetenschappelijke uitgeverij Bunge, 1996.

33. Horlick M, Arpadi SM, Bethel J, et al. Bioelectrical impedance analysis models for prediction of total body water and fat-free mass in healthy and HIV-infected children and adolescents. Am J Clin Nutr 2002;76:991-9.

34. Gallagher M, Walker KZ, O'Dea K. The influence of a breakfast meal on the assessment of body composition using bioelectrical impedance. Eur J Clin Nutr 1998;52:94-7.

35. Gualdi-Russo E, Toselli S. Influence of various factors on the measurement of multifrequency bioimpedance. Homo 2002;53:1-16.

36. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 1985;41:810-7.

37. Deurenberg P, Weststrate JA, Paymans I, van der Kooy K. Factors affecting bioelectrical impedance measurements in humans. Eur J Clin Nutr 1988;42:1017-22.

38. Kushner RF, Schoeller DA. Estimation of total body water by bioelectrical impedance analysis. Am J Clin Nutr 1986;44:417-24.

39. Johansson A, Andrew R, Forsberg H, et al. Glucocorticoid metabolism and adrenocortical reactivity to ACTH in myotonic dystrophy. J Clin Endocrinol Metab 2001;86:4276-83.

40. Arkouche W, Fouque D, Pachiaudi C, et al. Total body water and body composition in chronic peritoneal dialysis patients. J Am Soc Nephrol 1997;8:1906-14.

41. Demura S, Yamaji S, Goshi F, Nagasawa Y. The influence of posture change on measurements of relative body fat in the bioimpedance analysis method. J Physiol Anthropol Appl Human Sci 2001;20:29-35.

42. Krick J, Murphy-Miller P, Zeger S, Wright E. Pattern of growth in children with cerebral palsy. J Am Diet Assoc 1996;96:680-5.

43. Stallings VA, Zemel BS, Davies JC, Cronk CE, Charney EB. Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. Am J Clin Nutr 1996;64:627-34.

44. Kyle UG, Bosaeus I, De Lorenzo AD, et al. Bioelectrical impedance analysis-part I: review of principles and methods. Clin Nutr 2004;23:1226-43.

45. Hills AP, Leyell L, Byrne NM. An evaluation of the methodology for the assessment of body composition in children and adolescents. Med Sport Sci 2001;44:1-13.

Chapter 4

Should we use Criteria or Eyeballing to reject Post-Interruption Tracings?

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ABSTRACT

Objective During the analysis of interrupter resistance (Rint)-measurements, most authors reject post-interruption tracings based on the shape of the pressure-time and flow-time curves. However, objective criteria for rejection are lacking. We aimed to formulate explicit rejection criteria that correspond to eyeballing the curve pattern (daily practice), in order to simplify the analysis. Inter-observer agreement within and between both methods was studied.

Methods Results obtained with the developed rejection criteria were compared to those of current practice (eyeballing) using 54 measurements (807 interruptions) of children with severe neurological impairment.

Results Inter-observer agreement on rejection was similar using the criteria or eyeballing (85.6% versus 82.8%). Using the criteria, more individual interruptions were rejected (43.4% versus 29.8% using eyeballing), while discarding total measurements (<5 remaining interruptions) was similar (9.2% versus 7.4% using eyeballing). Results using only the criteria for pressure-time curves were comparable to eyeballing. Outcome values were comparable between any of the used rejection methods and not rejecting at all.

Discussion In this first detailed study on rejection of post-interruption tracings, explicit rejection criteria were developed. None of the rejection methods influenced the outcome value relevantly. However, rejection criteria can contribute to the standardisation of the Rint technique and simplify decision-making in daily practice.

INTRODUCTION

Pulmonary function measurements with standard measurement techniques, such as spirometry, are usually not feasible in young children or in persons with intellectual or severe motor disabilities due to lack of cooperation [1,2]. The interruption technique however requires only tidal breathing and no active cooperation. It measures the resistance of the respiratory system (Rint) which is closely correlated to other parameters of pulmonary function [1,3-6]. Therefore it appears to be especially suitable for young or disabled children. Furthermore, reproducibility is good [5-7], and reference values (2-13 years) are available [8-11].

A Rint-measurement involves a rapid occlusion of the airflow during tidal breathing. During this occlusion the pressure at the airway opening (mouth) equilibrates with the alveolar pressure within a few milliseconds. Pressure directly after the interruption is estimated from a registered pressure-time-curve [12,13]. Rint (kPa/L/s) is calculated as the ratio between this pressure change (kPa), and the pre-interruption flow (L/s). To improve validity, the outcome value (mRint) is based on multiple Rint values.

A disadvantage of the method is the lack of standardization, leading to incomparable study results [14-20]. The ATS/ERS working group on Infant and Young children Pulmonary Function Testing, will soon publish a consensus guideline for standardized use of the interruption technique. However, this guideline will not include a policy for the rejection of irregular recordings [19]. Nowadays, many rejection methods are used, of which eyeballing* the pressure-time curve pattern for irregularities is most commonly reported. Although some examples have been published, a clear description of an 'irregular' curve is lacking. 'Normally' shaped curves are shown in Figure 1.

In the literature, reported rejection of tracings is based on both observation of the measuring conditions and the shape of the recorded curves. Measuring conditions leading to rejection are e.g. irregular breathing [20,21], including tachypnoea [5,8] and respiratory pause [11], moving [11], extreme neck flexion or extension [5,8,20] and tongue movement [20]. Even though this paper only discusses the relevance of post-test evaluation of curves, certainly the first part should not be omitted.

Reported reasons to reject pressure-time curves in the post-test evaluation are: inconsistent shape [9-11,15,16,21,22], described as signs of air leakage [4] , a horizontal or declining pressure signal [5,8], an obvious lack of rise inpressure or a rapid decline [17] or a reduction in initial high frequency oscillations [6]. Furthermore, rejection is

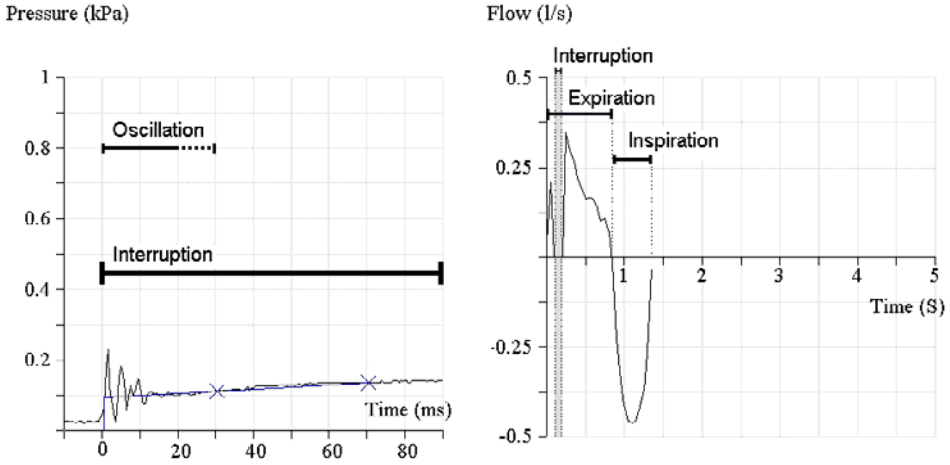


Figure 1 'Normally'-shaped interruption curves
Figure 1, In this normal pressure-time curve, there is a sudden very rapid change in pressure immediately on occlusion (t=0 msec) which reflects airway resistance. This is followed by a slower and somewhat smaller change that has been ascribed to both stress relaxation in the thorax and redistribution of gas (30). Damped pressure oscillations occur during the first phase due to the inertia and compressibility of the air in the airways that is suddenly put to a rest (26). The flow-time curve shows an interruption at an expiratory flow of 0.20 L/s, followed directly by expiration at a higher flow level than before the interruption.

based on: an altered ventilation pattern visible on the pressure curve [5,8], dampening of the pressure oscillations (swallowing) [4], an extreme increase of pressure (coughing) [4], a ragged appearance (vocalization) [4], suddendecreases or increases in pressure resulting from breathing efforts or incomplete relaxation[17] or any drift in the baseline [7]. In most cases, single tracings are rejected, but two authors continued a measurement until five undisturbed consecutive interruptions were registered [1,4]. Some authors base their decision for rejection on the value of the recorded pressure [7,11] or on the variation of either the remaining or all measured Rint values [11,22,23]. Although all these descriptions of when to reject a pressure-curve exist, they can sometimes be difficult to apply since clear cut-off points are lacking.

Some authors also reject tracings based on flow curves when the timing of an interruption is not shown [5,8], when flow rates were not between 0.3 – 0.7 L/s, not occurring during mid-inspiration or mid-expiration [3] or not within one standard deviation from the mean flow [11]. However, most authors do not reject measurements based on flow-criteria.

To our experience, it is difficult to evaluate measurements without the use of explicit criteria, especially in difficult-to-test groups in which measurements show a large variety of shapes. We therefore aimed to formulate explicit rejection criteria, but in such a way, that the results correspond to the current daily practice of eyeballing the curve pattern. Therewith, evaluation should become easier due to clear cut-off points between normal and abnormal, especially in slightly irregular curves which are difficult to evaluate.

Our research aims were: (1) To formulate explicit rejection criteria based on the existing eyeballing method (2) To compare inter-observer agreement between rejection using explicit criteria and the eyeballing technique (3) To assess the agreement rate between the formulated rejection criteria and eyeballing (4) To evaluate the effect of the rejection methods on the outcome value (median Rint (mRint)). We hypothesize that explicit rejection criteria improve inter-observer agreement without significantly affecting the mean outcome value, as compared to the commonly used eyeballing technique.

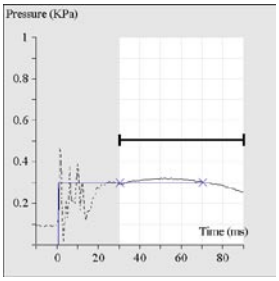
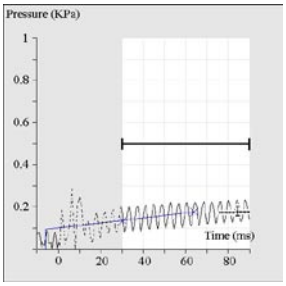
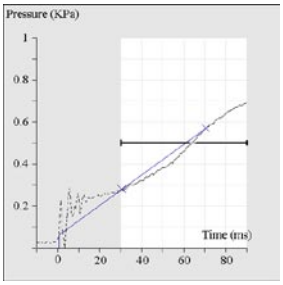
This study was performed children with severe generalized cerebral palsy. This population was considered favourable for the development and evaluation of rejection criteria because, to our experience, interrupter resistance curves of these children show a large variety of shapes. These shapes vary from 'normally' shaped to large irregularities corresponding to obvious measurement errors. However, since no reference data and reproducibility studies are available, results are presented on a group level only.

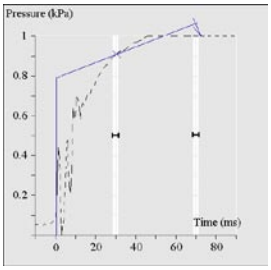
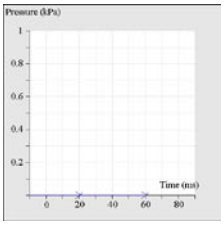
METHODS

Dataset

This study was part of a large-scale evaluation of pulmonary function in a population-based sample of children with severe generalized cerebral palsy [24], for which ethical approval was obtained from the Dutch ethical committee (Central Committee on Research Involving Human Subjects). Directly after the interrupter measurements, the investigators subjectively labelled the measurements based on the behaviour of the child during the measurement as "easy to perform", "acceptable" or "most likely failed". Of the first category, 27 measurements were randomly selected and form Set 1. Set 2 consists of 27 randomly selected measurements (405 interruptions) from the "acceptable" category. The measurement data of these 54

Table 1 Criteria for rejecting pressure-time curves

Decline criterion	After t = 30 msec, the pressure curve shows no continuing increase of pressure (exception: a horizontal end phase).
	Characteristic for a leakage of air. - reject when the slope is negative at any time interval after t=30 msec. (appendix 1: example 1 and 4) - reject when the curve is horizontal starting at t= 30 msec and onward (appendix 1: example 2) - Note: if the pressure curve only ends with a horizontal phase, do not reject. - also reject if the slope is only negative after t= 70 msec (example 3) - also reject if the slope is negative at or after t=30 due to prolonged oscillation.
Fluctuation criterion	After t = 30 msec, the curve shows a fluctuation ≥ 0.05 kPa around the regression line of the curve.
	Characteristic for vocalisation. The airway resistance is likely to be increased due to using of the vocal cords, and measurement errors are likely to occur. - reject when a fluctuation ≥ 0.05 kPa around the regression line of the curve - at any time point after t=30 msec - Note: the regression line should be used, not the line drawn for back-extrapolation
Hollow-criterion	After the period of oscillation, pressure shows a growing increase resulting in a hollow curve.
	A normal curve shows an gradually lowering increase in the second phase due to stress relaxation in the thorax and redistribution of gas - reject when the curve shows a increasing slope, - Note, this is easily seen since the pressure-line is then visible under the extrapolation line. - at any time interval after t=30 msec - also if this only occurs after t= 70 msec (appendix 1: example 2)

Maximum-criterion	Pressure values at t + 30 ms and/or t + 70 ms exceed the range of registration.
	The measurement points are needed for a correct back-extrapolation. - reject if the pressure at t=30 and/or at t=70 msec exceeds the maximum range of registration
Empty	No registration of pressure.
	If no pressure is registered the device will set the Rint value at 0,00 kPa/L/s. - reject when no pressure curve is registered

children were used to formulate rejection criteria for post-interruption pressure-time and flow-time curves and to estimate inter-observer agreement.

Measurement protocol

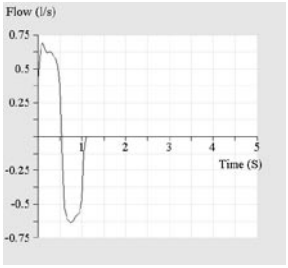
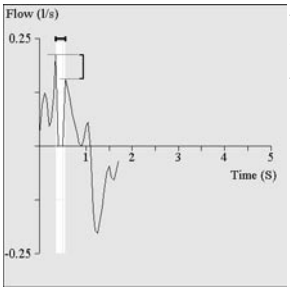
The interruption measurements were performed on-site (day care or specialized school), to prevent anxiety and distress. Similar to Arets et al. and Merkus et al. [5,8], Rint measurements were performed during the expiratory phase of tidal breathing using a commercially available, ambulatory device (MicroRint, v 1.113, Micromedical, UK). The trigger method was random with a continuous operating mode while cheek support was applied. The device automatically rejects individual interruptions if an apparent artifact on the pressure curve occurs (R_{int}=0,00, $P_{t=30} > P_{t=70}$, $P_{t=30}$ or $P_{t=70}$ > measuring range). Back-extrapolation to t = 15 ms after shutter closure (100 ms) is used to calculate Rint. Children were abstained from anti-asthmatic medication during 8 hours prior to the measurement.

A fitting non-compliant facemask (Intersurgical, Uden, The Netherlands) that covers the nose and mouth was used, because these children are unable to close their lips intentionally around a mouthpiece. We aimed to record 15 separate tracings per measurement with a trigger level of 0.20 L/s. Measurements were imported into the RIDA software (Micro Medical Ltd, RintBase 5, version 1.002 for Windows 2002). The median value of at least 5 interruptions was used as outcome value (mRint).

Development of rejection criteria

To formulate rejection criteria for the pressure-time curves, we used descriptions of the eye-balling method from the literature [3-11,15-17,21,22] and practical experience of pulmonary assistants and two paediatric pulmonologists experienced in Rint research (HA and PM). This resulted in a provisional set of objective criteria that were applied to our dataset. Differences in rejection using the criteria and eyeballing methods were studied and criteria were adjusted repeatedly, to correspond better with the eyeballing method. After discussion in the research team, a final set was agreed upon (Table 1 and Table 2).

Table 2 Criteria for rejecting flow-time curves

Visibility criterion	
	- reject If the interruption is not visible on the registration
Expiration level criterion	
	- reject when the flow directly preceding the interruption does not start at the same level of expiration or higher - Note: regardless of the shape of the cure outside this time interval

During the development process it became clear that a "logarithmic" shape of the pressure-time curve or so-called L-shape (Figure 2), which is uncommon in healthy children and adults, occurred frequently in our study group. These occurred together with normally shaped pressure curves in the same individuals. In total, 30% of the included interruptions were L-shaped, and in 85% of the 54 measurements at least one L-shaped curve was observed. Since the physiological basis of this shape is unclear, we decided to compare L-shaped to normally shaped curves by studying their correlation with oscillation, pre-interruption flow

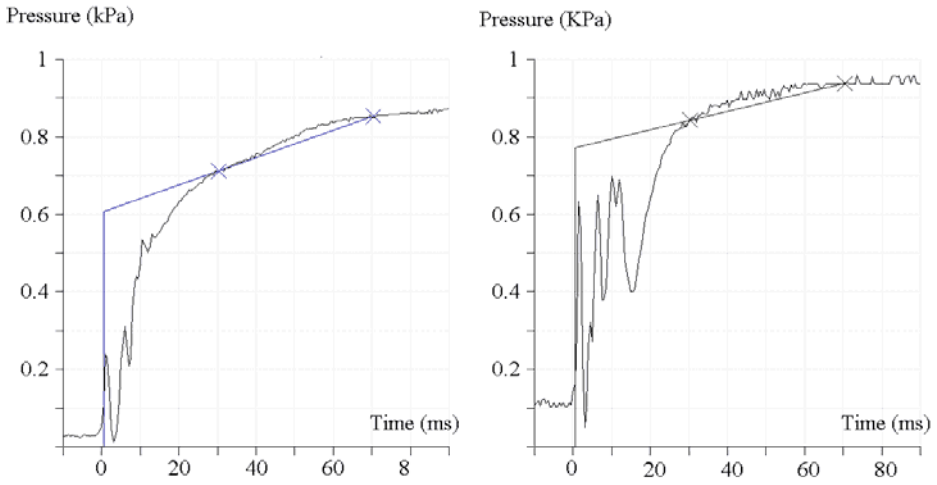


Figure 2 Example of a logarithmic-shaped pressure time curve (L-shape)
Figure 2. This figure shows examples of the logarithmic like pressure time curve (L-shape) that occurred frequently in children with severe generalized cerebral palsy but is uncommon in children without disabilities.

and Rint value in Set 1. Oscillation frequency was expressed as the number of peaks between t=0 and t=30 msec. Oscillation amplitude was expressed as the highest value (kPa) in the same time interval.

Agreement

Paper copies of the pressure-time and flow-time curves of the total set of 54 measurements were evaluated (rejection or not) by four independent pulmonology researchers using either the formulated rejection criteria (C1 (RV) and C2 (RR)), or eyeballing (E1 (JB) and E2 (MJ)). All observers were blinded for the evaluation of the other observers. Furthermore, E1 and E2 were unfamiliar with the developed rejection criteria. Evaluations of C1 and C2 based on pressure criteria only, were studied separately as T1 and T2. These rejection methods will be indicated as "*rejection criteria*" (based on pressure-time and flow-time curves), "*eyeballing*" and "*pressure criteria*" (based on pressure-time curves only).

Agreement between observers and between methods, was studied on two levels; firstly on agreement of rejection and secondly on the consequent mRint values. These were also compared to mRint without any rejection.

Sample size

Sample size was calculated for the within-method and the between-method agreement (*rejection criteria* versus *eyeballing*) using Epi6 software (Epi Info version 6.04d, 2001, CDC and WHO). Assuming a Cohen's kappa of 0.50 (0.45-0.55), we required a sample of 400 interrupter-tracings.

Data analysis

The relations between L-shape and oscillation, flow and Rint value were tested using the Mann-Whitney test since the normality assumption was not met. A p-value of <0.05 was considered significant. The inter-observer agreement within each method (*rejection criteria*, *eyeballing* and *pressure criteria* only) was calculated using percentile agreement and Cohen's Kappa (SPSS 11.0.1, SPSS Inc. Chicago, Illinois, USA). The between-method agreement was expressed as intraclass correlation coefficient (ICC) using a general linear model (SAS version 8.02, SAS institute inc, Cary, NC, USA) to allow two levels (observer and method). Within each method, the differences in mRint between observers were expressed as the median difference with 95% confidence intervals, using a 1000 replications bootstrap (Stata SE 8.2, StataCorp LP, Collage Station, USA). Only successful measurements (> 5 remaining interruptions) were used. Differences between the methods (*rejection criteria*, *eyeballing* and *pressure criteria*) were calculated similarly, using the results of one randomly selected observer per method if the differences between both observers within each method were negligible. Comparisons to a situation without rejection were analysed similarly. Differences were not expressed as Z-scores [25] to avoid comparison with reference values from non-disabled children.

RESULTS

Patient characteristics (age, gender, height and weight) from Set 1 and 2 were comparable (Table 3).

Rejection criteria

The developmental phase resulted in a final set of five rejection criteria for pressure-curves (Table 2) and two rejection criteria for flow-curves (Table 3). The appendices show examples of the application of these criteria during the study.

Table 3 Characteristics per dataset

	Total set	Subsets	
		Set 1	Set 2
number of measurements	54	27	27
mean age (years)			
mean (±sd)	9.1 (±4.4)	9.0 (±4.21)	9.2 (±4.6)
gender (%boys)	51.9	55.6	48.1
height (m)			
mean (±sd)	123.0 (±21.5)	123.9(± 21.8)	122.1 (±21.6)
weight (kg)			
mean (±sd)	25.2 (±9.5)	25.6 (± 9.25)	24.8 (±10.0)

Agreement on rejection

Inter-observer agreement within each evaluation method (*rejection criteria*, *eyeballing* and *pressure criteria*), and rejection rates are shown in Table 4. Observer E2 omitted 8 (1.9%) interruptions because she was unable to evaluate these based on her experience. In the analysis these interruptions were considered rejected. Table 5 shows the agreement of rejection between methods.

Disagreement on discarding total measurements (<5 accepted interruptions), was similar within all methods. Observers using *rejection criteria* disagreed on 5 measurements, observers using *eyeballing* on 4 and observers using only *pressure criteria* also on 4. Only one measurement was discarded in Set 1 (by observer C2). In Set 2, observer C1 discarded 9 measurements, while observers C2, E1, E2, T1 and T2 discarded 9, 4, 0, 5 and 3 measurements in this set respectively.

Median outcome value

The differences in mRint between observers using the same method of evaluation were all zero with narrow 95% confidence intervals (Table 6). The differences in mRint between methods, and compared to not rejecting interruptions at all, were also very small but larger in set 2 compared to set 1.

L-shaped pressure curves

L-shaped pressure curves (Figure 2) were significantly correlated with higher Rint-values ($p<0.000$), higher flow-values ($p=0.005$), higher oscillation amplitude ($p<0.000$) and higher oscillation frequency ($p<0.000$). We were able to mimic such

Table 4. Inter-observer agreement on rejection and rejection rates within the methods of evaluation

	Total		set 1		set 2	
	%agreement (kappa)	% rejection	%agreement (kappa)	% rejection	%agreement (kappa)	% rejection
criteria-method*	85.6 (0.73)	43.4	88.4 (0.65)	30.7	82.8 (0.71)	57.8
eyeballing	82.8 (0.58)	29.8	86.9 (0.54)	18.8	77.9 (0.59)	41.2
pressure criteria**	83.9 (0.57)	33.7	85.7 (0.64)	23.0	82.1 (0.64)	47.1

set 1 = 27 measurements performed "good"

set 2 = 27 measurements performed "acceptable"

total = set 1 and set 2

* evaluation based on criteria in Table 1 and Table 2

** evaluation based on criteria in Table 1

Table 5. Agreement of rejection between the methods evaluation

	Total ICC	set 1 ICC	set 2 ICC
rejection criteria versus eyeballing	0.45	0.43	0.39
pressure criteria versus eyeballing	0.46	0.41	0.42
rejection criteria versus pressure criteria	0.67	0.63	0.42

ICC = Intraclass Correlation Coefficient

pressure-curves by tightening our throat muscles during otherwise tidal breathing. No criterion to reject these curves was included in the final set of pressure criteria.

These curves were rejected based on other criteria in 9.8% (C1) and 2.5% (C2). Observers using eyeballing rejected these curves in 1.5% (E1) and 4.9% (E2).

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Inter-observer agreement within each evaluation method (*rejection criteria*, *eyeballing* and *pressure criteria*), and rejection rates are shown in Table 4. Observer E2 omitted 8 (1.9%) interruptions because she was unable to evaluate these based on her experience. In the analysis these interruptions were considered rejected. Table 5 shows the agreement of rejection between methods.

Table 6. Difference in outcome value mRint

	Total			**Set 1**			**Set 2**		
	Δ mRint	95% CI	N	Δ mRint	95% CI	N	Δ mRint	95% CI	N
between observers within each method									
within criteria method	**0**	(-0.009 –0.009)	*42*	**0**	(-0.006 –0.006)	*26*	**-0.010**	(-0.055 –0.035)	*16*
within eyeballing	**0**	(-0.010 –0.010)	*50*	**0**	(-0.004 –0.004)	*27*	**-0.020**	(-0.053 –0.013)	*23*
within pressure criteria	**0**	(-0.009 –0.009)	*48*	**0**	(-0.010 –0.010)	*27*	**0**	(-0.040 –0.040)	*21*
between methods									
rejection criteria versus eyeballing	**0.015**	(0.000 –0.030)	*44*	**0.015**	(0.000 –0.030)	*26*	**0.010**	(-0.059 –0.079)	*18*
eyeballing versus pressure criteria	**-0.010**	(-0.023 –0.003)	*49*	**-0.010**	(-0.020 –0.000)	*27*	**-0.020**	(-0.082 –0.042)	*22*
rejection criteria versus pressure criteria	**0**	(-0.006 –0.006)	*45*	**0**	(-0.006 –0.006)	*27*	**0**	(-0.036 –0.036)	*18*
compared to not rejecting at all									
rejection criteria versus non-rejection	**-0.020**	(-0.037 – 0.003)	*44*	**-0.020**	(-0.038 – -0.002)	*26*	**-0.030**	(-0.095 –0.035)	*18*
eyeballing versus non-rejection	**0**	(-0.005 – 0.005)	*50*	**0**	(-0.003 – 0.003)	*27*	**0**	(-0.042 –0.042)	*23*
non-rejection versus pressure criteria	**0**	(-0.014 – 0.015)	*49*	**0**	(-0.012 – 0.012)	*27*	**0**	(-0.058 –0.058)	*22*

Δ mRint = median difference in mRint (median Rint of the remaining interruptions) between the observers

N = number of measurements taken into account, evaluated successful by both researchers

Disagreement on discarding total measurements (<5 accepted interruptions), was similar within all methods. Observers using *rejection criteria* disagreed on 5 measurements, observers using *eyeballing* on 4 and observers using only *pressure criteria* also on 4. Only one measurement was discarded in Set 1 (by observer C2). In Set 2, observer C1 discarded 9 measurements, while observers C2, E1, E2, T1 and T2 discarded 9, 4, 0, 5 and 3 measurements in this set respectively.

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L-shaped pressure curves

L-shaped pressure curves (Figure 2) were significantly correlated with higher Rint-values ($p<0.000$), higher flow-values ($p=0.005$), higher oscillation amplitude ($p<0.000$) and higher oscillation frequency ($p<0.000$). We were able to mimic such pressure-curves by tightening our throat muscles during otherwise tidal breathing. No criterion to reject these curves was included in the final set of pressure criteria.

These curves were rejected based on other criteria in 9.8% (C1) and 2.5% (C2). Observers using eyeballing rejected these curves in 1.5% (E1) and 4.9% (E2).

DISCUSSION

This is the first detailed report on rejection of interrupter resistance measurements based on post-interruption curve patterns. We developed a valid set of rejection criteria based on the current standard of eyeballing the curve-pattern. In contrast to our hypothesis, application of these explicit *rejection criteria* versus *eyeballing* did not improve inter-observer agreement. Similar outcomes were found, although the rejection percentage of tracings was higher using these *rejection criteria*. When only the *pressure criteria* were applied, the rejection percentage and the inter-observer agreement were comparable to the *eyeballing* method. As was hypothesised, similar Rint values were obtained using either one of the methods. All methods had the same inter-observer agreement on discarding unsuccessful measurements. A remarkable finding was that rejecting curves using either one of the rejection methods, had no real effect on the value of mRint. Although this implies that one could do without rejecting any interruptions (as long as at least 5 interruptions per measurement are obtained), this is not the case. Measurements consisting of mostly incorrect interruptions should be rejected based on common sense. Although this study was performed in a disabled population, results should be applicable to a non-disabled population, since the outcome is likely to be more favourable in such a population. However, this study does not provide data to confirm this.

For this study, measurements of children with severe generalized cerebral palsy were used, which show more irregularities than those of non-disabled children. Possible explanations include limb or tongue movement or non-optimal posture as well as intrinsic factors such as involuntary changes in muscle tone, or shifting of mucus. In these children, this is more likely to occur to a measurable extent. However, until the corresponding effects on shape and mRint can be explained

in more detail, consensus should be reached on which shapes are considered acceptable and which are not.

The formulated pressure-criteria

In the developed criteria, cut-off points were chosen for both physiological and practical reasons. In the *'decline-criterion'* the difference between a horizontal line due to leakage and a normal horizontal end phase needed to be defined. We chose "from t=30 ms and onward" because it was easy to judge since this point was marked for back-extrapolation. For the *'fluctuation-criterion'* we defined a maximal fluctuation based on current practice in our clinic, without further physiological arguments. For the *'hollow-criterion'* we chose "hollow to any extent" for practical reasons. Other options e.g. *'curve degree within a certain time frame'* would be harder to work with and lacks physiological arguments as well.

Clear criteria should also define the time interval for each criterion. For these three criteria *'any time interval after t=30 ms'* was set, except for a horizontal end phase. This is based on the assumption that any irregularity after the last point for back-extrapolation (t=70 ms) could have started earlier and therewith could have affected the course of the pressure curve.

The formulated flow criteria

Rejection rates were more comparable between *eyeballing* and the *pressure criteria,* than between *eyeballing* and the total set of *rejection criteria*. This can be explained by the fact that rejection of measurements based on flow-criteria only plays a minor role in the literature and therefore in daily practice (eyeballing). The *'expiration-level-criterion'* is based on the assumption that during interruption, pressure on the shutter increases because the air supply continues undiminishedly. After opening, the airflow should be at least as fast or faster than before the interruption. This can also be seen in the flow-tracings of Mead [13]. Reduced airflow after interruption may be explained by leakage. In our dataset 46.0% of the interruptions rejected by the 'expiration level criterion' are also rejected on the 'decline criterion'. Of the total set of interruptions, 20.5% were rejected by the "decline criterion", which confirms this assumption.

L-shape

The pressure change after interruption depends on compliance, resistance and inertia of the thoraco-pulmonary system [26], but evidence to explain the L-shape is lacking. L-shape was significantly correlated with higher values of Rint, flow,

oscillation amplitude and frequency. The correlation with high Rint values does not explain the fast equilibration into a plateau-phase, since in asthmatic patients with severe obstruction a plateau is often not established [27]. Higher oscillation amplitude might be explained by the increase in kinetic energy with higher flow values. However, in Frey's mechanical model, oscillatory pattern is not influenced by flow or compliance [26]. Increased oscillation frequency can occur due to decreased thoracic gas volume [26], or low upper airway compliance [28]. The closest resemblance of the L-shape we found in the literature, is the curve of infants measured in supine position with interruption duration of 500 ms published by Hall [17]. We hypothesize that an L-shape in our population might result from a temporary increased resistance in the upper airway (mouth to pharynx), due to e.g. abnormal muscle tone or increased sputum retention. In our opinion, L-shaped pressure curves should not be rejected because these are presumably not due to measurement error but caused by a true varying resistance of the respiratory system. If this is true, the contribution of the peripheral airways to mRint is smaller in measurements with several L-shaped curves, and will consequently be less sensitive to peripheral airway problems.

Agreement statistics

In this study a face-mask was used in stead of a mouthpiece. However, scientific data on how this affects the pressure-time and flow-time curves is lacking. Although the use of a face-mask has not influenced inter-observer agreement, an effect on the difference in median outcome value can not be ruled out. However, the small effect on the total Rint of rejecting tracings in general leads us to believe that this overall effect might be small.

We base our statement on inter-observer agreement (acceptable within all evaluated methods) on the percentile agreement rather than on Cohen's kappa value. Cohen's kappa statistic adjusts the agreement based on the proportion of rejections, to adjust for agreement based on chance alone [29]. This was less suitable, since rejection rates were different when evaluating the same measurements.

The ICC also is less suitable to compare the rejection methods, since it is based on the individual interruption values and therefore the within-measurement variability is incorporated in this outcome value. As a result, ICC values were relatively low.

Effect of rejection on mRint

We found a striking lack of effect on mRint of all rejection methods, as compared to not rejecting at all. The median difference between results using the formulated *rejection criteria* and *eyeballing* was 0.015 (0.000, 0.030) kPa/L/s. This implies

a 95% certainty that the real difference in mRint between these methods, is at most 0.030 kPa/L/s. Considering the large within-measurement variation of this technique, this difference is negligible.

In conclusion

We have developed an accurate set of rejection criteria that can support decision-making in the evaluation process of the post-interruption tracings. Although it only slightly improves inter-observer agreement and the effects of rejection on mRint are minimal in general, this set provides support for the evaluation of measurements that are difficult to judge and for investigators with little experience. This set of criteria can be applied in any Rint measurement regardless of the population under study.

To compare feasibility in a certain population with published studies, one should realize that the rejection rate using these criteria is higher. One could consider using only the pressure criteria since this corresponds nicely to the current eyeballing standards, although the flow criteria are based on physiological considerations.

In general, authors should make rejections in a reproducible way and should always describe the used method in detail. These criteria provide a clear method to establish this.

REFERENCES

1. Bisgaard, H. and B. Klug, Lung function measurement in awake young children. Eur Respir J, 1995. 8(12): p. 2067-75.
2. Crenesse, D., et al., Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuvers. Pediatr Pulmonol, 2001. 32(1): p. 56-61.
3. Carter, E.R., et al., Evaluation of the interrupter technique for the use of assessing airway obstruction in children. Pediatr Pulmonol, 1994. 17(4): p. 211-7.
4. Klug, B. and H. Bisgaard, Measurement of lung function in awake 2-4-year-old asthmatic children during methacholine challenge and acute asthma: a comparison of the impulse oscillation technique, the interrupter technique, and transcutaneous measurement of oxygen versus whole-body plethysmography. Pediatr Pulmonol, 1996. 21(5): p. 290-300.
5. Arets, H.G., H.J. Brackel, and C.K. van der Ent, Applicability of interrupter resistance measurements using the MicroRint in daily practice. Respir Med, 2003. 97(4): p. 366-74.
6. Chowienczyk, P.J., et al., A flow interruption device for measurement of airway resistance. Eur Respir J, 1991. 4(5): p. 623-8.
7. Phagoo, S.B., N.M. Wilson, and M. Silverman, Evaluation of a new interrupter device for measuring bronchial responsiveness and the response to bronchodilator in 3 year old children. Eur Respir J, 1996. 9(7): p. 1374-80.
8. Merkus, P.J., et al., Measurements of interrupter resistance: reference values for children 3-13 yrs of age. Eur Respir J, 2002. 20(4): p. 907-11.
9. Lombardi, E., et al., Reference values of interrupter respiratory resistance in healthy preschool white children. Thorax, 2001. 56(9): p. 691-5.
10. McKenzie, S.A., et al., Airway resistance measured by the interrupter technique: normative data for 2-10 year olds of three ethnicities. Arch Dis Child, 2002. 87(3): p. 248-51.
11. Beydon, N., et al., Pre/postbronchodilator interrupter resistance values in healthy young children. Am J Respir Crit Care Med, 2002. 165(10): p. 1388-94.
12. Jackson, A.C., H.T. Milhorn, Jr., and J.R. Norman, A reevaluation of the interrupter technique for airway resistance measurement. J Appl Physiol, 1974. 36(2): p. 264-8.
13. Mead, J. and J.L. Whittenberger, Evaluation of airway interruption technique as a method for measuring pulmonary airflow resistance. J Appl Physiol, 1954. 6(7): p. 408-16.
14. Hadjikoumi, I., A. Hassan, and A.D. Milner, Effects of respiratory timing and cheek support on resistance measurements, before and after bronchodilation in asthmatic children using the interrupter technique. Pediatr Pulmonol, 2003. 36(6): p. 495-501.
15. Pao, C.S., M.J. Healy, and S.A. McKenzie, Airway resistance by the interrupter technique: which algorithm for measuring pressure? Pediatr Pulmonol, 2004. 37(1): p. 31-6.
16. Child, F., et al., How should airways resistance be measured in young children: mask or mouthpiece? Eur Respir J, 2001. 17(6): p. 1244-9.
17. Hall, G.L., et al., Evaluation of the interrupter technique in healthy, unsedated infants. Eur Respir J, 2001. 18(6): p. 982-8.
18. Bridge, P.D. and S.A. McKenzie, Airway resistance measured by the interrupter technique: expiration or inspiration, mean or median? Eur Respir J, 2001. 17(3): p. 495-8.
19. Carter, E.R., It is time to consider standardizing the interrupter technique. Eur Respir J, 1997. 10(6): p. 1428-9.

20. Sly, P.D. and E. Lombardi, Measurement of lung function in preschool children using the interrupter technique. Thorax, 2003. 58(9): p. 742-4.

21. Bridge, P.D., S. Ranganathan, and S.A. McKenzie, Measurement of airway resistance using the interrupter technique in preschool children in the ambulatory setting. Eur Respir J, 1999. 13(4): p. 792-6.

22. Klug, B., K.G. Nielsen, and H. Bisgaard, Observer variability of lung function measurements in 2-6-yr-old children. Eur Respir J, 2000. 16(3): p. 472-5.

23. Chan, E.Y., et al., Repeatability of airway resistance measurements made using the interrupter technique. Thorax, 2003. 58(4): p. 344-7.

24. Veugelers, R., et al., 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): p. 25.

25. Gappa, M., S.C. Ranganathan, and J. Stocks, Lung function testing in infants with cystic fibrosis: lessons from the past and future directions. Pediatr Pulmonol, 2001. 32(3): p. 228-45.

26. Frey, U., A. Schibler, and R. Kraemer, The interrupter technique--a renaissance of a non-invasive approach for lung function testing in infants and children. Agents Actions Suppl, 1993. 40: p. 64-72.

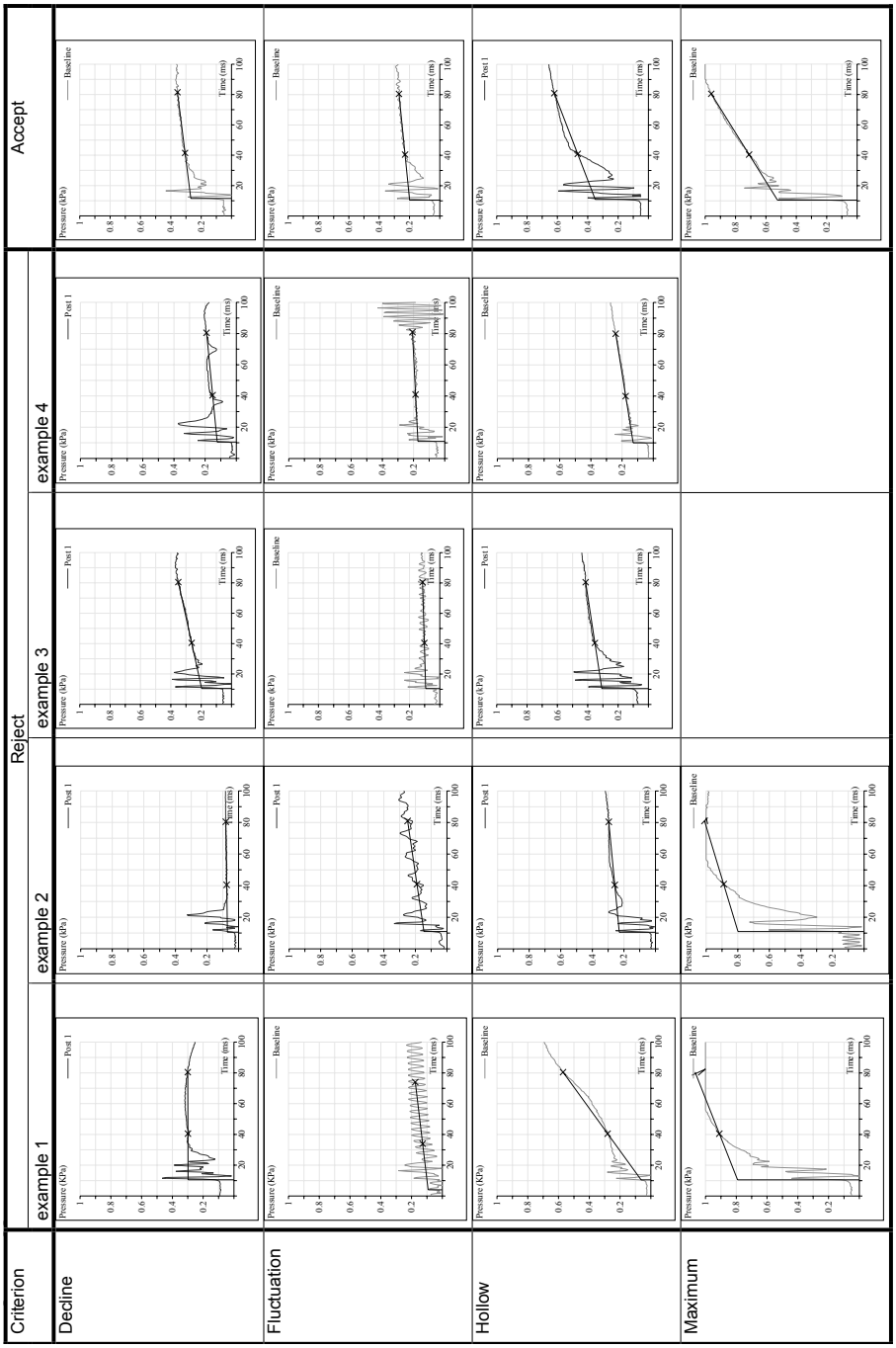
27. Frey, U. and R. Kraemer, Interrelationship between postocclusional oscillatory pressure transients and standard lung function in healthy and asthmatic children. Pediatr Pulmonol, 1995. 19(6): p. 379-88.

28. Bates, J.H., et al., The effect of a proximal compliance on interrupter measurements of resistance. Respir Physiol, 1987. 70(3): p. 301-12.

29. Cohen, J., A coefficient of agreement for nominal scales. Educational and Psychological Measurement, 1960. 20: p. 37– 46.

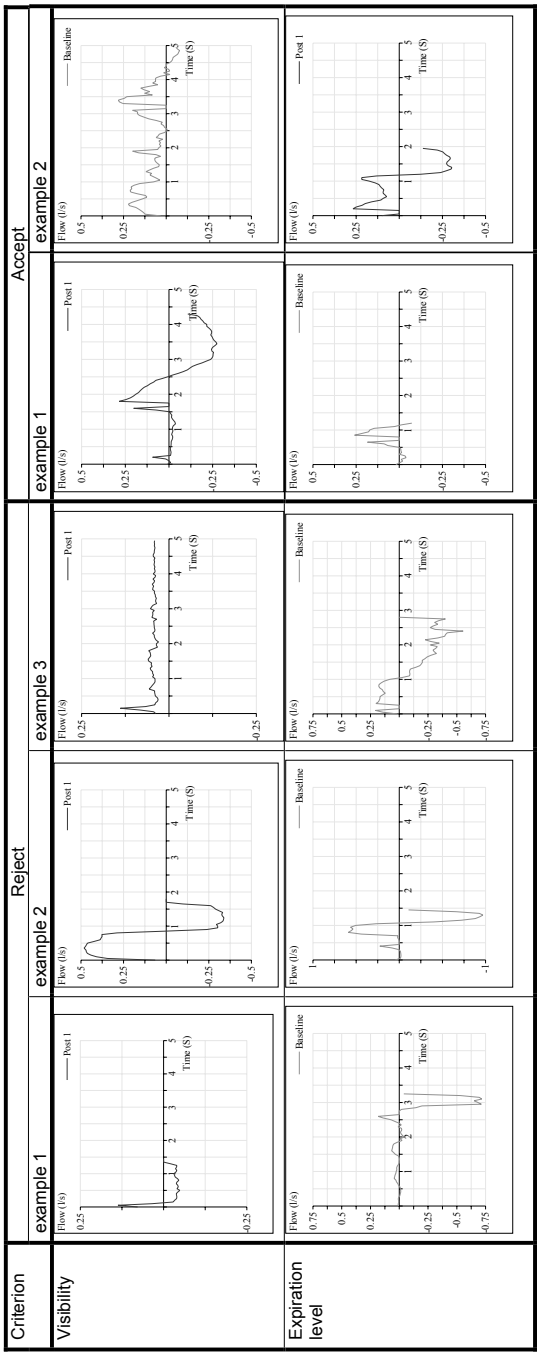
Appendix 1 shows several examples of pressure-time curves that were rejected or accepted based on de developed criteria described in chapter 4. Please note that these are un-revised examples and therefore the horizontal axis is shifted 10 msec compared to the literature text.

Appendix 1 Application of the pressure criteria



Appendix 2 shows several examples of flow-time curves that were rejected and accepted based on de developed criteria described in chapter 4. Please note that these are un-revised examples and therefore the horizontal axis is shifted 10 msec compared to the literature text.

Appendix 2 Application of the flow criteria



Chapter 5

Feasibility and Outcome of the Interrupter Technique in Pediatric Severe Generalized Cerebral Palsy

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ABSTRACT

Rationale In children with severe neurological impairment, respiratory problems are common. Conventional pulmonary function tests cannot be used due to lack of cooperation.

Objectives To assess reproducibility, feasibility, outcome values and measurement characteristics of the interrupter technique in children with severe generalized cerebral palsy.

Methods In Part 1, short-term (one hour) and long-term (two weeks) reproducibility was assessed in 35 children. The other objectives were studied in Part 2, in a representative population-based sample of 175 children. Measurements were performed on site, in the expiratory phase of tidal breathing using a non-compliant facemask.

Main results Reproducibility appeared moderate but acceptable (ICC=0.58 (short term) / 0.56 (long-term)). Recordings were tolerated by 86% and were successful in 73%. The reversibility test (bronchodilation) was successful in 63%. Median interrupter resistance (Rint) values were significantly related to age, height and bronchorrhea during the measurement. Median Rint values corresponded to reference data from non-disabled children. However, in young children, Rint values were decreased and in older children increased, as compared to reference values. Within-measurement and within-population variability were considerable. Bronchodilation decreased Rint (>2 standard deviation) in 3% of the children (suggestive of asthma), but increased Rint in 28% of the children.

Conclusions Measuring respiratory resistance was possible in most children with severe generalized cerebral palsy, but precision was less than in a healthy population. To our view, feasibility and usefulness should be monitored over time to further prove its clinical value. Despite its limitations, the interrupter technique could be considered for these children.

INTRODUCTION

Respiratory problems are a major concern in children with severe generalized cerebral palsy: 59% of all deaths result from respiratory disease, predominantly pulmonary infections [1-3]. However, studies on epidemiology and etiology of respiratory problems are lacking. It is commonly presumed that in this population respiratory problems are an indirect result of neurological damage [1]. Both restrictive and obstructive respiratory disorders are likely to occur. Restrictive disorders might result from a dysfunction of the diaphragm, increased abdominal and thoracic muscle tone, scoliosis or other thoracic deformities. Obstructive disorders might result from a combination of excessive mucus secretion and impaired clearance due to secondary ciliary dyskinesia, altered mucus consistency, poor or absent cough reflex, medication side effects, pulmonary damage (effects of recurrent of chronic pulmonary disease), malnutrition or a combination of these. Low inflation levels might further increase the risk of respiratory problems, in case of common lying position and immobility. Together with dysphagia and gastro-esophageal reflux, these respiratory disorders are likely to increase the risk of aspiration pneumonias and consecutive pulmonary damage. In addition, allergic asthma might also contribute to poor respiratory function.

Despite these common respiratory problems, objective methods to study respiratory function are neither routinely applied, nor well studied in severely disabled children. Conventional respiratory tests such as spirometry and peak-flow measurement, are not applicable in very young children [4,5] or severely disabled children. The interrupter technique however, requires only tidal breathing and no active cooperation. Its reproducibility in healthy and asthmatic children is satisfactory [6-8], and reference values for healthy children (2-13 years) are available [9-12]. The technique measures resistance of the respiratory system (Rint; kPa/L/s), which correlates closely to other parameters of pulmonary function [4,7,8,13,14].

During tidal breathing, a shutter interrupts the airflow for 100 msec, during which mouth pressure equilibrates to the alveolar pressure. Rint is the ratio between this pressure change and the preceding flow. Pressure directly after the interruption is estimated from the registered pressure-time-curve [8,15,16]. To improve validity, the outcome value is based on multiple Rint values. In (non-disabled) children the within-subject variability is sufficiently small to assess the response to bronchodilating agents [4,6,17]. This, together with the quick and noninvasive nature of the method, suggests that the technique is a potentially useful diagnostic tool to evaluate respiratory function and treatment effectiveness in disabled children too.

The present study in children with a combination of severe motor and intellectual disabilities consists of two Parts. Part 1 evaluates reproducibility of Rint values, and Part 2 evaluates feasibility (tolerance, success and its determinants) and outcome values (Rint, reversibility, precision, determinants of Rint and z-scores) of the interrupter technique.

METHODS

Study population

Reproducibility (Part 1) was evaluated in 35 children (2–18 years) with a combination of moderate to profound intellectual disabilities and severe motor impairment (GMFCS-level IV or V [18]).

Part 2 was performed as part of a large population-based cohort study of 194 children with similar disabilities, representative for the total population in the Netherlands [19]. It consisted of 175 measurements, since the first 12 measurements were used as a pilot-study and therefore discarded, the parents of 2 children did not give consent for this specific measurement and 5 children dropped out earlier. To keep the burden in this extensive cohort-study to a minimum, participants for Part 1 were recruited elsewhere. Inclusion criteria for both groups were identical.

Legal representatives of all participants gave written informed consent. The national ethical committee (Central Committee on Research Involving Human Subjects) approved the study.

Measurement procedure

Interruption measurements were performed on-site (daycare centre or specialized school), to prevent anxiety and distress. Measurements were performed in the expiratory phase of tidal breathing using a commercially available, ambulatory device (MicroRint, v1.113, Micro Medical, Rochester UK) [7,9]. The trigger method was random with a continuous operating mode while cheek support was applied. Children abstained from anti-asthmatic medication during eight hours prior to the measurement.

Because these children are unable to close their lips intentionally around a mouthpiece, a fitting non-compliant facemask (Intersurgical, Uden, The Netherlands), covering the nose and mouth, was used. Per measurement, we aimed to record 15 separate tracings with a trigger level of 0.20 L/s.

In Part 1, three identical Rint measurements (3x15 interruptions) were performed on day 1, with intervals of approximately one hour. A fourth measurement was performed two weeks later.

In Part 2, baseline measurements were obtained, followed by bronchodilator administration and a postbronchodilator measurement 15 minutes later. Measurements were identical to Part 1 measurements. The procedure was stopped if either baseline measurement or bronchodilator administration failed. Bronchodilation was evaluated after administering 800 µg Salbutamol aerosol (Ventolin®, GlaxoSmithKline B.V., Zeist, The Netherlands) using a spacer (AeroChamber Plus, Boehringer Ingelheim, Alkmaar, The Netherlands).

A significant response to Salbutamol was defined as a sensitivity index (SI) (change/standard deviation of the individual baseline measurement) over 2 [17]; SI < -2 indicates reversible airway obstruction.

Determinants

To identify possible determinants of a successful measurement, we recorded: age, Body Mass Index (BMI), gender, scoliosis, level of intellectual disability, Gross-Motor-Function-Classification-Scale (GMFCS) level, estimated level of involuntary and aimed movements; as well as measuring conditions: bronchorrhea (distinctly audible without a stethoscope), positioning, physical activity, state of mind (calm or not), setting and the number of people present.

These variables (except the last four) and height were assessed to identify predictors of Rint value.

Measurement analysis

Rejection of incorrect pressure-time curves was done by one researcher, using strict rejection criteria, to improve reproducibility of the analysis (Table 1). The median values of the remaining interruptions per measurement were calculated. A measurement was considered successful if at least 5 interruptions remained.

The success rate is the percentage of successful measurements to the total number of measurements.

The data supplement provides additional information on the measurement procedure, measuring device, data gathering and statistical analysis.

Table 1 Criteria used for the manual rejection of interruptions

An interruption was rejected for the analysis when in the pressure-time curve:

- After t = 30 msec, the pressure curve showed no continuing increase of pressure (exception: a horizontal end phase).
- After t = 30 msec, the curve shows a fluctuation ≥ 0.05 kPa around the regression line of the curve.
- After t = 30 msec, the curve shows a growing increase of pressure resulting in a hollow curve
- Pressure values at t + 30 ms and/or t + 70 ms exceeded the range of registration.
- If no pressure-curve was registered.

RESULTS

The characteristics of the two studied populations are shown in Table 2.

Table 2 Children's characteristics

		Part 1	Part 2
Cohort size	number	35	175
Age (years)	mean (sd)	12,3 (4,0)	9.5 (4.4)
Gender	% boys	69,2	53.7
Intellectual disability	% mild	2.9	0.0
	% moderate	35.3	10.4
	% severe	20.6	40.0
	% profound	41.2	49.6
GMFCS	% level III	8.0	0.0
	% level IV	10.0	17.4
	% level V	82.0	82.6
Full chest during measurement	% yes	12.8	24.5
Positioning at measurement	% optimal	69.8	65.8

GMFCS = Gross Motor Function Classification Scale, optimal positioning = upright in an upright positioned wheel chair, valid = fraction of the population with known information.

Reproducibility (Part 1)

Short-term reproducibility of Rint had an intraclass correlation coefficient (ICC) of 0.58, a within subject variation (SD_w) of 0.13 kPa/l/s and a coefficient of variation (CoV_{repeat}) of 19.4%. Long-term ICC was 0.56, SD_w 0.14 and CoV_{repeat} 30.3%. Figure 1 presents the Bland and Altman plots for short and long-term reproducibility showing similar results on short and long term. Table S1 (data supplement) presents these and other measures of reproducibility with results from other studies as a reference.

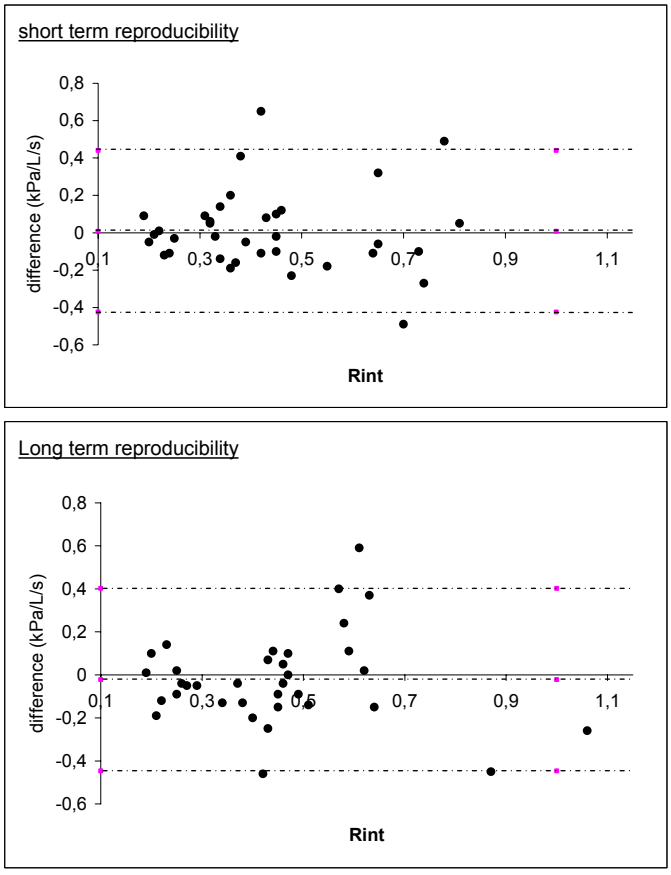

Figure 1 Short and long term reproducibility
Figure 1 The upper Bland and Altman plot shows the difference between two measurements that were one hour apart plotted against the median Rint value. The horizontal lines represent the average difference (0.008 kPa/L/s) and the 1.96*SD borders (-0.424, 0.440). The plot below, shows the long term (2 week) reproducibility (–0.022(-0.446, 0.402)).

Feasibility (Part 2)

Tolerance

In 151/175 children (86,3%) we were able to perform a baseline measurement, consisting of 15 (74.9%) or 5-14 interruptions (11.4%). Less than 5 interruptions were obtained in 24 children (13.7%).

Postbronchodilator measurements were performed in 136 children (10 stopped early, 5 stopped < 5 interruptions).

Measurement success

The performed measurements were analyzed using the criteria mentioned above to reject irregular pressure-curves. This resulted in 128/175 (73,1%) successful baseline measurements and 113/136 (83.1%) successful postbronchodilator measurements. Success percentages (baseline measurements) per age category were 46.7% (2-5 years), 76.8% (5-12 years) and 82.4% (>12 years).

Figure 2 shows that although in some children the measurement was stopped early, the absolute number of successful interruptions remains roughly similar.

In 111/175 children (63.4%) both baseline and postbronchodilator measurement were successful.

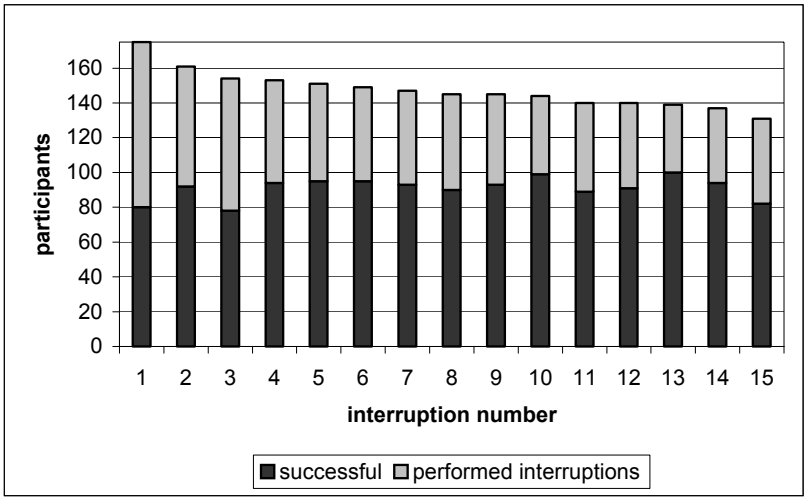

Figure 2 Interruptions in chronological order; execution and success numbers
Figure 2 The horizontal axis shows the sequential number of interruptions of the baseline measurements (with a maximum of 15 interruptions per measurement). The bars indicate in how many participants the corresponding interruption was attempted, while the dark parts indicate how many of these interruptions proved successful on analysis.

Table 3 Determinants of measurement success

			Univariate	Multivariate	
		measurement success %	p-value	OR	CI
age	years		0.005 *	1.15	1.04 – 1.27
BMI	kg/ m		0.087 *		
age category	2-5 years	46.7			
	5-12 years	76.8			
	> 12 years	82.4	<0.001*		
gender	boy	75.3			
	girl	71.3	X		
scoliosis	yes (41.7%)	67.2			
	no (58.3)	89.6	0.007*		
intellectual	moderate	71.4			
disability	severe	74.1			
	profound	77.6	0.841		
GMFCS	level IV	65.5			
	level V	76.1	0.237		
involuntary	< 2 hours a week	81.6			
movements	regularly	73.8			
	most of the day	68.4	0.190		
aimed	none	79.1			
movements	little	78.8			
	regularly	67.4	0.204		
bronchorrhea	yes	60.0			
	no	78.8	0.028 *	0.45	0.16 - 1.22
positioning	optimal	76.5			
	not optimal	76.5	X		
activity during	not hindering (70.6%)	87.0			
measurement	measurement difficult (20.9%)	75.0			
	meas. not well possible (8.5%)	7.7	<0.001*	0.06	0.001 – 0.66
state of mind	calm (58.2%)	92.1			
	not calm (41.8%)	57.8	<0.001*	0.22	0.06 - 0.76
room	separate (58.7%)	77.4			
	classroom (41.3%)	74.6	0.423		
number of people present			0.984		

measurement success % = percentage of the measurements that proved successful (at least 5 remaining interruptions after analysis), BMI= Body Mass Index, * significant at an 0.05 level, using Chi square tests (linear by linear) for categorical variables and logistic regression for continue variables. GMFCS = gross motor function classification scale, X = not calculated

Determinants of success

Measurements were significantly less successful in younger children, children with bronchorrhea or scoliosis and in children who were physically active during the measurement, or were not in a calm state of mind. No relationship was found between success rates and other determinants (Table 3).

Multiple logistic regression analysis resulted in a model with the following variables: age, bronchorrhea, physical activity during the measurement and state of mind. This model had a mean explained variance (R^2) of 36%.

Per measurement we aimed for 15 interruptions, while aiming for 10 is common in the non-disabled population. If we would have aimed for 10 interruptions, our success percentage (>5 remaining interruptions) would have been 62.9%, compared to 73.1% with 15 interruptions (Figure 3).

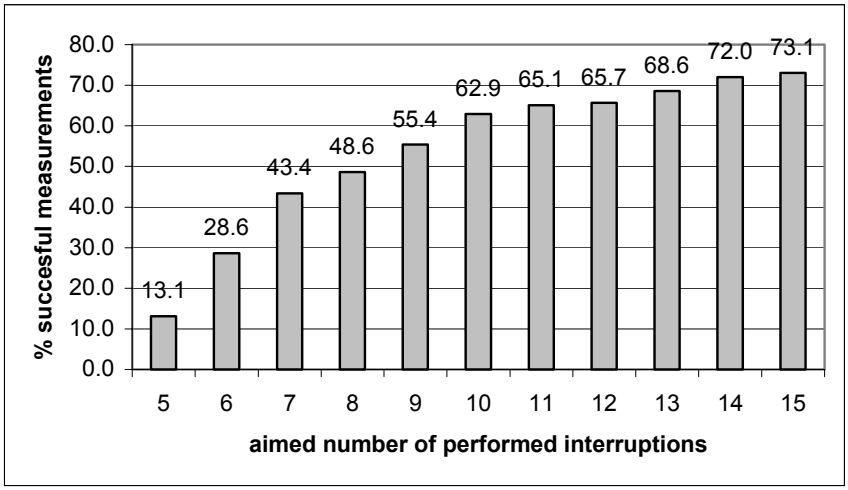

Figure 3 Aiming for 15 interruptions or less
Figure 3. The bars represent the percentage of successful measurements (at least 5 acceptable interruptions) when aiming to perform the number of interruptions presented in the horizontal axis. The current situation is represented by the last bar, aiming to perform 15 interruptions, corresponding to a success rate of 73.1%.

Respiratory resistance (Part 2)

Rint values, reversibility and precision

Median Rint value [inter quartile range] of the cohort was 0.67 [0.50] kPa/L/s for the baseline measurement and 0.69 [0.55] kPa/L/s for the postbronchodilator measurement.

Table 4 Determinants of Rint value

			univariate	multivariate	
		median [IQR]	p- value	B coefficient	CI
age	years		0.005*		
height			0.015*	0.99	0.99 - 1.00
BMI	kg/ m		0.380		
age category	2-5 years	0.68			
	5-12 years	0.73			
	> 12 years	0.53	0.012*		
gender	boy	0.71			
	girl	0.66	0.327		
scoliosis	yes (41.7%)	0.70			
	no (58.3)	0.59	0.699		
intellectual	moderate	0.82			
disability	severe	0.60			
	profound	0.57	0.320		
GMFCS	level IV	0.69			
	level V	0.66	0.568		
involuntary	< 2 hours a week	0.55			
movements	regularly	0.69			
	most of the day	0.60	0.898		
aimed	none	0.58			
movements	little	0.66			
	regularly	0.69	0.743		
bronchorrhea	yes	0.71			
	no	0.58	0.018*	1.35	1.04 – 2.99
positioning	optimal	0.66			
	not optimal	0.71	0.300		

BMI = Body Mass Index, * significant at an 0.05 level using linear regression, GMFCS = gross motor function classification scale, B-coefficients are presented for Rint (transformed from the logRint model)

Reversible airway obstruction (SI<-2) was measured in three children (3% of 111 successful reversibility tests). On the other hand, 31 children (27.9%) had a significant increase in Rint (SI>2). Mean SI was 0.82 (±1.9) with a range –3.29 to 8.38.

Within-measurement variation (median CoV_{within})[inter quartile range] was 0.38 [0.23] for the baseline and 0.38 [0.26] for the postbronchodilator measurement.

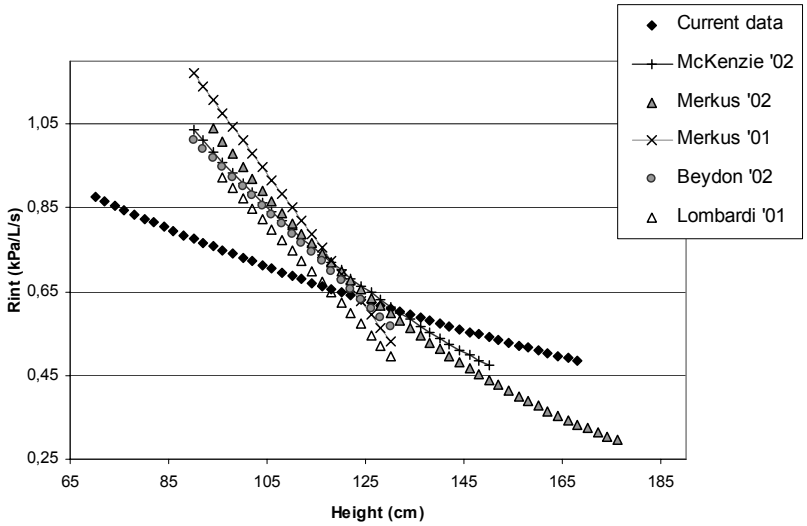

Figure 4 Regression lines for Rint against height
Figure 4 shows the regression line of Rint against height based on the measurements of 128 children with severe generalized cerebral palsy. The other lines represent corresponding regression lines from previously published studies in healthy non-disabled individuals. Lines are presented in their appropriate height range.

Determinants of Rint-value

Rint (log transformed) was significantly related to age, height and bronchorrhea (Table 4). However, a multivariable model showed that age had no relevant contribution in predicting Rint when both height and bronchorrhea were already taken into account (R^2 remained 11.1%). No correlation was found with the other variables.

In the group of children without a bronchorrhea, height (p=0.013, R^2=7.2%) and age (p=0.014, R^2=4.9%) had a significant univariate relationship with logRint. In the multivariate model only height remained (p=0.16, R^2=7.2%).

Comparison to reference data

The expected median Rint value based on height, using a published reference equation [9], was similar (0.677 [0.285] kPa/L/s) to the observed value (0.670 [0.499] kPa/L/s), although the inter quartile ranges in our sample were larger.

To gain insight into the differences with non-disabled populations, the regression line is plotted in Figure 4 together with published regression lines from studies in non-disabled populations. This demonstrates a tendency toward relatively high Rint-values in taller children and lower Rint-values in smaller children in children with severe generalized cerebral palsy.

The data supplement provides additional results on z-scores, CoV_{within} and the success-model.

DISCUSSION

This study is the first to measure respiratory function in a large group of children with severe generalized cerebral palsy, using the interrupter technique. Measurements were tolerated by 86% of the children, and successful in 73%. We found that short and long-term reproducibility were similar and comparable to long-term reproducibility under field conditions in a healthy population [20]. Reversibility tests were successful in 63.4%, showing a decreased Rint in 3% of the children, suggestive of asthma, but an increased Rint in 27.9%. Median baseline Rint value was similar to the predicted value based on the reference data of healthy children [9], although Rint values were relatively low in small (younger) children, and relatively high in tall (older) children. Rint was also influenced by bronchorrhea during the measurement. Although these results were favorable, within-measurement and within-population variability were larger in this population than in non-disabled populations.

Reproducibility (Part 1)

In contrast to reports from other populations [10,20,21], short term reproducibility was not better than long term reproducibility in this study. Only CoV_{repeat} indicated a better reproducibility on short versus long term.

On short term reproducibility was poorer than in other populations. Long term reproducibility was comparable to reproducibility in a healthy population measured under field conditions [20] and comparable to that of coughers and wheezers [21] if based on ICC, and/or SD_w. However, if based on CoV_{repeat}, long-term reproducibility seemed poor in our sample. This can be explained by the large CoV_{within} (0.38). The CoV_{repeat} uses Rint-values of the separate interruptions, whereas other reproducibility measures are based on the outcome (median Rint) values of measurements. Although the CoV_{repeat} provides information on the variation of separate interruption-values, it is not the most appropriate measure to express reproducibility.

We conclude, that reproducibility is acceptable, but within-measurement variation is large.

Feasibility (Part 1)

Tolerance

Measurements were not tolerated by 14% of our cohort. Reported refusal rates in non-disabled populations vary between 0 and 44% [9,10,12,22,23]. The relatively low

tolerance in our population was expected since these children are unable to fully understand the measurement, the instructions and reassurement. Aversive reactions may be worsened by visual impairment, hyper-sensibility of the mouth area and unpleasant associations with hospital masks, which are more common in this population.

Measurement success

As in other pediatric populations, success rate of Rint measurements was age dependent [22,23]. Our success rates are somewhat lower than reported success rates for non-disabled populations which vary between 80 and 100% in children over 3 years of age [7,10,12,21,22,24-28]. This was most likely due to limited comprehension, anxiety, hyper sensibility and motor impairment.

We have shown that the success rate (73%) was raised by increasing the number of aimed interruptions to 15 (Figure 3). Based on the observed trend, we do not expect that a further increase in the aimed number of interruptions will increase the success rate further. However, some children might benefit from an adjustment period to get used to the device. In clinical practice, it might thus be considered to repeat the measurement in for the child acceptable intervals, until enough acceptable interruptions have been obtained.

Respiratory resistance (Part 2)

Rint reversibility and precision

Increased Rint after bronchodilation was observed in 27.9% of the children. This may be explained by sputum release that was not expectorated before the post measurement, due to decreased cough reflex and decreased motor abilities for an efficient cough. Increasing the time interval between baseline and postbronchodilator test might resolve this.

The precision of a single measurement was expressed as CoV_{within}. In our population median CoV_{within} was 38%, which is poor compared to 11.4 – 14.4%, described by others [12,28-30]. CoV_{within} is a measure of variation in single interruption values within a measurement. It is not a measure of reliability of the outcome, which should be judged based on the repeatability of the outcome value (studied in Part 1).

We conclude that within measurement variation is large; therefore it is important to take the median of several Rint values as outcome measure.

Determinants of Rint-value

As in studies in non-handicapped children we found a relationship between Rint and age (both strongly related to height). Unlike other populations we measured children with bronchorrhea, which increased Rint: increased amounts of sputum in the airways will narrow the passage and therefore increase the resistance.

Comparison to reference data

Over the total group (median), Rint values were almost equal to the predicted Rint values for non-disabled children. However, in smaller children, Rint values were low compared to non-disabled populations, whereas and in taller children values were relatively high (Figure 4). We hypothesize that deviation from reference values of healthy populations can be explained by (subclinical) bronchitis, abnormal muscle tone and the use of a facemask. Muscle tone tends to increase with age [31,32], possibly resulting in a relative increase in respiratory resistance. Chronic bronchitis, poor/absent cough reflexes or pulmonary damage (recurrent pulmonary disease) might further explain the relatively high Rint values seen in older children. Especially when combined with scoliosis and other thoracic malformations, these factors might contribute to the smaller decrease in resistance with age, compared to healthy populations.

The data supplement provides additional discussion on COV, z-scores, bronchorrhea and the comparison to reference data.

Implications for future use

Based on our results, we expect that measurements using the interrupter technique are possible in the majority of children with severe generalized cerebral palsy. There are three main areas in which its use could be considered. Firstly, to study Rint longitudinally in populations. For this purpose the technique could be considered, because reproducibility on a group level proved favorable. Secondly, reversibility testing of the individual child. Significant change has been shown. Nevertheless, due to within-measurement variability, clinically relevant changes will not always result in a measurable significant change. In daily practice, some profit might be gained by introducing adjustment periods for the facemask. Furthermore, we recommend a longer time interval (well over 15 minutes) between bronchodilator administration and post measurement. Thirdly, changes in respiratory resistance of an individual child. Trends in respiratory resistance of a child might provide valuable information, but individual measurements should be handled with caution since the within-measurement variation is considerable and repeatability moderate. In trend monitoring, repeated measurement should be

done over a period of time (variation is likely due to both non-optimal measurement precision and health status), before and during/after a treatment. Hopefully, respiratory function can be effectively monitored this way, but future studies need to prove that this can be done. To monitor changes in respiratory resistance on long term, the physiological changes due to growth should be taken into account. Therefore population specific reference values should be available.

CONCLUSION

The need for a method to monitor short term and long term changes in pulmonary function and treatment effects in children with severe generalized cerebral palsy is evident.

We have shown that it is possible to measure respiratory resistance in this population. Repeatability was moderate but in our view acceptable. Within-measurement variation was relatively large. Compared to a non-disabled population, Rint values were relatively low in small (young) children and high in tall (older) children, which might be due to muscle tension development and chronic bronchitis or thoracic disorders.

Despite the limitations of this method, it is at this moment, the only (studied) pulmonary function parameter method available. This lack of a reference standard makes a proper validation impossible. To our view, feasibility and usefulness should be monitored over time, to obtain insight into the clinical usefulness of this pulmonary function test in neurologically impaired populations.

REFERENCES

1. Seddon, P.C. and Y. Khan, Respiratory problems in children with neurological impairment. Arch Dis Child, 2003. 88(1): p. 75-8.
2. Toder, D.S., Respiratory problems in the adolescent with developmental delay. Adolesc Med, 2000. 11(3): p. 617-31.
3. Blair, E., et al., Life expectancy among people with cerebral palsy in Western Australia. Dev Med Child Neurol, 2001. 43(8): p. 508-15.
4. Bisgaard, H. and B. Klug, Lung function measurement in awake young children. Eur Respir J, 1995. 8(12): p. 2067-75.
5. Crenesse, D., et al., Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuvers. Pediatr Pulmonol, 2001. 32(1): p. 56-61.
6. Phagoo, S.B., N.M. Wilson, and M. Silverman, Evaluation of a new interrupter device for measuring bronchial responsiveness and the response to bronchodilator in 3 year old children. Eur Respir J, 1996. 9(7): p. 1374-80.
7. Arets, H.G., H.J. Brackel, and C.K. van der Ent, Applicability of interrupter resistance measurements using the MicroRint in daily practice. Respir Med, 2003. 97(4): p. 366-74.
8. Chowienczyk, P.J., et al., A flow interruption device for measurement of airway resistance. Eur Respir J, 1991. 4(5): p. 623-8.
9. Merkus, P.J., et al., Measurements of interrupter resistance: reference values for children 3-13 yrs of age. Eur Respir J, 2002. 20(4): p. 907-11.
10. Lombardi, E., et al., Reference values of interrupter respiratory resistance in healthy preschool white children. Thorax, 2001. 56(9): p. 691-5.
11. McKenzie, S.A., et al., Airway resistance measured by the interrupter technique: normative data for 2-10 year olds of three ethnicities. Arch Dis Child, 2002. 87(3): p. 248-51.
12. Beydon, N., et al., Pre/postbronchodilator interrupter resistance values in healthy young children. Am J Respir Crit Care Med, 2002. 165(10): p. 1388-94.
13. Carter, E.R., et al., Evaluation of the interrupter technique for the use of assessing airway obstruction in children. Pediatr Pulmonol, 1994. 17(4): p. 211-7.
14. Klug, B. and H. Bisgaard, Measurement of lung function in awake 2-4-year-old asthmatic children during methacholine challenge and acute asthma: a comparison of the impulse oscillation technique, the interrupter technique, and transcutaneous measurement of oxygen versus whole-body plethysmography. Pediatr Pulmonol, 1996. 21(5): p. 290-300.
15. Jackson, A.C., H.T. Milhorn, Jr., and J.R. Norman, A reevaluation of the interrupter technique for airway resistance measurement. J Appl Physiol, 1974. 36(2): p. 264-8.
16. Mead, J. and J.L. Whittenberger, Evaluation of airway interruption technique as a method for measuring pulmonary airflow resistance. J Appl Physiol, 1954. 6(7): p. 408-16.
17. Bridge, P.D., H. Lee, and M. Silverman, A portable device based on the interrupter technique to measure bronchodilator response in schoolchildren. Eur Respir J, 1996. 9(7): p. 1368-73.
18. Palisano, R., et al., Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol, 1997. 39(4): p. 214-23.
19. Veugelers, R., et al., 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): p. 25.

20. Beelen, R.M., et al., Short and long term variability of the interrupter technique under field and standardized conditions in 3-6 year old children. Thorax, 2003. 58(9): p. 761-4.

21. Chan, E.Y., et al., Repeatability of airway resistance measurements made using the interrupter technique. Thorax, 2003. 58(4): p. 344-7.

22. Merkus, P.J., et al., Interrupter resistance in preschool children: measurement characteristics and reference values. Am J Respir Crit Care Med, 2001. 163(6): p. 1350-5.

23. Bridge, P.D., S. Ranganathan, and S.A. McKenzie, Measurement of airway resistance using the interrupter technique in preschool children in the ambulatory setting. Eur Respir J, 1999. 13(4): p. 792-6.

24. Panagiotis, P., et al., Use of interrupter technique in assessment of bronchial responsiveness in normal subjects. BMC Pulm Med, 2004. 4(1): p. 11.

25. Beydon, N., et al., Pulmonary function tests in preschool children with asthma. Am J Respir Crit Care Med, 2003. 168(6): p. 640-4.

26. Hadjikoumi, I., A. Hassan, and A.D. Milner, Effects of respiratory timing and cheek support on resistance measurements, before and after bronchodilation in asthmatic children using the interrupter technique. Pediatr Pulmonol, 2003. 36(6): p. 495-501.

27. Klug, B. and H. Bisgaard, Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2-7 years. Pediatr Pulmonol, 1998. 25(5): p. 322-31.

28. Child, F., et al., How should airways resistance be measured in young children: mask or mouthpiece? Eur Respir J, 2001. 17(6): p. 1244-9.

29. Bridge, P.D. and S.A. McKenzie, Airway resistance measured by the interrupter technique: expiration or inspiration, mean or median? Eur Respir J, 2001. 17(3): p. 495-8.

30. van Altena, R. and F. Gimeno, Respiratory resistance measured by flow-interruption in a normal population. Respiration, 1994. 61(5): p. 249-54.

31. Albright, A.L., Spasticity and movement disorders in cerebral palsy. J Child Neurol, 1996. 11 Suppl 1: p. S1-4.

32. Russman, B.S., Cerebral Palsy. Curr Treat Options Neurol, 2000. 2(2): p. 97-108.

Data Supplement to Chapter 5

Feasibility and Outcome of the Interrupter Technique in Pediatric Severe Generalized Cerebral Palsy

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METHODS

Study population

Part 2 of this study was performed as part of a large-scale epidemiological cohort study of pulmonary and feeding problems in children (2 – 18 years) with a combination of moderate to profound intellectual disabilities (ID) and severe motor impairment in the Netherlands [1]. The intellectual disability was defined as an IQ below 55 (or estimated by dividing the developmental age by the calendar age times 100). ID was categorized as moderate (IQ= 35-55), severe (IQ=25-35) or profound (IQ <25). The motor disability was defined by 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 Scale (GMFCS) score IV or VModerate.

Measurement procedure

All measurements were performed by two researchers, in a group setting or in a quiet room, depending on preferences of the care centre. Caregivers were invited to be present at each measurement. Stop criteria were explained in advance. If the child did not tolerate the recording, the measurement was paused or stopped immediately. One researcher sat in front of the child and briefly explained the procedure to the child. The facemask and the sound of the occlusions were demonstrated before the start of the measurement. The other researcher stood behind the child and fixated the child's head during the measurement while supporting the cheeks, holding the facemask in place at the same time. The researcher in front observed the child and held the arms of the child if necessary.

The MicroRint automatically rejects an interruption if an apparent artifact on the pressure curve occurs, and uses back-extrapolation to t = 15 ms after shutter closure (100 ms) to calculate Rint. Measurements were imported into the RIDA software (Micro Medical Ltd, RintBase 5, version 1.002 for Windows 2002).

Part 2

Salbutamol aerosol (Ventolin®, GlaxoSmithKline B.V., Zeist, The Netherlands) was administered after the baseline session, in 4 subsequent doses of 200 µg using a spacer (AeroChamber Plus, Boehringer Ingelheim, Alkmaar, The Netherlands). The first 3 doses were inhaled in 5 breaths and the last dose in 10 breaths.

Additional information on determinants

Arm span and standing height were measured using a flexible tape measure. Because height is sometimes difficult to measure due to contractures, arm span was converted to height if necessary (9 children) [2]. In 166 children both arm span and height were measured. The median difference [inter quartile range] between measured height and height calculated from arm span was 0.0 [6.0] cm.

Measuring conditions were recorded. Positioning was scored 'optimal' if the child was (supported) upright in an upright positioned wheel chair. Researchers also recorded whether the child had a full chest, which was scored positive if it was apparent without using a stethoscope. Level of intellectual disability (ID) (the developmental age or the IQ) was noted from the school or day care file. Information on scoliosis, aimed and involuntary movement was gathered from questionnaires. Scoliosis was scored positive if the child visited an orthopedic specialist for this condition.

Analysis, part 1

Short and long-term reproducibility were expressed by intraclass correlation coefficient (ICC), within subject variation (SD_w) [3], Coefficient of variation (CoV_{repeat}) and shown in a Bland and Altman plot [4].

In current literature on reproducibility of Rint, several different measures are used. To allow comparison with several studies, several measures of reproducibility were calculated. Besides the ICC, SD_w and CoV_{repeat} mentioned in the print version, we also calculated the mean difference ± SD (range) and the repeatability (variance of the mean difference between pairs of measurements).

CoV_{repeat} was calculated as: SD of the Rint-value of the single interruptions of 2 repeated measurements divided by the mean of those interruptions. These individual measures were averaged for the population. The individual mean differences with SD (and the corresponding "*repeatability*") were also averaged to one population measure. The other measures ICC, SD_w and Bland and Altmann plots directly result in one summarizing result for the population. ICC is the only measure without a dimension; the other reproducibility measures are expressed in kPa/L/s.

Two of the three measurements from day 1 were randomly chosen to represent the short-term reproducibility in a Bland and Altman plot [4]. For long-term reproducibility, the difference between the last day measurement and a randomly chosen measurement of day 1 were used.

Analysis, part 2

Rint precision

Precision of a measurement was expressed as median within-measurement coefficient of variation CoV_{within} (CoV = SD/mean) CoV_{within} was calculated using the Rint values of all acceptable individual occlusions.

Age, height and bronchodilation have been shown to affect this precision [5,6] therefore these relations were analyzed using linear regression. Differences in CoV between base and post measurement were analyzed using the Wilcoxon Signed Ranks test.

Determinants of success

Logistic regression was used to identify multivariable relationships between measurement success and the previously described determinants. Individual determinants with a univariate relationship with $p<0.20$ were used for stepwise logistic regression, to identify most relevant variables. Results are compared with a model in which missing variables are imputed using multiple imputations. For the imputation procedure we used a multiple imputation technique with five imputed data sets [7]. Odds ratio's (OR) 95% confidence intervals and p-values are presented.

The necessity of aiming for 15 interruptions (in non-disabled children it is common to aim for 10 interruptions) was assessed by calculating success rate for fictive situations when only the first 5 to only the first 14 interruptions would have been performed. For example: only the first performed 8 interruptions per child were analyzed. For this (fictive) situation the success rate was calculated, which represents what success rate we would have found, would we have aimed for only 8 interruptions. This was done for all numbers from 5 to 14.

Determinants of Rint-value

To identify relationships between logRint-values and described determinants a similar procedure was performed using linear regression. The log of the Rint values was used in order to conform to assumptions underlying linear regression (normal distribution of the residuals). This was performed for the total group and for children without a distinct bronchorrhea separately. The predictive ability of these models was expressed by the explained variances (R^2).

Comparison to reference data

Z-scores were calculated [8]. Z-scores reflect the deviation from reference values adjusting for the predicted value and therefore allows comparison in deviation at different ages [9]. This equation [8] was most appropriate since it uses a log-scale and our data were heteroscedastic (SD increased with increasing Rint value).

A p-value below 0.05 was considered statistically significant.

RESULTS

Determinants of success

In the multiple logistic regression analysis of determinants for measurement success, the variable "physical activity during the measurement" was significant but only for 'not hindering' versus 'measurement not well possible'.

The multiple logistic regression analysis using multiple imputations resulted in a model with a mean explained variance of R^2=36%. Without imputation of missing data a similar model was obtained with an $R^2$of 45%.

Rint precision

CoV_{within} was not significantly related to age (p=0.418) or height (p=0.605), nor did it differ between baseline and postbronchodilator measurement (p=0.292).

Comparison to reference data

Mean z-score (SD) was -0.016 (2.70), which was strongly related to Rint-value (p=0.000, R^2=64.7%) and log Rint (p=0.000, R^2=71.7%). Z-score was also significantly related to height (p=0.000, R^2=10.8%) and age (p=0.000, R^2=3.3%).

In Figure 4 the regression line for Rint to height was plotted according to the following model: logRint=0.125 - 0.0026 height (cm) (R^2 of 4.6%; standard deviation of the residuals (RSD)=0.23). Studies in non-disabled populations, which did not use back-extrapolation to calculate Rint, were not plotted.

DISCUSSION

Reproducibility (Part 1)

Even though the mean difference (between two measurements from one child) (Figure 5) on short term indicates a good reproducibility on a group level, the corresponding wide interval confirms a poor individual reproducibility on short term.

Feasibility (Part 1)

Tolerance

Motor impairment might either hamper or facilitate measurement execution: children with continuous involuntary movements and resisting movements will be more difficult to measure than healthy children or children without the ability to move. However, a correlation between success rate and movement during the measurement was univariately not statistically significant.

Respiratory resistance values (Part 2)

Rint reversibility and precision

Previous studies in non-disabled children showed a relationship between the variation within a measurement (CoV_{within}) and age, height [5] or bronchodilation [6]. Theoretically, the first could explain the relatively high CoV_{within} found in this study, since the average age (and height) is higher than in other studies. However analysis showed no significant relationship between the CoV_{within} and age or height.

Bronchorrhea

Bronchorrhea (distinctly audible without a stethoscope) is not easily quantified. Nevertheless, we chose to record and analyze this parameter. Main reason was, that this manifestation of (chronic) sputum stasis is very common in these children. To judge the applicability of the interrupter technique in these children, data on the effect of sputum stasis on Rint measurements is necessary

Because bronchorrhea was recorded before the start of the measurement, misclassification is likely to be random (underestimation of relationships). Missing data were not random since difficult to judge cases, are more likely to be left blanc, leaving them out of the analysis has most likely caused a small overestimation, however, when missings were randomly allocated difference remained significant (p=0.013). Based on this we feel our results represent a true effect of bronchor-

rhea, even though quantification is problematic.

Since a representative population-based sample (including children with symptoms) was included, results can be easily extrapolated to daily practice.

Comparison to reference data

For the total group (median), Rint values were almost equal to the predicted Rint values based on reference values of non-disabled children, but the inter-quartile range (IQR) was larger. This has a three-fold explanation. Firstly, the repeatability values indicate that our measurement precision is relatively low, thereby increasing the IQR. Secondly, predicted values are by definition exactly on the regression line, whereas observed data will scatter around it. Thirdly, Rint-values were influenced more often by comorbidity (some had a history of severe respiratory and other illnesses) than in non-disabled populations. The effects of these conditions on Rint-value could not be analyzed properly in our sample without categorizing these conditions, which would be very arbitrary and could therefore introduce chance findings.

The results of our study can also be compared with those of studies in non-disabled populations, using regression lines of Rint against height. Rint-values in our population are below those in non-disabled populations in smaller children and above these in taller children (Figure 4). This was confirmed by the correlation of the z-scores to age and height. Z-scores reflect the deviation from reference values adjusting for the predicted value and therefore allow comparison in deviation at different ages [9]. Z-scores correlated to Rint values as well, indicating that the variation in Rint-values was not solely based on variation in height. The regression line is plotted with those of other studies to visualize the differences between this population with severe generalized cerebral palsy and healthy children. Although we included a representative cohort of children with severe generalized cerebral palsy, our population is not large enough to be used as reference for other children.

We should also bear in mind that our prediction model for Rint based on height has a low predictive value (R^2=4.6%, RSD=0.23), compared to the model of Merkus (R^2=63%, RSD=0.09 [8]). However, the predictive value of our model is comparable with the precision of the other models (R^2 =14% [10] and RSD=0.18 [11]). Another measure used in literature, the standard error of the coefficient, is less informative since it also depends on the number of participants (SE_B=0.001 in our data versus reported data SE_B=0.002 - 0.13 [10,12,13]). We conclude that the low model precision can be explained by the moderate reproducibility and the heterogeneity of the study sample, including children with a history of respiratory problems.

Table S1 Reproducibility compared to studies in non-disabled populations

Measures of reproducibility	CoV (%)	ICC	Repeatability (kPa/L/s)‡	SDw (kPa/L/s)	mean difference ± SD (kPa/l/s)
Short term reproducibility					
Current data	**19.4#**	**0.58**	**0.43**	**0.13**	**0.008 ± 0.216**
Arets '03	7,1#	-	0.22º	-	-0.005 ± 0.11
Beelen '03	-	-	± 0.28ºº	0.10	-
Chan '03 *	6,5 ##	0,97†	0.17	-	-
Child '01	-	0.76††	0.22º	-	-0.02 ± 0.11
	-	0.77	0.34º	-	-0.01 ± 0.17
Lombardi '01	-	0.87	0.242	-	0.007 ± 0.12º
Nielsen '01 '00	-	-	-	0.078$	-
Klug '00**	-	-	0.24º	0.085$$	–0.03 ± 0.12
	-	-	0.18º	0.063	0.00 ± 0.09
Bridge '99	-	-	0.21	-	-
	-	-	0.17	-	-
	-	-	0.15	-	-
Oswald-mammoser '97*	9%	-	-	-	-
	7%	-	-	-	-
Long term reproducibility					
Current data	**30.3**	**0.56**	**0.42**	**0.14**	**-0.0221 ± 0.212**
Beelen '03	-	-	± 0.36ºº	0.13	-
	-	-	-	0.10	-
Chan '03 *	11	0,75	0.23	-	-
	16	0,56	0.38	-	-
	15	0,66	0.44	-	-
Lombardi '01	-	0.91	0.208	-	0.034 ± 0.10‡‡

* measurements with CoV > 20 were excluded

** each interruption is within 15% of the mean value of 5 (inclusion criterion)

sd of the Rint-value of single interruptions of 2 measurements / mean

sd of the difference/√2/mean of the measurements

† 1-((sd difference between measurements/√2)^2 / sd of the measurements^2))

Additional information on these studies					
	time interval	**n**	**age**	**population**	**other**
Short term reproducibility					
Current data	30 minutes	38	2-18 years	severe generalized	-
Arets '03	consecutive	212	2-4 years	healthy and asthmatic	-
Beelen '03	20-30 minutes	32	3-6 years	Healthy	field conditions
Chan '03*	after placebo	85	2-10 years	healthy, cough and wheeze	-
Child '01	consecutive	45	4-7 years	healthy and asthmatic	mouthpiece
	"	43		"	mask
Lombardi '01	1 minute	69	4.7 ± 0.8	Healthy	-
Nielsen '01 '00	?	<67	2-5 years	healthy and asthmatic	used for revers. calculat.
Klug '00	consecutive	22	2-6 years	asthmatic	observer A
	"			"	observer B
Bridge '99	30 seconds	79	2-3 years	Healthy	-
	"	104	3-4 years	"	-
	"	88	4-5 years	"	-
Oswald-mammoser '97	15 minutes	36	10.8 ±3.5	Healthy	-
	"	96	8.2±3.4	Asthmatic	-
Long term reproducibility					
Current data	2 weeks	"	"	cerebral palsy	-
Beelen '03	median 38 days	15	3-6 years	"	field conditions
	"	"	"	"	standardized conditions
Chan '03	3 weeks (2-20)	18		Healthy	-
	"	28		Coughers	-
	"	39		Wheezers	-
Lombardi '01	2.5 (1.5) months	26	4.3 ± 0.8	"	-

[††] ±1-sided lower 95% CL, calculated form 1 way anova[‡] variance (2sd) of the mean difference between pairs of measurements

[°] calculated based on reported values

[°°] estimated from Bland and Altman plot

[$] the difference between paired baseline measurements divided by √2

[$$] sd of the differences between the 2 measurements obtained in all subjects divided by √2

REFERENCES

1. Palisano, R., et al., Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol, 1997. 39(4): p. 214-23.
2. Gerver, W. and R. de Bruin, Paediatric Morphometrics: a reference manual. 1996, Utrecht, The Netherlands.
3. Chinn, S., Statistics in respiratory medicine. 2. Repeatability and method comparison. Thorax, 1991. 46(6): p. 454-6.
4. Bland, J.M. and D.G. Altman, Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1986. 1(8476): p. 307-10.
5. Arets, H.G., H.J. Brackel, and C.K. van der Ent, Applicability of interrupter resistance measurements using the MicroRint in daily practice. Respir Med, 2003. 97(4): p. 366-74.
6. Beydon, N., et al., Pulmonary function tests in preschool children with cystic fibrosis. Am J Respir Crit Care Med, 2002. 166(8): p. 1099-104.
7. Rubin, D.B. and N. Schenker, Multiple imputation in health-care databases: an overview and some applications. Stat Med, 1991. 10(4): p. 585-98.
8. Merkus, P.J., et al., Measurements of interrupter resistance: reference values for children 3-13 yrs of age. Eur Respir J, 2002. 20(4): p. 907-11.
9. Gappa, M., S.C. Ranganathan, and J. Stocks, Lung function testing in infants with cystic fibrosis: lessons from the past and future directions. Pediatr Pulmonol, 2001. 32(3): p. 228-45.
10. Lombardi, E., et al., Reference values of interrupter respiratory resistance in healthy preschool white children. Thorax, 2001. 56(9): p. 691-5.
11. Beydon, N., et al., Pre/postbronchodilator interrupter resistance values in healthy young children. Am J Respir Crit Care Med, 2002. 165(10): p. 1388-94.
12. McKenzie, S.A., et al., Airway resistance measured by the interrupter technique: normative data for 2-10 year olds of three ethnicities. Arch Dis Child, 2002. 87(3): p. 248-51.
13. Merkus, P.J., et al., Interrupter resistance in preschool children: measurement characteristics and reference values. Am J Respir Crit Care Med, 2001. 163(6): p. 1350-5.

Chapter 6

Prevalence and Clinical Presentation of Constipation in Children with Severe Generalized Cerebral Palsy

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ABSTRACT

Objective Constipation is a common problem in neurologically impaired children. Nevertheless, studies concerning prevalence and clinical characteristics of constipation in this population are scarce. This study aimed to determine the prevalence and clinical presentation of constipation in neurologically impaired children.

Methods This cross-sectional study was done in a representative populationbased cohort study, as part of a large-scale study on risk factors of pneumonia and on nutritional state in neurologically impaired children. A symptom-based definition of constipation was formulated and applied. Between 2002 and 2004, the researchers visited 152 children with severe generalized cerebral palsy attending day-care centres. All participating children had a combination of moderate to profound intellectual disability (ID) and a profound motor disability, mean age was 9.5±4.5 years, 53% boys, 52% had profound ID, 3.6% could say yes and no.

Results The prevalence of constipation was 22%. 54% of the children used laxatives, which was successful in 64% of the children. Six percent of the children without laxatives were constipated. Water intake was deficient in 86.5% of the children and fibre intake in 53%. No causal factors of constipation were found. Trends were observed between constipation and BMI (on average one higher in constipated, p=0.102) and with level of intellectual disability (less constipation in profoundly than in moderately-severely disabled, p=0.084), however these were not statistically significant. In addition, defecation frequency was not significant correlated to insufficient fibre intake, water intake, BMI (p=0.056) or age.

Discussion The formulated symptom-based definition was well applicable, a validation should be recommended, before common application in daily practice. The found prevalence was low compared to the prevalence in non-disabled children (0.3-29%) [20], however, a high percentage of the children were already treated. Results indicated that laxative was not effective in all children, stressing the importance of regular treatment re-evaluation. We were unable to establish causal effects of life style factors, this could indicate that neurological factors are causally more important. There are however many other explanations. As long as the etiology remains unclear, possible influencing life-style factors should be managed properly. In our view, consensus on defining constipation in children with severe neurological impairments would be an important step in the improvement of health care for these children.

INTRODUCTION

Children with severe generalized cerebral palsy, often experience comorbidity, amongst which constipation is common [1-4]. In these children constipation is likely to be caused by both neurological factors such as muscular tone and innervation problems [5-10] and life-style factors such as dietary fibre intake, immobility and drug side-effects [9,11-19]. Prevalence estimates widely range from 26% to 62% [1,2,8,18], depending on the definition used for constipation, the diagnostic method and patient selection. However, population based data are lacking. In the general pediatric population, the prevalence of constipation is 0.3-37% [20-23].

The aim of the present study is to determine the prevalence of constipation in a representative group of children with severe generalized cerebral palsy, without intervening in treatment or diet. Since this study is performed in care facilities, the diagnosis was based on symptoms and defecation patterns rather than on hospital-based diagnostic criteria. We will also study the correlation between constipation and medication, diet, personal and demographic factors and evaluate the clinical presentation of constipation and current laxative use.

Patients and methods

Study design

This cross sectional study on constipation was part of a large cohort study (n=194) on risk factors of recurrent pneumonias and malnutrition. That study included a representative sample of the Dutch population of children with severe generalized cerebral palsy. All diagnostic measurements of this study were carried out at specialized care facilities (day-care centres and schools), in order to avoid visits to hospital. Ethical approval was obtained from the national ethics committee (Central Committee on Research Involving Human Subjects). Prior to the study, parents or legal guardians had given informed consent. The design and characteristics of the study sample have been described in detail elsewhere [24].

Study population

All children were 2 – 18 years of age at the time of inclusion in the cohort study and had a combination of moderate to profound intellectual disabilities (ID) and a severe motor disability. This was defined by an IQ below 55 (or estimated by dividing the developmental age by the calendar age times 100) and a hypertonic or hypotonic generalized cerebral palsy or a developmental delay, maximally allowing a child to crawl.

Definition of constipation

We formulated a specific symptom-based definition for constipation, since for neurologically impaired children no commonly accepted and feasible definition exists. Previous studies in neurologically impaired children either diagnosed constipation based on the defecation frequency alone [1,18], or on a altered need for laxatives. The present definition was based on the definitions of the PACCT group [25], the pediatric Rome II criteria [26] and a definition used in intellectually disabled adults [27]:

large stools palpable on abdominal examination (scybala)
and/or
the occurrence of two or more of the following characteristics, during the 2-week study period:
- scybalous, pebble-like, hard stools in the majority of defecations
- defecation frequency less than three times per week
- laxatives use or manual disimpaction

Data collection

The diagnosis constipation was based on data gathered from a two-week diary evaluating defecation patterns and laxative use followed by a limited physical examination. During the study period of two weeks no alterations in diet were allowed and laxative-use was continued as always. The presence or absence of large palpable stools (scybala) was assessed by abdominal palpation during the physical examination. A digital rectal examination to study fecal impaction had to be omitted, since the ethics committee considered it too invasive.

In the two-week defecation diary, parents and carers registered for every single defecation its shape, consistency and amount, use of a diaper or toilet, and observable pain during defecation. In addition, laxative use during that period was registered. Oral laxatives were categorized as polyethylene glycol (Transipeg®, Movicolon®), disaccharides (Lactulose and Lactitol (Duphalac® / Legendal® and Imporal®)) and other oral laxatives (Magnesiumoxide, Bisacodyl, Natriumpicosulphate, Senna granules and probiotics).

Dietary intake was assessed using a one-week diary (concomitant with the defecation-diary). Parents and carers were carefully instructed to estimate the amount a child really consumed (both orally and per tube) and not the amount that was offered to the child.

Children's basic characteristics (age, gender, GMFCS-score [28], level intellectual disability and living situation) and regular drug use were inquired per questionnaire

and medical files in the beginning of the cohort study. Body Mass Index (BMI) was calculated from length and weight. Relevant potential side-effects such as diarrhea or constipation were registered for each individual type of medication that the children used, based on an incidence rate in the general population of 1% or more (Dutch Pharmacotherapeutic compass online; *http://www.cvzcompassen.nl/fk*).

To improve the accuracy of the recordings, great effort was put in informing and instructing parents and care-givers. Half-way during the diary period, parents were contacted by phone in order to check their progress and, if necessary, to answer their questions.

Analysis

From the defecation diaries we calculated defecation frequency per week, percentages of defecations with hard stools and pebble like stools.

From the defecation diary, 'hard or pebble like stool' was scored as present "in a majority of stools" when one or both characteristics were present in 25% of the recorded stools or more. Using the previously described definition, constipation is based on the presence of 4 separate items. When data on one of the items was missing, the item was scored 'not present'. Since this might have underestimated the population prevalence, an additional analysis was done with only cases with complete data. When children did not use diapers they were scored as toilet trained.

Dietary intake was analyzed by a dietitian, using specific software ("De Eetmeter", 2002, 'Voedingscentrum', The Hague and the 'Consumentenbond'). Per child, daily average intakes of fibre (gr) and water (ml) were calculated, since these nutrients are reported to influence stool frequency [5,12,14,27,29-32]. Minimal daily recommended fibre intake (age+5 gr) [33] and water intake [34] were calculated for each child individually and subtracted from mean daily intake. In addition, tube feeding was scored.

Statistics

Correlations between constipation and GMFCS-score, level of intellectual disability, living at home, 'water intake requirement met' and polyethylene glycol use were calculated using Chi-2 tests. The relation between constipation and 'water intake minus required', 'fibre intake minus required' and BMI was calculated using a one-way ANOVA. The correlation between defecation frequency and 'water intake minus required', 'fibre intake minus required', BMI and age was calculated using

linear regression. Square root transformation was used to obtain normal distribution of the residuals. Missing variables were regarded as randomly missing, unless reported otherwise. Calculations were performed using SPSS 12.0.1 (SPSS Inc. Chicago, Illinois, USA). The 95% confidence interval of constipation prevalence was calculated using Stata (SE 8.2, StataCorp LP, Collage Station, USA). A p-value of below 0.05 was considered statistically significant.

RESULTS

From the 194 children in the original cohort, 11 children were lost to follow-up at the time of this cross-sectional study on constipation. For 31 children no defecation diary was completed. Since in the present study the diary is the primary measure for defining constipation, these children were not included in the analysis. The characteristics of the remaining 152 children are shown in Table 1, and were comparable to those of the baseline cohort. In 135 cases, data on all items of the definition were available. Dietary intake diaries were not filled in sufficiently in 11 children (7%). A defecation diary consisted on average of 13.4 ± 2.2 days.

According to our definition, the prevalence of constipation was 22% (34/152 children) (95% CI was 15.8 - 29.0%), the prevalence was similar when only the complete cases were analyzed (22% (29 /135)). Constipation-related symptoms are presented in Table 2

In 64% (53/83) of the children who used laxatives, treatment was successful, since no other signs of constipation were present in these children. Six percent (4/69) of the children without laxative treatment, was constipated.

In the majority of children, recorded dietary intake of both fibre and water was poor (Table 3). Average fibre intake was nearly one gram below the required daily amount, but individual variation was considerable. 41% had a shortage of more than 6 gr fibre in daily intake, while 6 children had a diet without any fibre (tube feeding). However, no significant relation between fibre intake and constipation was found.

Water intake was deficient in 86.5% of the children, and more than 500 ml short per day in 48% of all children.

No significant relationships were found between constipation and age, BMI, gender, GMFCS-level, ability to express yes and no, living situation, disability,

Table 1 Participants characteristics and representativeness

		cross-sectional study on constipation (n=152)	Total study (n=194)
Age (mean years ± sd)		9.5 ± 4.5	9.3 ± 4.3
Gender (% boys)		53.1	53.1
BMI (mean kg/m^2 ± sd)		16.0 ± 1.3	15.9 ± 3.1
GMFCS score V (%)		83.0	82.7
Intellectual Disability (%)	moderate	8.3	10.3
	severe	40.0	39.3
	profound	51.7	50.3
Can communicate "yes" and "no" (%)		23.0	20.6
Can verbally communicate "yes" and "no" (%)		3.6	3.1
Tube feeding (%)		33.1	35.1
Toilet trained (%)		4.0	unknown

GMFCS = Gross Motor Function Classification Scale, BMI = body mass index

Table 2 The occurrence of symptoms used in the definition of constipation

		Total study population (n=152)	constipation No (n=118)	Yes (n=34)
* large (abdominal) palpable stools (%)		5.3	0	23.5
defecation frequency (mean ± sd)		7.5±4.4	8.3±4.5	4.9±2.9
* frequency < 3 /week (%)		12.5	5.9	35.3
> 25% hard stools (%)		19.6	5.1	29.0
> 25% pebble-like stools (%)		20.5	14.2	42.4
* > 25% hard and/or pebble-like stools (%)		28.3	16.1	70.6
> 50 % hard stools (%)		10.1	5.1	29.0
> 50 % pebble-like stools (%)		8.2	7.1	12.1
> 50% hard and/or pebble-like stools (%)		14.6	8.8	35.5
* laxative use (%)	any	54.6	44.9	88.2
oral laxative use (%)	polyethylene glycol	13.2	14.4	8.8
	disaccharide	24.3	22.9	29.4
	other	7.9	5.1	17.6
rectal laxative use (%)		22.4	14.4	50.0
manual disimpaction (%)		9.2	8.5	11.8

* items in the used definition of constipation

Table 3 Daily dietary intake

			Total study population (n=152)	Constipation no (n=118)	yes (n=34)	*p*
water (ml)	intake	mean ml ± sd	1185±341	1186±330	1184±383	
	intake - requirement	mean ml ± sd	-441±393	-450±377	-413±456	*0.648*
	requirement met	%	13.5	12.8	15.6	*0.685*
fibre (g)	intake	mean g ± sd	13.8±6.2	13.4±6.0	15.1±6.5	
	intake - requirement	mean g ± sd	-0.76±7.01	-0.94±6.44	-0.12±8.7	*0.656*
	requirement met	%	46.8	46.8	46.9	

Minimal daily required water intake [34] and fibre intake [33] were subtracted from mean daily intake, relation with constipation using one-way anova. Percentage of children meeting these requirements, were tested to constipation using Chi-2.

Table 4 Possible influencing factors of constipation

		Total study population (n=152)	Constipation No (n=118)	Yes (n=34)	P
age	mean ± sd	9.5±4.5	9.3±4.4	10.3±4.6	
BMI	mean ± sd	16.0±1.3	15.8±3.1	16.8±3.2	0.102
gender	%boys	52.6	54.2	47.1	
GMFCS	%V	83	81.4	88.2	0.353
express yes-no	%	23	22.6	24.2	
speak yes-no	%	3.6	2.9	6.1	
living at home	%	80.3	81.4	76.5	0.528
intellectual disability	%mod-sev	48.3	44.1	63.0	
	%profound	51.7	55.9	37.0	0.084
tube fed	%	33.1	34.2	29.4	0.604
toilet trained	%	4	3.4	5.9	
medication use with possible side effect	constipation	43.6	39.8	55.2	0.147
	diarrhoea	38.5	43.2	24.1	0.068

BMI = body mass index, GMFCS = Gross Motor Function Classification Scale, P-value on constipation and BMI using one-way ANOVA, other p-values using Chi-2 testing

tube feeding, being toilet trained or side-effects of drugs. Trends were observed between constipation and BMI (on average one higher in constipated, p=0.102) and with level of intellectual disability (less constipation in profoundly than in moderately-severely disabled, p=0.084), however, these were not statistically significant (Table 4)

No significant correlation was observed between defecation frequency and insufficient fibre or water intake, BMI (p=0.056) or age (Fig. 1-4).

DISCUSSION

This first population-based study on constipation in children with severe generalized cerebral palsy demonstrates a 22% prevalence of constipation. Seventy percent (30/43) of the constipated children already used laxatives. Of the overall study population 55% used laxatives, of which 64% were treated successfully since no other signs of constipation were present. Dietary intake of water and fibre were below the required standards in 86.5% and 53.2% respectively. However, no causal factors for constipation or stool frequency could be demonstrated in this study.

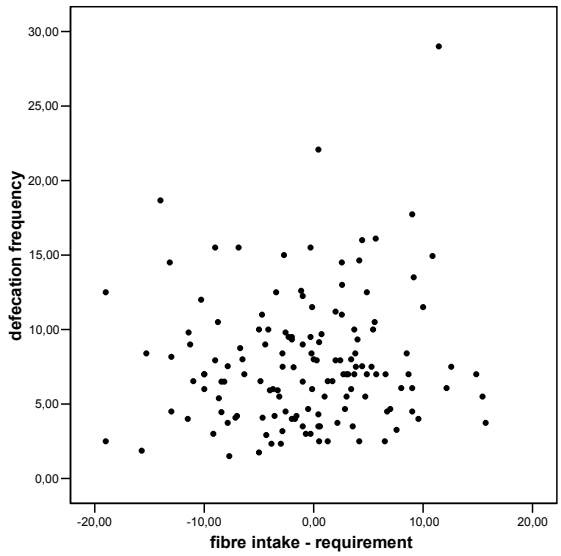


Figure 1 Correlation between defecation frequency and adjusted fiber intake
Figure 1 shows a scatter plot of the correlation between defecation frequency on (vertical axis) and adjusted fibre (fibre intake – requirement) (horizontal axis). The corresponding correlation coefficient was 0.085, with a p-value of 0.316.

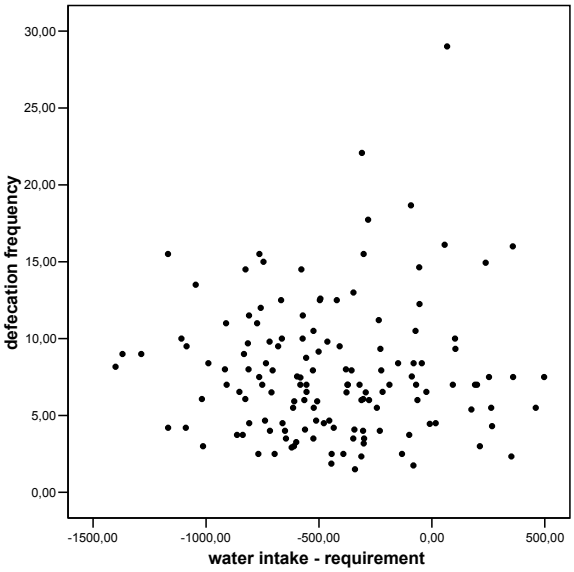


Figure 2 Correlation between defecation frequency and adjusted water intake
Figure 2 shows a scatter plot of the correlation between defecation frequency on (vertical axis) and adjusted water (water intake – requirement) (horizontal axis). The corresponding correlation coefficient was 0.020, with a p-value of 0.813.

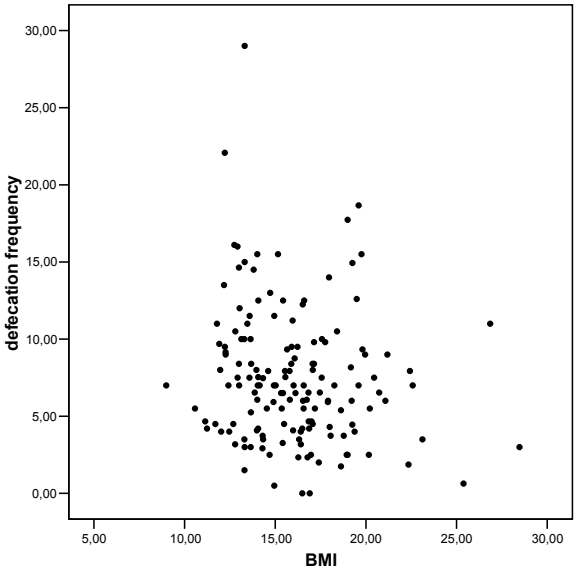


Figure 3 Correlation between defecation frequency and BMI
Figure 3 shows a scatter plot of the correlation between defecation frequency on (vertical axis) and BMI (horizontal axis). The corresponding correlation coefficient was -0.160 , with a p-value of 0.056.

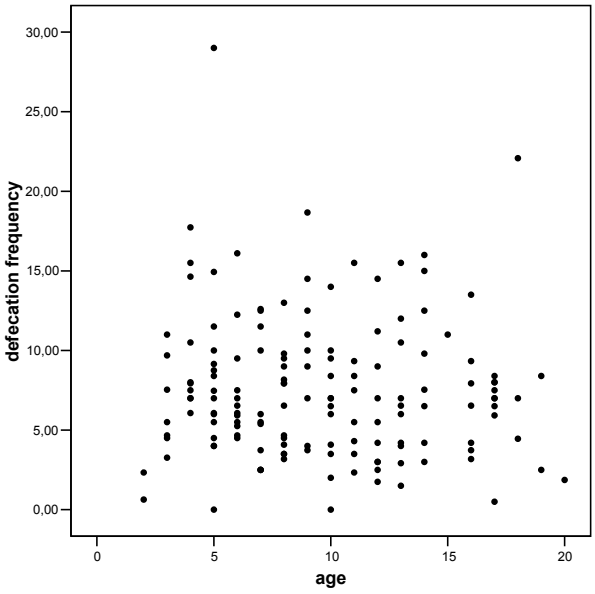


Figure 4 Correlation between defecation frequency and age
Figure 3 shows a scatter plot of the correlation between defecation frequency on (vertical axis) and age (horizontal axis). The corresponding correlation coefficient was -0.048 , with a p-value of 0.556.

Defining constipation

For the non-disabled population consensus definitions on constipation exist. These are based on clinical sighs and symptoms since constipation is a symptom rather than a disease. Therefore, a gold-standard method to assess constipation does not exist. Total and segmental transit time can however be assessed using radio-opaque markers. This can be useful since colonic transit time is correlated to sympoms of constipation in non-disabled children [20].However approximately 50 percent of constipated non-disabled children have transit times within the normal range [20,35]. A previous study in children with cerebral palsy showed that colon transit time was significantly related to defecation frequency [18]. However, 61% of the children with a normal defecation frequency, had delayed transit times in at least one segment [18]. Other studies showed that segmental transit times are delayed in all children with severe generalized cerebral palsy who had decreased stool frequency [8,18,36]. In 90% of the children this delay was situated in the proximal segment with or without rectal transit delay and in 10% at the sigmoid only [18]. Other studies situated the delay in 20 -52% of the children at the left colon, 36-56% at the left colon and rectum and 3-25% at rectum only [8,36].

In our study we formulated and used a symptom-based definition. Not only does this resemble the normal diagnostic procedure best, it can also be performed on-site. The aim of our study was to determine a population-prevalence of constipation. For that purpose it was necessary to include a representative cohort. By performing all diagnostics at the day-care centres and specialized schools, hospital visits were avoided, therewith increasing the inclusion rate. In addition, symptom-based diagnosing also avoids radiation exposure and fulfils the need for a specific symptom-based definition for neurologically impaired children.

Previous studies on constipation using symptom-based diagnosis in comparable populations have compared defecation frequency or laxative use between groups or following an intervention [5,12,14,31], based their diagnosis on defecation frequency only [1,8,18,36], or used a combination of these [27]. However, symptom-based definitions for this population have never been based on the pediatric Rome criteria for functional gastrointestinal disorders or the PACCT-definition.

Defining constipation based on symptoms is difficult in neurologically impaired children because definitions for non-disabled children [25,26] include items that can not be used, such as 'with-holding behaviours' and 'no evidence of structural disease'. In addition, faecal incontinence can not be assessed since most disabled children use diapers.

The definition we have developed is a combination of the applicable items of the definitions for non-disabled children combined with laxative use. We chose a two-week observation period in accordance with the pediatric Rome II criteria, which should be sufficient due to the usually chronic nature of constipation in these children. For carers this period proved feasible: diaries were kept 13.4 days on average and were filled out properly by most parents. Some concerns could be raised on judging stool consistency in diapers (which nearly all children used), however, most parents had no difficulty to distinguish this.

Overall, we conclude that the developed symptom-based definition is feasible in daily practice. However, before using it in practice, we would recommend adding faecal impaction to the definition, in accordance with the PACCT-definition. This established sign of constipation is even more important in children with severe generalized cerebral palsy since it is one of the few observable symptoms. We would suggest the following:

Large stools in the rectum or palpable on abdominal examination
and/or
the occurrence of two or more of the following characteristics, during the 2-week study period:

- scybalous, pebble-like, hard stools for a majority of stools
- defecation frequency less than three times per week
- laxative use or manual disimpaction

Before common application, this definition should however be validated using colon transit time. In our view, consensus on defining constipation in children with severe neurological impairments would be an important step in the improvement of health care for these children.

The prevalence of constipation

This study indicates that 22% of the children with severe generalized cerebral palsy in the Netherlands are constipated, regardless laxative use. Compared to the prevalence in non-disabled children (0.3-29%) [20], the problem appears to be limited. However, if the percentage of children that already used laxatives was added to that of non-diagnosed constipation, this study would suggest a prevalence rate of 57% (87/152).

Previous studies in disabled children found constipation in 26-90% of children [1,2,8,18,36]. This large interval can be explained in many different ways. Firstly, by the chosen study population. When studying severely disabled children from a gastroentrology out-patient clinic, the prevalence of constipation will be overestimated due to selection bias of children with symptoms. In addition, the applied definition of constipation is of influence. Would we have defined constipation as only a defecation frequency < 3 /week, the prevalence would be 12,5%.

Etiology and contributing factors

In children with neurological impairments constipation etiology is believed to be due to a combination of neurological and life style factors. Aspects of this neurological pathway include: decreased neuromuscular tone of the gastrointestinal tract [5], defect in gut innervation [6], disruption of neural modulation due to central structure damage [7-9], lack of conscious urge to defecate [10] and motor paralysis of the abdominal and perineal muscles [10].

In addition, life style factors can contribute to a reduced defecation frequency. Insufficient dietary fibre intake for example, is a generally accepted causal fac-

tor for the pathogenesis of constipation in disabled [27,29,30,37,38] and non-disabled [13] children. In children with severe generalized cerebral palsy, feeding problems are common and therefore dietary intake is often problematic. In our study, nearly 53% of the children had an inadequate fibre intake.

Previous studies on the effects of increasing dietary fibre in severely handicapped children showed inconsistent results. A decrease in laxative use [12,14] and an improved stool frequency [14,32] were demonstrated, although others only showed improved consistency and stool size [31]. Two other studies showed no relation with colon transit time [14,18]. Whereas others found no relationship between dietary fibre and constipation [18,39,40], which is in accordance with our results. An other well accepted cause of constipation in handicapped is insufficient fluid intake [5,27,29,30], which is described as part of treatment as well [2,38]. A study in non-disabled adults showed that fluid deprivation decreases stool frequency and stool weight [16]. In the present study, nearly 87% had an inadequate intake of water. However, like two previous studies [18,40], we found no relationship between constipation and fluid intake.

Most likely the combination between both fibre and fluid intake is important. A study in adults with chronic functional constipation showed that the effect of high fibre intake on stool frequency was enhanced by increasing fluid intake as well.

An other possible influencing life style factor is immobility [9,18] which we did not study. The studied GMFCS-score for motor impairment is a crude measure and therefore not a good indicator. Also drug side effects [9], such as anticonvulsants and antispasmodics [19] are known to affect constipation. In our population multi-drug use was common, however no relation with constipation was found.

A trend was shown towards a higher prevalence of constipation in children with milder intellectual disability. This is most likely a confounding effect due to related motor impairment, prescribed drugs, dietary intake or tube feeding.

Since we were unable to establish causal effects of these life style factors, this could indicate that neurological factors are causally more important. There are however many other explanations. The definition might be inadequate since proper validation is lacking, the group of constipated children was relatively small for a proper risk factor analysis, in a multi-factorial etiology the use of laxatives might have clouded the causal relations. As long as the etiology remains unclear, possible influencing life-style factors should be managed properly.

Treatment and recommendations

Laxatives were used in 55% of the children, of which 64% had no observable signs of constipation and therefore we conclude that in those children treatment was successful. For the remaining 36%, laxative treatment was not adequate, indicating either insufficient dosage, inadequate usage or unresponsiveness to treatment. Treatment might have been indicated in 6% (4/69) of the children who did not receive laxatives.

To our clinical experience, physicians tend to be prudent in prescribing laxatives in these children. Many articles have been published, speculating on the best treatment of these children, however, the effects are barely studied. Most authors argue that treatment should be conform the standards for non-disabled children [6,29].However, it has been previously suggested that constipation in neurologically impaired children is often less responsive to treatment [22,30]. Our study showed, that many children were not treated with polyethylene glycol, although these are nowadays often considered as the laxative of first choice in pediatric constipation[41]. To develop an optimal treatment of constipation in children with severe generalized cerebral palsy, intention studies should be performed

Besides the prescription of effective laxatives, proper attention should also be paid to a treatment plan regarding not only effectiveness but also feasibility and clarity for the carers. Since many carers are involved with the care for one child, and it is difficult to maintain a proper overview of the defecation pattern and the treatment plan.

Furthermore, it is important that constipation and the effectiveness of prescribed treatment is regularly re-evaluated. A validated symptom-based definition of constipation could offer support for these evaluations.

However, the ultimate goal should be prevention of constipation. Although our study failed to demonstrate a significant contribution of life style factors to constipation, optimizing mobility, fibre and water intake should be promoted.

IN CONCLUSION

This study indicates that 22% of the children with severe generalized cerebral palsy in the Netherlands are constipated, regardless the use of laxatives. Interpretation of this prevalence rate is difficult since the diagnostic value of our definition has not been established yet. Still, this is the first study on symptoms and signs regarding

constipation in a large, representative population of children with severe generalized cerebral palsy. Due to the specified definition and due to the publication of the separate symptoms, this study is not only of great epidemiologic value, but might contribute to future diagnosing and treatment evaluation of neurologically impaired children.

No relation between life-style factors and constipation or defecation frequency was shown, therefore many questions on etiology and prevention remain. Dietary intake of water and fibres was poor in many children. Also many constipated children use laxatives without it resolving their defecation problems. The effect of laxatives should therefore be monitored properly. More importantly care-givers should be instructed properly on how to adjust dosages when necessary.

For the future it is important to reach consensus on a symptom-based definition of constipation in neurologically impaired children. Ideally this would be based upon a validation study of the proposed definition using colonic transit times. Also studies on primary causes of constipation, for example studying gastro-intestinal motility problems in general, could learn us more on the etiology and therewith on prevention and treatment of constipation in children with severe generalized cerebral palsy.

REFERENCES

1. Sullivan, P.B., et al., Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. Dev Med Child Neurol, 2000. 42(10): p. 674-80.
2. Feldkamp, M., et al., [Vegetative disorders in children with cerebral palsy. Results of an inquiry of parents] Vegetative Storungen bei zerebralparetischen Kindern. Ergebnisse einer Elternbefragung. Monatsschr Kinderheilkd, 1976. 124(8): p. 583-9.
3. Klein, H., Constipation and fecal impaction. Med Clin North Am, 1982. 66(5): p. 1135-41.
4. Gonzalez, L., C.M. Nazario, and M.J. Gonzalez, Nutrition-related problems of pediatric patients with neuromuscular disorders. P R Health Sci J, 2000. 19(1): p. 35-8.
5. Frame, P.S., et al., Use of colchicine to treat severe constipation in developmentally disabled patients. J Am Board Fam Pract, 1998. 11(5): p. 341-6.
6. Sullivan, P.B., Gastrointestinal problems in the neurologically impaired child. Baillieres Clin Gastroenterol, 1997. 11(3): p. 529-46.
7. Johanson, J.F., et al., Association of constipation with neurologic diseases. Dig Dis Sci, 1992. 37(2): p. 179-86.
8. Staiano, A. and E. Del Giudice, Colonic transit and anorectal manometry in children with severe brain damage. Pediatrics, 1994. 94(2 Pt 1): p. 169-73.
9. Del Giudice, E., Cerebral palsy and gut functions. J Pediatr Gastroenterol Nutr, 1997. 25 Suppl 1: p. S22-3.
10. Staiano, A., et al., Cisapride in neurologically impaired children with chronic constipation. Dig Dis Sci, 1996. 41(5): p. 870-4.
11. Burkitt, D.P., A.R. Walker, and N.S. Painter, Dietary fiber and disease. Jama, 1974. 229(8): p. 1068-74.
12. Tse, P.W., et al., Dietary fibre intake and constipation in children with severe developmental disabilities. J Paediatr Child Health, 2000. 36(3): p. 236-9.
13. Morais, M.B., et al., Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr, 1999. 29(2): p. 132-5.
14. Staiano, A., et al., Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr, 2000. 136(1): p. 41-5.
15. Anti, M., et al., Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology, 1998. 45(21): p. 727-32.
16. Klauser, A.G., et al., Low fluid intake lowers stool output in healthy male volunteers. Z Gastroenterol, 1990. 28(11): p. 606-9.
17. Benson, J.A., Jr., Simple chronic constipation: pathophysiology and management. Postgrad Med, 1975. 57(1): p. 55-60.
18. Park, E.S., et al., Colonic transit time and constipation in children with spastic cerebral palsy. Arch Phys Med Rehabil, 2004. 85(3): p. 453-6.
19. Talley, N.J., et al., Risk factors for chronic constipation based on a general practice sample. Am J Gastroenterol, 2003. 98(5): p. 1107-11.
20. Benninga, M.A., W.P. Voskuijl, and J.A. Taminiau, Childhood constipation: is there new light in the tunnel? J Pediatr Gastroenterol Nutr, 2004. 39(5): p. 448-64.

21. Miele, E., et al., Functional gastrointestinal disorders in children: an Italian prospective survey. Pediatrics, 2004. 114(1): p. 73-8.

22. Loening-Baucke, V., Constipation in children. N Engl J Med, 1998. 339(16): p. 1155-6.

23. de Araujo Sant'Anna, A.M. and A.C. Calcado, Constipation in school-aged children at public schools in Rio de Janeiro, Brazil. J Pediatr Gastroenterol Nutr, 1999. 29(2): p. 190-3.

24. Veugelers, R., et al., 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): p. 25.

25. Benninga, M., et al., The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. J Pediatr Gastroenterol Nutr, 2005. 40(3): p. 273-5.

26. Rasquin-Weber, A., et al., Childhood functional gastrointestinal disorders. Gut, 1999. 45 Suppl 2: p. II60-8.

27. Bohmer, C.J., et al., The prevalence of constipation in institutionalized people with intellectual disability. J Intellect Disabil Res, 2001. 45(Pt 3): p. 212-8.

28. Palisano, R.J., et al., Validation of a model of gross motor function for children with cerebral palsy. Phys Ther, 2000. 80(10): p. 974-85.

29. Elawad, M.A. and P.B. Sullivan, Management of constipation in children with disabilities. Dev Med Child Neurol, 2001. 43(12): p. 829-32.

30. Chong, S.K., Gastrointestinal problems in the handicapped child. Curr Opin Pediatr, 2001. 13(5): p. 441-6.

31. Fischer, M., et al., The effects of dietary fibre in a liquid diet on bowel function of mentally retarded individuals. J Ment Defic Res, 1985. 29 (Pt 4): p. 373-81.

32. Liebl, B.H., et al., Dietary fiber and long-term large bowel response in enterally nourished nonambulatory profoundly retarded youth. JPEN J Parenter Enteral Nutr, 1990. 14(4): p. 371-5.

33. Williams, C.L., M. Bollella, and E.L. Wynder, A new recommendation for dietary fiber in childhood. Pediatrics, 1995. 96(5 Pt 2): p. 985-8.

34. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. American Society for Parenteral and Enteral Nutrition. JPEN J Parenter Enteral Nutr, 1993. 17(4 Suppl): p. 1SA-52SA.

35. de Lorijn, F., et al., Prognosis of constipation: clinical factors and colonic transit time. Arch Dis Child, 2004. 89(8): p. 723-7.

36. Del Giudice, E., et al., Gastrointestinal manifestations in children with cerebral palsy. Brain Dev, 1999. 21(5): p. 307-11.

37. Laidler, J., Jr., Nutritional assessment of common problems found among the developmentally disabled. Ment Retard, 1976. 14(4): p. 24-8.

38. Bishop, P.R. and M.J. Nowicki, Defecation disorders in the neurologically impaired child. Pediatr Ann, 1999. 28(5): p. 322-9.

39. Mooren, G.C., et al., Het verband tussen inname van voedingsvezels en chronische obstipatie bij kinderen. Ned Tijdschr Geneeskd, 1996. 140(41): p. 2036-9.

40. Tolia, V., J. Ventimiglia, and L. Kuhns, Gastrointestinal tolerance of a pediatric fiber formula in developmentally disabled children. J Am Coll Nutr, 1997. 16(3): p. 224-8.

41. Voskuijl, W., et al., PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. Gut, 2004. 53(11): p. 1590-4.

Chapter 7

General Discussion

Non-orthopedic comorbidity in children with severe motor and intellectual disabilities (SMID) has seldom been studied, and population-based data have been lacking entirely. Healthcare professionals are often uncertain about the actions needed to prevent and treat comorbidity in these children. Moreover, as long as valid research data are not available, development of evidence-based guidelines on the prevention and treatment of co-morbid disorders is not possible. After having performed a population-based study, it is easier for our research group to understand why such data are lacking, i.e. since this type of research in these children is far from easy. Our population-based study in children with severe generalized cerebral palsy has, however, not only provided a lot of data but has also resulted in much practical experience, which future researchers studying this complex population may benefit from.

This chapter consists of three main sections:

1 "Reflections on study results" places the results of this study within a time perspective, and addresses the practical value of the diagnostic methods used.
2 "Considerations for future research", addresses decisions to be made when preparing a study among children with SMID`, concerning study design, measurement setting, and diagnostic methods.
3 "Recommendations for future research" are presented and discussed.

Reflections on study results

The chapters of this thesis addresses different topics, which are all related to one major issue: comorbidity in children with SMID. The epidemiologic study described in this thesis is one of the first steps towards compiling guidelines on the prevention and treatment of these co-morbidities; however, many more steps need to be taken. Historically, answers to clinical questions are obtained through studies with increasing scientific value.

In most medical specialties, these steps were taken many decades ago, resulting in highly sophisticated research and guideline development. However, in Intellectual Disability Medicine, research is relatively new or even just starting. Most of the literature in this field consists of case reports, retrospective studies, clinical observational studies in small selected groups, and uncontrolled intervention studies, all resulting in relevant preliminary information and ideas, but not in robust scientific evidence.

However, well-designed epidemiological studies are needed to validly identify the size of a problem and risk groups. Subsequently, well-designed intervention studies should be performed, preferably with a double-blind randomized-con-

trolled design. Based on (meta-analysis of) such studies, practice guidelines may then be developed.

Value of the diagnostic methods in practice

Most of the diagnostic methods used in the present study are not 'gold standard' methods. Such methods are often not feasible in children with SMID because their motor and intellectual disabilities prevent them from meeting the required level of cooperation. Furthermore, ethics committees stipulate that in persons unable to give informed consent, the diagnostic methods must be non-invasive unless the necessity of such a method is incontrovertible.

In addition, the present study was performed on-site (i.e. not in hospital) requiring that all diagnostic methods be ambulatory available.

Bioelectrical Impedance Assessment (BIA)

Nutritional assessment is important in children with SMID, since nutritional status is easily compromised due to many concomitant factors such as: dysphagia, altered energy needs, gastro-oesophageal reflux, constipation, prolonged feeding times and feeding dependency. A reference standard method for assessment of nutritional state is available (deuterium dilution technique); however, this method is laborious and very expensive. Therefore, we studied Bioelectrical Impedance Assessment (BIA) as a possible easily applicable and reliable substitute. We have demonstrated that BIA is a feasible method in most of these children, and that the percentage body fat calculated with BIA was significantly related to BMI values. However, some concerns remain about the fluctuating measurement values and the high resistance (Rz) values. Our research team has already started a validation study to compare the outcome of BIA with that of the deuterium dilution technique, and to develop population-specific equations to calculate percentages of body fat and total body water. Furthermore reproducibility, and the additive value to standard nutritional parameters (such as BMI) needs to be established. In conclusion, the first results of BIA in children with SMID were promising; nonetheless, the exact position of BIA in the diagnostic apparatus of nutritional assessment still needs to be established.

Interrupter technique

Pulmonary problems are a major cause of concern in children with SMID, causing considerable morbidity and mortality. However, no method that has been validated for disabled children was available to quantify pulmonary function in this population. We demonstrated that the interrupter technique is feasible in most of these children, and that reproducibility was similar to that of on-site measurements

in non-disabled children. It was possible to diagnose reversible airway obstruction using the interrupter technique. However, for many children the time interval used of 15 minutes between bronchodilator administration and the measurement to test its effect was not long enough to expectorate their mucus. This may have led to underdiagnosis of reversible airway resistance. Therefore, we suggest a time interval of at least 30 minutes between bronchodilator administration and reversibility testing in children with SMID.

Nevertheless, several aspects still need to be studied before clinical application can be recommended. Some concerns exist over the pressure curves used to estimate respiratory resistance. These frequently showed patterns that are seldom seen in non-disabled children, which might be explained by impaired sputum clearance or abnormal muscle tension.

Furthermore, each new diagnostic tool should be validated against a reference standard. Unfortunately, such a standard does not exist for pulmonary function in children with SMID. Measured respiratory resistance significantly declined with age, which makes these results plausible since similar results were found in non-disabled children.

To gain more insight into the diagnostic value of the interrupter technique, the outcome values should be related to clinical signs of pulmonary function. In an intervention study, applying for example aerosol or physical therapy, results can be analysed both on clinical signs and interrupter resistance. Although this would not be a high-quality validation, it could give an idea of the diagnostic value of this measurement. As long as no population-adjusted reference values exist, this tool is not yet suitable for the screening of pulmonary function, irrespective of its precision.

In the meantime, pulmonology specialists might apply this method in children with SMID for treatment evaluation, and reversibility testing. However, they should be aware of its limitations and use the results only as support; from our study it remains unclear whether the method is sensitive enough to detect small changes in pulmonary function in children with SMID.

Defining constipation

Constipation is common in children with SMID, and many of these children receive laxatives. For non-disabled children, international guidelines exist for the diagnosis of constipation, based on clinical signs. However, these are not applicable in children with SMID, and no specific consensus definition exists.

In the present study, we formulated and applied an adapted definition and the results show that it can be easily applied. According to this symptom-based definition, 22% of the children with SMID in the Netherlands were constipated (even though 55% used laxatives). Interpretation of this prevalence rate is difficult since the diagnostic value of our definition has not yet been established.

Because no relation was found between lifestyle factors and constipation or defecation frequency, many questions concerning etiology and prevention remain. Dietary intake of water and fibres was poor in many children. Also, because many constipated children used laxatives without resolution of their defecation problems, the effect of laxatives should be monitored properly. Care-givers should also receive appropriate instruction on how to adjust dosages when necessary.

We suggest that, in addition to the consensus definition used for non-disabled children, a consensus definition of constipation in children with SMID should be agreed upon. We recommend to use the definition employed in the present study, after adding "large stools in the rectum" to it:

Large stools in the rectum or palpable on abdominal examination and/or the occurrence of two or more of the following characteristics, during the 2-week study period:

- scybalous, pebble-like, hard stools for a majority of stools
- defecation frequency less than three times per week
- laxative use or manual disimpaction

Future studies could relate such a symptom-based definition to colonic transit times. Studies on the primary causes of constipation (e.g. gastro-intestinal motility problems in general) could also help to elucidate the etiology and thereby the prevention and treatment of constipation in children with SMID.

CONSIDERATIONS FOR FUTURE RESEARCH

Choice of study design and setting

In this population of severely handicapped children, many research questions still need to be addressed. Based on the particular research question to be studied, the following issues need to be considered: Is a representative population-based cohort necessary? Should the study be performed on-site or in hospital?

Population-based cohort

Some questions can only be addressed using a population-based cohort with a representative subset of a specific population. Examples of these are epidemiological studies to determine prevalence rates, and some studies investigating the feasibility of diagnostic methods. However, creating and maintaining a population-based cohort of children with SMID is complicated.

In general, including a representative subset of a population requires all individuals in a specified area to be invited to participate. When studying individuals with an intellectual disability this is complex since in most countries (including the Netherlands) no registry of disabled persons exists. There are many ways to locate and approach parents of children with SMID; for example, through hospitals, outpatient clinics, patient organisations, and providers of specialized intellectual disability or child rehabilitation services. For a representative cohort, only the latter two may be suitable since most children with SMID need specialized care. In the Netherlands, inclusion through specialized service providers is a time-consuming process. Firstly the management of each care centre has to decide whether or not to participate in the study, based on the judgement of local ethics committees, parent boards, and healthcare professionals at each centre. Only then can the informed consent procedure start. Thereafter, during the study period itself, all people involved need to be kept informed and motivated, which is complicated when there are frequent changes in staff. In addition, the more people involved, the more complicated the measurement logistics become.

Only for those studies not requiring a representative subset of a population, is it possible to include participants through one service provider or hospital, which makes the inclusion procedure less complicated. Table 1 lists the advantages and disadvantages of an inclusion procedure through specialized services versus hospitals.

Another aspect of a population-based cohort is that a high participation rate without selection bias is required in order to include a representative sample. This implies that participation should be as effortless as realistically possible. If not, only the most motivated parents and the parents who relate most to the topic of interest will participate, resulting in a selection bias including relatively more children with the comorbidity of interest.

A representative cohort requires the inclusion of children from different native backgrounds. As a result, difficulties can arise due to both language and cultural barriers. For example, in some non-western cultures it is uncommon to present

Table 1 Advantages and disadvantages of participant inclusion via intellectual disability service providers or hospitals.

Inclusion procedure through:	
Intellectual disability service providers	Hospital
population-based cohort	selected population
- epidemiologic research possible	- no epidemiologic studies possible
usually multi-centre	one location is often enough
- extra time and effort for participation	- one ethics procedure
- more people involved per child	- one procedure to approach parents
- several different inclusion procedures	- less people involved

all information in an extensive brochure, whereas in the Netherlands it is not only common practice but it is also obligatory according to the CCMO (Central Committee involving Human Subjects). In the Netherlands, these barriers are mostly encountered when approaching Turkish and Moroccan families; in order to include children from these families, we have translated all written information. However, all non-Dutch speakers preferred to have the questionnaires in the Dutch language and then asked their relatives to translate. In our experience, only a short introduction in several languages should be available, and this should then be offered together with the more extensive Dutch brochure. Such an introduction could be written or on a spoken compact disk, particularly if many parents are likely to be illiterate.

In conclusion, when a representative cohort is required to address the study questions many obstacles need to be overcome and the process of locating and approaching parents becomes more complex. Therefore, in all other cases we would recommend to recruit children via an outpatient clinic or hospital, or via only a few large care centres.

Should diagnostic measurements be performed on-site?

Depending on the research question and the inclusion procedure selected (see previous paragraph), the researchers have to decide at which location the measurements should be performed, i.e. in hospital or on-site (for example, at the day-care centre, school, or residential facility). Both options have advantages and disadvantages. Such decisions can be simplified when, for example methods

require a hospital setting (e.g. an X-ray), but sometimes decisions can be more difficult, as discussed below.

The informed consent procedure and diagnostic measurements are usually performed at the same location (hospital or care centre), but this is not always necessary.

A major advantage of performing measurements in hospital is the wider range of diagnostic options, since not all diagnostic methods are ambulatory available for on-site measurements. In addition, logistics tend to be less complicated, researchers invest less time in travelling, and the measuring conditions remain constant for each measurement. Another aspect in favour of performing measurements in hospital is the more positive attitude towards research (notwithstanding the positive attitude in a few care centres) and the relatively limited influence of the personal opinions of staff members. Physicians and nurses are more used to scientific research and can usually relate to the research questions more easily. Also, the relationship of physicians/nurses and the children is generally less emotionally involved than that of the personnel of day-care centres or residential facilities. In addition, parents need to be present during the measurements in hospital, whereas on-site the children are often accompanied by the personnel only. In contrast to the parents who gave informed consent, the on-site personnel did not and can, therefore, have a negative attitude towards the study; this may affect the participating children and consequently influence the feasibility of the measurements.

In contrast to hospital-based studies, a major advantage of performing measurements on-site is that children remain in a familiar setting, thus reducing the stress due to a more 'hostile' environment and therefore, the burden of participation. This may improve both the feasibility of the measurements and the participation rate. Apart from being in a familiar environment, on-site measurements allow the children to follow their own scheduled day programme (meals, naps, physiotherapy, diaper changes, swimming, etc). On the other hand, when performing a measurement on-site, parents and day-care personnel are likely to be more demanding about interference with one or more of these activities.

Another important advantage of on-site measurement is that children and parents do not need to travel to a hospital. For many children with SMID, travelling is tiring, not only due to a prolonged time in their wheelchair, but also due to additional and different stimuli and possible negative associations with the hospital setting itself. As a result, the feasibility of diagnostic tests performed in hospital might be reduced. In addition, when parents do not have to invest time and

money on transport, they are more likely to participate in the study thus increasing the inclusion rate. When a study requires the use of hospital-based diagnostics, it might be considered to combine study measurements with planned hospital visits of the child. One should consider whether the burden of a specialist visit or admission, together with the planned research, is bearable for the child.

When choosing a measurement setting for a study, it is important to realise that some people in principle oppose on-site measurements because they believe that the day-care should be a safe environment, which is undermined by performing study measurements on-site. This issue can often be resolved by choosing an appropriate room in the care centre that is not (or only occasionally) visited by the child. In our study we chose to leave this decision to the day-care staff.

For each intended study and each measurement the most appropriate measurement location should be chosen. No clear-cut recommendations can be given, but one should weigh all the advantages and disadvantages to make a well-considered choice. In case of hospital-based studies, always consider the option of combining study measurements with regular hospital visits. Table 2 summarises the advantages and disadvantages when choosing between hospital-based or on-site measurements. We are aware that we may seem to be presenting a 'black and white' picture, and many creative options are available to overcome certain difficulties (e.g. organising a mobile X-ray bus to avoid visiting the hospital). However, these solutions are often costly and time consuming for the researchers.

Selecting diagnostic methods

Research in children with SMID is also complicated by the limited choice in diagnostic methods. Regular pediatric methods are usually not validated for children with SMID, others are not feasible or adjustments have to be made, and for almost all methods reference values for this population are lacking. For the parameter of interest, if no diagnostic test is yet available for children with SMID, probably the best choice is a method validated for infants. Due to these circumstances, feasibility pilot studies are necessary. For this, extra time and funding should be available.

In research, not all methods that are used in practice can be applied. An example from our study is digital rectal examination. This procedure is part of any routine assessment of constipation. Especially in children with SMID, information on faecal impaction is important for the diagnosis of constipation, since signs such as

Table 2 Advantages and disadvantages of on-site and hospital-based measurements.

	Measurement location	
	On-site (day-care)	Hospital
Advantage		
	known 'safe' environment - improves feasibility	more diagnostic test options
		logistics less complicated
	no transport necessary - higher inclusion rate	researchers need to travel less - saves research time and expenses
	no fatigue/over-stimulation due to travel - improves feasibility	constant measuring conditions
		personnel involvement
	less interference with daily activities - goodwill	- more used to scientific research - professional distance towards child
Disadvantage		
	ambulatory methods - not always available / first choice	children and parents need to travel - less enrolment - reduced feasibility
	complex logistics - more people involved - demands schedule around daily activities - time to set up the measurement equipment	unknown setting or unpleasant associations - reduced feasibility
	varying measurement conditions	
	personnel involvement - large influence on feasibility - research participation often without their consent - often close relationship with child	

'with-holding behaviour' and 'faecal incontinence' can not be used. However, in the preparation for our study, the ethics committee concluded that this method was too invasive for research purposes only.

In our study, we chose methods that were ambulatory available and that were validated for infants or children. Although none of the methods used had been validated for use in children with SMID, these were the most appropriate methods available. Therefore the studies described in this thesis have resulted in a large amount of feasibility data.

RECOMMENDATIONS FOR FUTURE RESEARCH

In the Introduction of this thesis, we commented on the diversity of terms and abbreviations used for children with a combination of motor and intellectual disabilities in practice and in literature. Consensus on the terms and definitions used to describe these children and the different levels of disabilities would not only enhance comparability of study results, but could also be used for registration purposes. An example of a well-accepted disability level is the Gross Motor Function Classification Scale (GMFCS); however for the SMID population this scale does not differentiate sufficiently. In the present study population, almost all children scored level V, whereas their abilities differed greatly. Designing such a motor disability score for children with SMID is challenging; it should be easy to apply and include not only mobility, but also spasticity and muscle tone.

A national register for persons with disabilities could serve several purposes. It could provide prevalence data on disabilities and data on morbidity and mortality in children with SMID. Furthermore, approaches for future study participation could be improved by providing data on eligible children, and prior study participation. However, many questions need to be addressed regarding privacy legislations, perusal, management, updates and funding. Even though we believe that a national registry with access for scientific studies will offer major advantages, its realisation is unlikely. In the Netherlands, a general care registration system is likely to be realized in the near future (*Zorg Identificatie Nummer, ZIN*); however, the way the systems would keep track of disabilities and comorbidity remains unclear.

We also recommend the formation of collaborations between care centres in order to review research proposals. For this purpose a review committee should be

formed. Together they can decide upon participation to the proposed study prior to the informed consent procedure for parents and children. Nowadays, it is still uncommon for many care centres to cooperate in, and review medical research, and approval guidelines are generally lacking. All these individual procedures are time consuming for both the research group and the care centres involved.

For the individual centres a review procedure usually includes management, parent boards, ethics committees, care personnel and (para)medical staff. In order to evaluate whether the study proposal is realistic, clinical relevant and scientifically well-designed, a collaborative review committee could also include a research methodologist, specialized physician, and a paramedical specialist when appropriate.

Once a collaborative review committee approves a research proposal, the informed consent procedure (from parents) could be started in the included care centres. This will save time and facilitate appropriate judgement of the proposal. Such collaboration will only function properly when the local management boards, parents and ethics committees feel they are represented by this committee, otherwise it might become yet another obstacle.

Another recommendation concerns the information given to parents and day-care personnel or nursing staff. The success of a study depends on the level of their cooperation and motivation; they should be well-informed prior to the study. We recommend the use of information brochures as well as personal presentation meetings. During the study those involved should be frequently informed about the progress and preliminary results. Use every means necessary to keep them involved, such as newsletters, posters, small lectures on relevant topics etcetera.

When performing on-site measurements, especially in multi-centre studies, the logistics are complicated. In these studies, measurement planning is more time consuming than is often acknowledged. Logistics concern planning the visits to one or more centres (including travelling time), the time needed for individual measurements and informing parents and care centre personnel of the definite time schedule.

In non-disabled children measurements can usually take place during class time or in a break; this is more difficult in children with SMID. Their days are often filled with necessary actions including several therapies, (prolonged) meal times, diaper changes, an afternoon nap and getting ready for the bus ride home. During these actions a study-related measurement is often not possible. Furthermore, carers often state that 'fun-times' (such as swimming or horseback riding), should not be withheld from the child due to participation in a study. When these activi-

ties and preferences are taken into account, it is difficult to plan measurements efficiently.

Additionally, it is important that parents have the opportunity to be present during the measurements; this usually improves the feasibility of a measurement and improves parental commitment to the study. However, having to take the parents' schedule into account complicates the logistics even further.

Once measurements are planned, it is essential to inform both parents and care personnel in writing in order to prevent miscommunications. Even then, a high percentage of cancelled appointments can be expected due to illness of the participating children. A logistics employee is therefore essential; however, most grants are not sufficient to employ such a person.

Our last recommendation is certainly not the least important and concerns the clustering of measurements. When performing on-site measurements in multiple centres it is important to perform all measurement in a centre in a short period of time, to ensure a high level of involvement during the period that the researchers are present. When measurements are done with a long interval in between, commitment of day-care personnel can become problematic.

When several different measurements have to be done per child, we recommend to cluster these as well. However, this is not always possible, for example when a follow-up time between consecutive measurements is required. We even recommend clustering if it means introducing a longer time period to gather one type of study measurement. We believe this will reduce the loss to follow-up since parents have to commit for only a short period of time, rather than several times with a longer interval. Disadvantages are that the researchers have to perform different measurements on one day, and diagnostic tests (such as a wheel-chair scale or a MicroRint©) have to be available for a longer period of time. In practice, such reasons will often be decisive. Nevertheless, we strongly recommend to cluster measurements (both per centre and per child) even though it does not always seem the easiest approach at the time.

In this chapter several recommendations have been made to improve the feasibility of research in children with SMID; these are summarized in Table 3.

Table 3 Recommendations to improve the feasibility of research in children with severe motor and intellectual disabilities.

International consensus on interest groups and disability levels
- improves comparability of research
- useful in registration (local and national)
Registration of people with disabilities
- representative cohorts can be found more easily
- questions for research participation can be spread among parents
- ideal source of epidemiologic data such as prevalence, mortality and use of specialized and general health care
Care centre collaborations to review study proposals
- one review procedure saves time for both care centre and researcher
- only cooperation on realistic, clinically relevant and scientifically well-designed studies
- avoiding concurrent overlapping studies
Additional:
- perform feasibility pilots
- be generous with information to (parents of) participants and centre personnel
- appoint a logistic employee (on-site measurements)
- cluster the measurements per care centre
Grants should allow a budget for:
- a logistics employee
- (pilot) studies on method feasibility

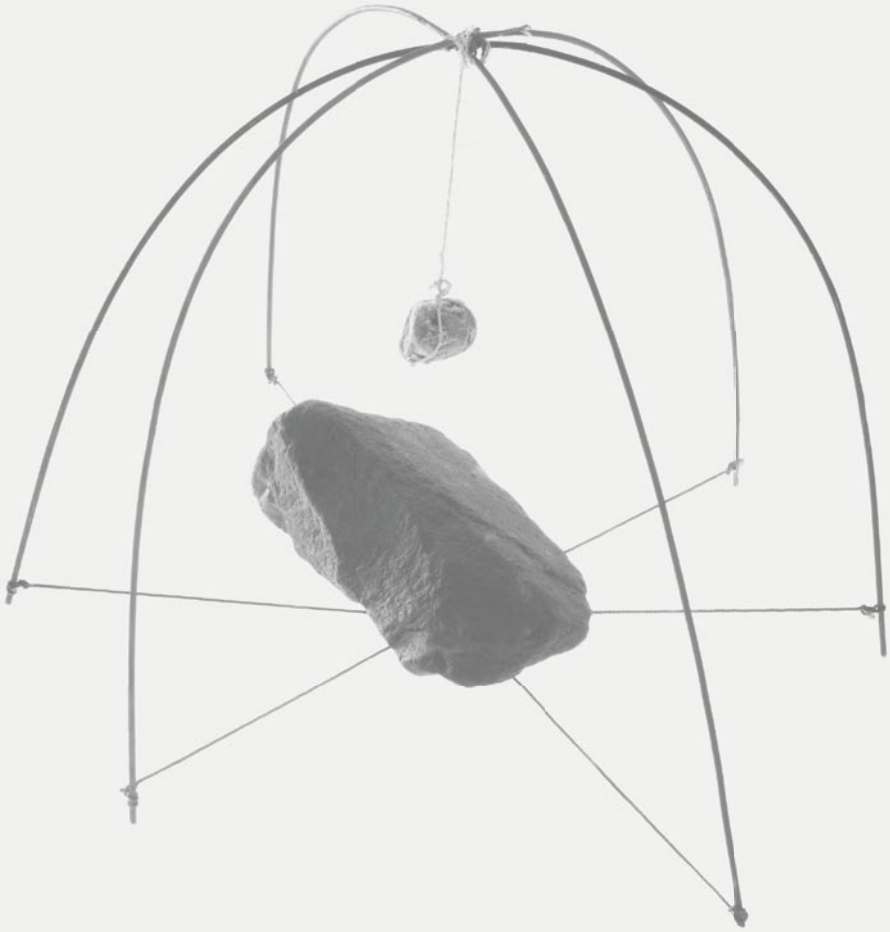
CONCLUDING REMARKS

In this thesis we have described a population-based study in children with severe motor and intellectual disabilities. We addressed the feasibility of performing a population-based study in children with SMID and of the diagnostics methods used, as well as prevalence data on respiratory resistance and constipation. Based on our practical experience we also formulated several recommendations for future research practice. However many basic research questions remain regard-

ing comorbidity in children with SMID and its prevention and treatment. The population-based study described here will, besides this thesis, result in another thesis that focuses mainly on observational data on risk factors for recurrent pneumonias, gastro-oesophageal reflux and nutritional state in children with SMID. Data on nutritional assessment in a hospital setting are also expected from our research team in the future.

Chapter 8

Summary



SUMMARY

Children with severe motor and intellectual disabilities (SMID) often suffer many co-morbidities. Their life expectancy is reduced, with respiratory disease as one of the leading causes of death. Their concomitant health problems negatively influence each other and put children with SMID at risk of developing other, or increasingly severe health problems. Dysphagia for example, can be a primary result of motor and sensory impairment due to the underlying brain damage. Dysphagia puts children at risk of aspiration and hence of pneumonias. This risk of developing pneumonias is further increased when a cough reflex is absent (primarily or due to prior infections), cilial movement is slow, and/or the immune system is compromised. This poor defence mechanism can be the result of malnutrition due to dysphagia. This is only one of many possible pathways in which disabilities and co-morbidities can interact with each other, compromising the health status of children with SMID.

The study described in this thesis focuses on two major issues: lower respiratory tract infections and malnutrition in children and adolescents with SMID. Prevalence data on these issues is lacking, therefore we designed and conducted the first population-based study for children with SMID in the Netherlands.

This thesis focuses on the feasibility of performing such a study, the feasibility and outcome values of Bioelectric Impedance Analysis, the interrupter technique and symptom-based diagnostics of constipation.

Chapter 1 focuses on the terminology, epidemiology and etiology of SMID. We address the current stage of scientific research in this field of medicine, and explain the choice for the studied health issues.

In **chapter 2** we have described the rationale, the study design and inclusion period in more detail. We have commented on the choice for a nested case-control design and presented the ethical considerations leading to some limited concessions in the study design. An overview is given of how we have dealt with the encountered obstacles in the design and realisation of this study.

The study population consisted of 194 participants recruited via 56 different care centres. We have presented an overview of the etiology of their disabilities, their basic characteristics and the flow-chart of the inclusion period. Basic characteristics of the participants were compared to those of the eligible children that did not participate. We concluded that the included population is slightly younger, and that parents had reported slightly more comorbidity in the participants. Despite

these discrepancies, our study sample is as representative as can be expected in population-based research.

Chapter 3 focused on the feasibility of Bioelectric Impedance Analysis (BIA), a method to assess nutritional status. Nutritional problems are common in children with SMID. In this population however, is not easy to assess the nutritional state. The diagnostic value of commonly applied methods such as anthropometry remains unclear. Anthropometry is often difficult to apply (e.g. due to contractures) and values are difficult to interpret (e.g. due to growth retardation and a lack of adjusted reference values). A gold standard method (deuterium dilution technique) exists, but is laborious and very expensive. A possible alternative is BIA. This technique is valid and easy to apply in non-disabled children.

We studied the feasibility of BIA in 35 children with SMID, as part of the epidemiologic study described in chapter 2. We demonstrated that BIA is a feasible method in children with SMID (97% tolerated, 72% correct positioning) and that the percentage body fat calculated with BIA was significantly related to BMI values. We expressed our remaining concerns regarding the observed fluctuation of the measurement values and the high resistance (Rz) values in these children. We advise future study on the reproducibility, the additive value of this technique to nutritional assessment and validation to the reference standard.

We concluded that the first results of BIA in children with SMID were promising; nonetheless, the exact position of BIA in the diagnostic apparatus of nutritional assessment still needs to be established.

Pulmonary problems are common in children with SMID, however, conventional methods to objectify pulmonary problems are not applicable to children with SMID because these methods require the ability to follow instructions as well as good motor skills. In **chapter 4 and 5** we focused on the interrupter technique. It can measure respiratory resistance, requires only little cooperation and is reliable in infants. A measurements of this technique consists of several interruptions (depicted in pressure- and flow-curves) that need to be evaluated by hand to exclude measurement errors. In **chapter 4** we describe criteria we have developed to evaluate these curves of the interrupter technique. We compare the results obtained by the application of the criteria to the results using the conventional method (eyeballing). Our aim was to simplify the evaluation and improve inter-observer variability, without affecting the outcome values.

We showed that inter-observer agreement was similar using the criteria or eyeballing. The rejection percentage was however higher when the criteria were applied, although the number of succeeded measurements was similar using both

methods. The resulting respiratory resistance values were comparable between the used rejection methods, and were similar to not rejecting any curves at all.

We concluded that none of the methods influenced the outcome value significantly. However, it remains important to evaluate measurements, in order to reject those consisting only of measurement errors. Although application of the criteria did not improve inter-observer variability, these criteria can contribute to the standardisation of the Rint technique and simplify its evaluation in daily practice.

In **chapter 5** we focussed on the reproducibility, feasibility and outcome values of the interrupter technique in children with SMID.

In phase 1 we studied reproducibility of Rint in 35 children with SMID who did not take part in the epidemiologic study. We showed that reproducibility was moderate but acceptable on both short (one hour) and long term (two weeks). Short-term reproducibility values were lower than in non-disabled children, whereas long-term reproducibility was comparable to that of a previous study under field conditions. In the **data supplement** to chapter 5, reproducibility values were compared with those of most previous studies in non-disabled children, using several different statistical measures of reproducibility.

In phase 2 feasibility of the technique and Rint values were studied in 175 children with SMID, as part of the epidemiologic study described in chapter 2. We showed that the measurement was tolerated by 86% of children with SMID and was successful in 73%. In 63% we were able to perform a successful reversibility test as well. The within-measurement variability was however considerable, and some concerns were raised on a high percentage of irregular pressure curves. We compared Rint values to the reference values for non-disabled children and found that Rint values were relatively low in short (young) children and relatively high in tall (older) children. This might be explained by muscle tension development in children with SMID and with increasing age they might have developed pulmonary damage due to recurrent pulmonary problems. Rint values were significantly correlated to distinct bronchorrhea. In the data supplement details on the measurement procedure, statistics and z-values are reported.

We concluded that the interrupter technique is feasible in most children with SMID.

Nevertheless, several aspects still need to be studied before clinical application can be recommended. Unfortunately, high-quality validation is not possible because a feasible reference standard is lacking. The diagnostic value of this technique remains a topic of interest. Despite these limitations, pulmonology experts could consider the use of the interrupter technique for treatment evaluation, and reversibility testing in children with SMID.

In **chapter 6** we focused on constipation in children with SMID. This common problem has seldom been studied in these children, and data on population prevalence are scarce. A difficulty of studying constipation is its subjective nature; no gold standard method is available. It is diagnosed based on consensus definitions. For non-disabled children such definitions are available, however, these are not applicable to children with SMID. Therefore, we developed a specific definition based on the useful components of several pre-existing definitions of constipation. We studied constipation in 152 children with SMID using diaries on defecation and dietary intake, interviews with parents, and by performing a small physical examination. We did not intervene in laxative use.

According to our definition, 22% of the children with SMID were constipated. Laxatives were used by 54%, however, 36% of these children were constipated. Six percent of the children that did not use laxatives were constipated.

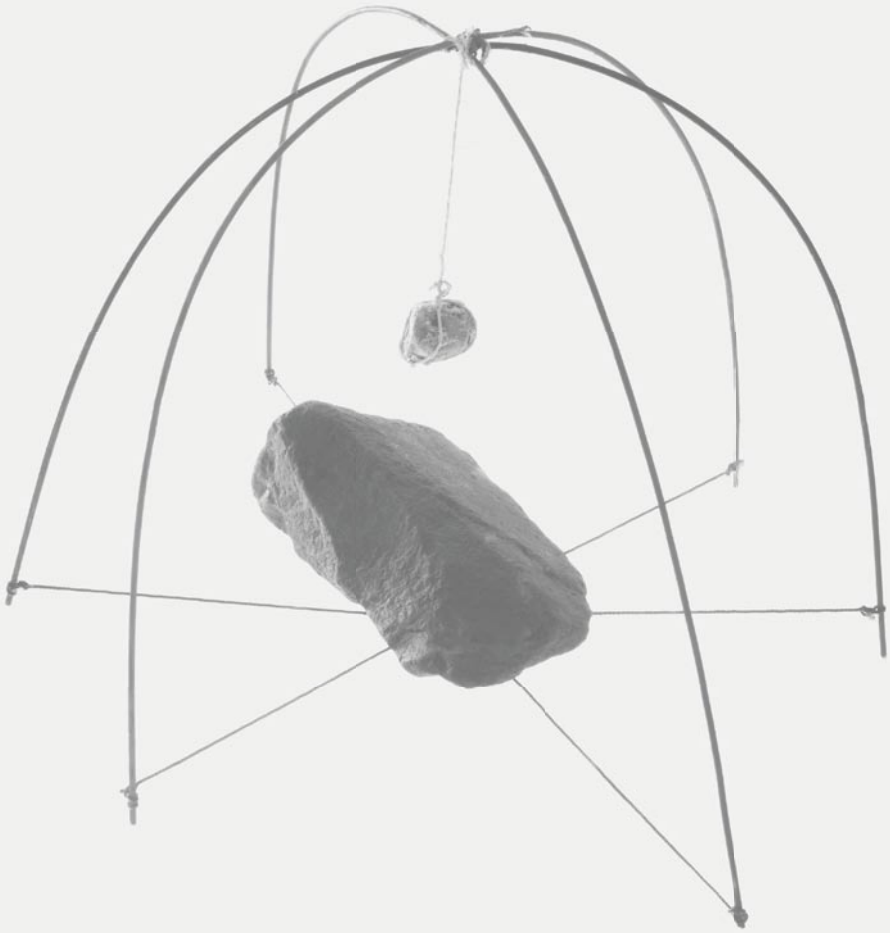
We also studied dietary intake and demonstrated that water and fibre intake were deficient in 87% and 53% of the children respectively. No causal factors of constipation were demonstrated. Trends were observed between constipation and BMI (higher BMI in constipated children, p=0.102) and between constipation and level of intellectual disability (less constipation in profoundly than in moderately-severely disabled, p=0.084), however these correlations were not statistically significant. In addition, defecation frequency was not significant correlated to insufficient fibre intake, water intake, BMI or age.

We concluded that the developed definition was applicable, however, due to a lack of reference standard, its validity could not be established. The observed prevalence rate was not higher than the prevalence in non-disabled children, however, a high percentage of the children were already treated. Results indicated that the use of laxatives was not effective in all children, stressing the importance of regular treatment re-evaluation. We were unable to establish causal effects of life style factors. As long as this etiology remains unclear, possible influencing life-style factors (e.g fiber and water intake, immobility, drug side effects) should be managed properly. Consensus on a definition of constipation in children with severe neurological impairments should be reached.

Chapter 7 includes the general discussion of this thesis. It addresses the practical value of the used diagnostic methods. We provide information on the preparation of future studies in children with SMID (e.g., concerning study design, measurement setting, and diagnostic methods). Based on our experience from the present study, we also formulated several recommendations to improve feasibility of future research in children with SMID.

Chapter 9

Samenvatting



SAMENVATTING

Comorbiditeit komt veel voor bij kinderen met ernstige motorische en verstandelijke beperkingen (Ernstige Meervoudige Beperkingen, EMB). Zij hebben een lage levensverwachting met longziekten als de belangrijkste doodsoorzaak. De simultaan aanwezige aandoeningen kunnen elkaar versterken, waardoor andere gezondheidsproblemen kunnen verergeren. Een voorbeeld daarvan is dysfagie (slikstoornis), wat primair het gevolg kan zijn van motorische en sensorische problemen als gevolg van de onderliggende hersenbeschadiging. Hierdoor hebben zij een vergroot risico op aspiratie (verslikking), waardoor de kans op lage luchtweginfecties toeneemt. Het risico op dergelijke ontstekingen kan toenemen door verminderde hoestreflex (primair, of als gevolg van eerdere ontstekingen), verminderde werking van de cilia (trilharen) of door een verminderde immunologische afweer. Een dergelijke verminderde afweer kan het gevolg zijn van ondervoeding, wat weer een direct gevolg kan zijn van dysfagie. Dit is slechts een van de vele mogelijke voorbeelden hoe verschillende aandoeningen elkaar kunnen verergeren, en daarmee de gezondheidstoestand van kinderen met EMB kunnen compromitteren.

Het onderzoek dat in dit proefschrift beschreven wordt richt zich op twee belangrijke gezondheidsproblemen: lage luchtweginfecties en ondervoeding bij kinderen en adolescenten met EMB. Cijfers over de prevalenties van deze aandoeningen ontbreken. ontbreekt. Om deze reden hebben wij de eerste Nederlandse representatieve populatiestudie bij kinderen met EMB ontworpen en uitgevoerd. Dit proefschrift richt zich met name op de toepasbaarheid en de meetwaarden van de Bio-elektrische Impedantie Analyse (BIA), de interruptietechniek en de diagnostiek van obstipatie op basis van symptomen.

In **hoofdstuk 1** wordt nader ingegaan op de terminologie, de epidemiologie (het vóórkomen) en de etiologie (de oorzaken) met betrekking tot kinderen met EMB. Het huidige peil van het medisch wetenschappelijk onderzoek in deze doelgroep wordt besproken alsmede de keuze van de te onderzoeken gezondheidsproblemen.

In **hoofdstuk 2** beschrijven we de rationale, de onderzoeksopzet (design) en de inclusieperiode. De keuze voor een genest case-controle onderzoek en de ethische overwegingen die geleid hebben tot minimale aanpassingen in de onderzoeksopzet, worden besproken. We geven een overzicht van hoe we zijn omgegaan met de tegengekomen obstakels in de opzet en realisatie van de studie.

Aan de studie namen 194 kinderen deel uit 56 verschillende zorginstellingen. Een overzicht van de etiologie van hun beperkingen en de basiskarakteristieken van de populatie worden gepresenteerd, alsook het stroomdiagram van de inclusie periode. Enkele basiskarakteristieken van de deelnemers werden vergeleken met die van de kinderen voor wie geen toestemming werd verkregen. Hieruit concluderen wij dat de deelnemers iets jonger zijn en bovendien iets meer comorbiditeit hebben volgens de rapportage van de ouders. Ondanks deze kleine verschillen is de huidige studiepopulatie zo representatief als verwacht kan worden bij een populatiestudie

Hoofdstuk 3 richt zich op de toepasbaarheid van de Bio-elektrische Impedantie Analyse (BIA) welke een methode is om voedingstoestand te bepalen. Bij kinderen met EMB komen vaak problemen met de voedingstoestand voor. Het is bij hen echter niet gemakkelijk om de voedingstoestand te meten. De diagnostische waarde van veel gebruikte methoden zoals antropometrie (het meten van o.a. lengte, omtrek, gewicht en huidplooien) in deze doelgroep is onbekend. Antropometrie is vaak niet goed uitvoerbaar (o.a. door contracturen en scoliose) en de resultaten zijn moeilijk te interpreteren (o.a. door groeiretardatie en het ontbreken van specifieke referentiewaarden). De “gouden standaard” methode voor het meten van de voedingstoestand (deuterium dilutie techniek) is echter bewerkelijk en zeer kostbaar. BIA is een mogelijk alternatief. Deze techniek is bij niet-gehandicapte kinderen valide en eenvoudig toepasbaar.

We onderzochten de toepasbaarheid van BIA bij 35 kinderen met EMB, als onderdeel van de epidemiologische studie die beschreven wordt in hoofdstuk 2. Uit de resultaten bleek dat BIA toepasbaar is bij kinderen met EMB (97% tolereerde de meting, bij 72% kon de meting in de voorgeschreven positie uitgevoerd worden) en dat het met de methode berekende percentage lichaamsvet significant correleerde met BMI waarden. Daarentegen bestaan er zorgen omtrent de geobserveerde fluctuatie van de meetwaarden en de hoge gemeten weerstandwaarden (Rz) bij deze kinderen. Toekomstig onderzoek zou zich moeten richten op de reproduceerbaarheid van de meetwaarden en validatie van de methode ten opzichte van de gouden standaard.

We concluderen dat de eerste resultaten van BIA bij kinderen met EMB veelbelovend zijn, echter, de exacte waarde van BIA bij het gestandaardiseerd bepalen van de voedingstoestand moet nog worden bepaald.

Longproblemen komen veel voor bij kinderen met EMB, echter, conventionele methoden om deze problemen te objectiveren zijn bij hen niet toepasbaar. Bij dergelijke methoden moeten kinderen niet alleen instructies kunnen opvolgen, het

vergt ook een behoorlijke motorische vaardigheid. In **hoofdstuk 4 en 5** richten wij ons op de interruptie techniek. Deze kan respiratoire weerstand meten, vereist slechts beperkte medewerking en is bovendien een betrouwbare methode bij niet gehandicapte kinderen. Een dergelijke meting bestaat uit meerdere interrupties (afgebeeld als druk- en flowcurves) die handmatig beoordeeld moeten worden om meetfouten te kunnen verwijderen. In **hoofdtuk 4** beschrijven wij door ons opgestelde criteria om deze curves te beoordelen. We vergeleken de resultaten van het gebruik van deze criteria met beoordeling op de conventionele methode (op basis van ervaring inschatten of een curve een normaal of afwijkend verloop heeft (*eyeballing*)). Ons doel was om criteria op te stellen die de interbeoordelaarbetrouwbaarheid zouden verbeteren en de beoordeling zouden vereenvoudigen zonder dat hiermee de uitkomstwaarden beïnvloed zouden worden.

We hebben aangetoond dat de interbeoordelaarsbetrouwbaarheid vrijwel gelijk was bij beide methoden. Bij toepassing van de criteria werden echter wel meer curves afgekeurd, het aantal afgekeurde metingen verschilde echter nauwelijks. Beide methoden (criteria en eyeballing) resulteerden in vergelijkbare uitkomstwaarden (respiratoire weerstand, Rint). Deze waren ook vergelijkbaar met de waarden wanneer er helemaal geen curves beoordeeld werden.

We concluderen dat het beoordelen van curves geen invloed heeft op de uitkomstwaarde van de meting, ongeacht of hiervoor criteria of eyeballing gebruikt wordt. Het beoordelen blijft echter wel van belang om mislukte metingen te kunnen herkennen. Hoewel de criteria de interbeoordelaarsbetrouwbaarheid niet verbeteren, kunnen deze criteria wel bijdragen aan de standaardisatie van de interruptietechniek en het beoordelen van curves in de dagelijkse praktijk vergemakkelijken.

In **hoofdstuk 5** richten wij ons op de reproduceerbaarheid, toepasbaarheid en uitkomstwaarden (Rint) van de interruptietechniek bij kinderen met EMB.

In fase 1 bestudeerden wij de reproduceerbaarheid van Rint bij 35 kinderen met EMB die niet deelnamen aan het epidemiologische onderzoek beschreven in hoofdstuk 2. We toonden aan dat de reproduceerbaarheid matig maar acceptabel was op zowel korte (1 uur) als lange termijn (2 weken). In vergelijking met de reproduceerbaarheid bij niet-gehandicapte kinderen was de korte termijn reproduceerbaarheid lager, terwijl de lange termijn reproduceerbaarheid vergelijkbaar was met waarden uit een andere veldstudie. In het **data supplement** van hoofdstuk 5 wordt met verschillende statistische methoden de reproduceerbaarheid vergeleken met de resultaten van eerdere studies bij niet-gehandicapte kinderen.

In fase 2 hebben wij de toepasbaarheid van de interruptietechniek en de Rintwaarden bestudeerd bij 175 kinderen met EMB die deelnamen aan de epidemiolo-

gische studie. De meting werd door 86% van de kinderen geaccepteerd, en was geslaagd bij 73%. De reversibiliteit (reactie op een luchtwegverwijdend middel) kon bij 63% met succes getest worden. De variabiliteit binnen de metingen was echter aanzienlijk, en ook het hoge percentage irreguliere curves baart zorgen.

Wij hebben de Rint-waarden vervolgens vergeleken met de referentiewaarden van niet-gehandicapte kinderen, hieruit bleek dat Rint relatief laag was in kleine (jonge) kinderen en relatief hoog in lange (oudere) kinderen. Dit kan mogelijk verklaard worden door de ontwikkeling van spierspanning en doordat oudere kinderen reeds luchtwegschade opgelopen kunnen hebben door recidiverende luchtwegproblematiek. De Rint-waarden waren naast lengte en leeftijd, ook significant gecorreleerd aan hoorbaar 'vol zitten'. In het datasupplement wordt ingegaan op de details van de meetprocedure, de statistiek en z-waarden.

We concluderen dat de interruptietechniek toepasbaar is bij de meeste kinderen met EMB. Echter, voordat we het gebruik van deze methode in de dagelijkse praktijk kunnen aanraden, moeten diverse aspecten van de techniek nog verder bestudeerd worden. Helaas is het valideren van de methode niet goed mogelijk aangezien er voor deze groep geen toepasbare referentiemethode is. De diagnostische waarde van deze techniek blijft hiermee onduidelijk. Ondanks deze beperkingen zouden gespecialiseerde longartsen het gebruik van deze techniek kunnen overwegen bij de evaluatie van het effect van medicatie en om reversibiliteit te onderzoeken bij kinderen met EMB.

In **hoofdstuk 6** richten wij ons op obstipatie bij kinderen met EMB. Deze veel voorkomende aandoening is in deze populatie weinig onderzocht en gegevens over het vóórkomen van obstipatie bij deze kinderen zijn zeldzaam. Het bestuderen van obstipatie wordt bemoeilijkt door het subjectieve karakter van de aandoening, er is voor de diagnostiek hiervan geen gouden standaard beschikbaar. Obstipatie wordt gediagnosticeerd op basis van consensus definities. Deze definities voor niet-gehandicapte kinderen zijn echter niet toepasbaar bij kinderen met EMB. Wij hebben daarom voor deze groep kinderen een definitie van obstipatie ontwikkeld op basis van de reeds bestaande definities. Bij 152 kinderen met EMB werd vervolgens onderzocht of zij obstipatie hadden met behulp van dagboeken over ontlasting en voedingsinname, interviews met ouders en een beperkt lichamelijk onderzoek. Het gebruik van laxantia werd hiervoor niet aangepast.

Volgens onze definitie had 22% van de kinderen met EMB obstipatie. Van de 152 kinderen gebruikte 54% laxantia, echter 36% van hen was nog geobstipeerd. Van de kinderen die geen laxantia gebruikten had 6% obstipatie.

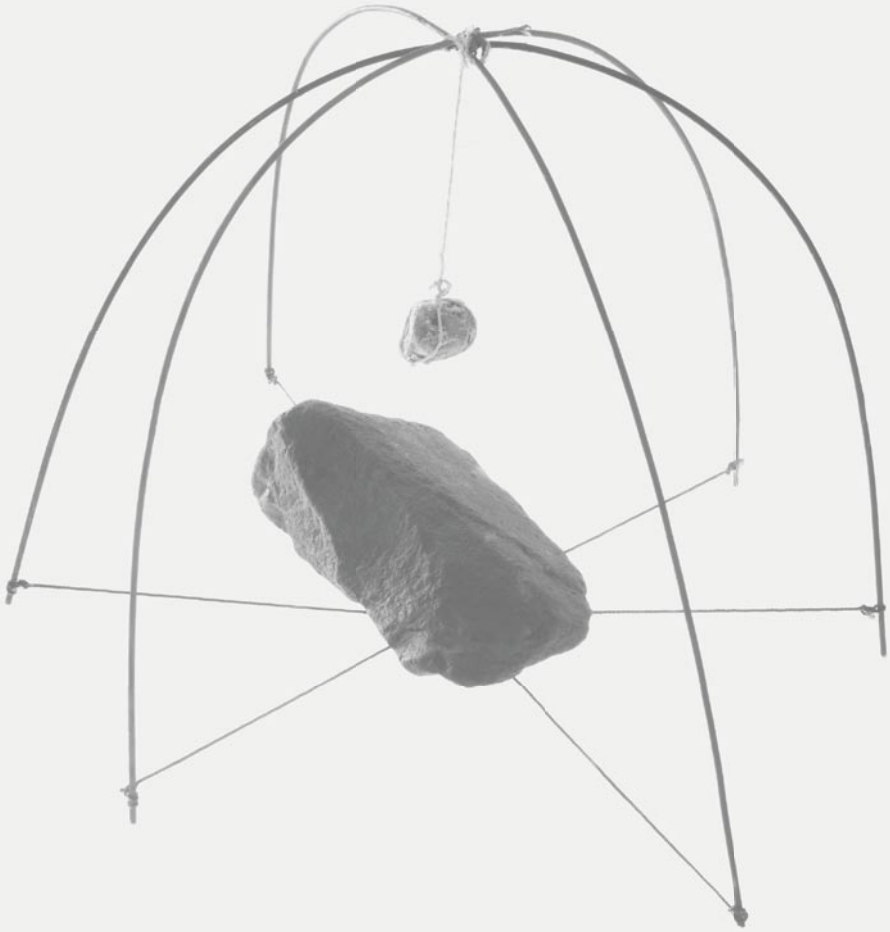
Tevens bleek dat de dagelijkse inname van water en voedingsvezel onvoldoende was bij respectievelijk 87% en 53% van de kinderen. Wij hebben geen

causale verbanden voor obstipatie aangetoond. Wel werden trends waargenomen tussen obstipatie en BMI (hogere BMI bij kinderen met obstipatie, p=0.102) en tussen obstipatie en de mate van verstandelijke beperking (minder vaak obstipatie bij de kinderen met zeer ernstige ten opzichte van matig tot ernstige verstandelijke beperkingen, p-0.084). Deze trends waren echter niet statistisch significant. Tevens kon er geen relatie worden aangetoond tussen de ontlastingsfrequentie en vezelinname, waterinname, BMI of leeftijd.

We concluderen dat de door ons ontwikkelde definitie toepasbaar is. Echter door het gebrek aan een referentiemethode, kunnen er geen uitspraken gedaan worden met betrekking tot de validiteit ervan. De gevonden prevalentie bij kinderen met EMB was niet hoger dan bij niet-gehandicapte kinderen, echter een aanzienlijk deel van de kinderen met EMB werd al behandeld. De resultaten impliceren dat de behandeling echter niet bij alle kinderen effectief was. Dit onderstreept het belang van regelmatige her-evaluatie van medicamenteuze therapie. We hebben geen relatie tussen obstipatie en levensstijl kunnen aantonen. Zolang de etiologie niet opgehelderd is moeten er goed met de mogelijk beïnvloedende levensstijl factoren (bijv. vezel en water inname, immobiliteit en bijwerkingen van medicatie) omgesprongen worden. Zowel voor onderzoek als voor de praktijk is het van belang dat er voor deze groep consensus bereikt wordt met betrekking tot een werkdefinitie voor obstipatie.

Hoofdstuk 7 bevat de overkoepelende discussie van dit proefschrift. Hierin wordt ingegaan op de praktische waarde van de gebruikte diagnostische methoden. Tevens worden handvatten geboden voor de opzet van toekomstig onderzoek bij kinderen met EMB (o.a. met betrekking tot de onderzoeksopzet, de meetlocatie en de te gebruiken diagnostische methoden). Op basis van de ervaring die met deze studie is opgedaan worden adviezen gegeven om de uitvoerbaarheid van wetenschappelijk onderzoek bij kinderen met EMB te verbeteren.

Dankwoord



DANKWOORD

Bij het schrijven van mijn dankwoord realiseer ik me dat dit het laatste stuk van mijn proefschrift is. Hoewel ik natuurlijk blij ben dat dit boekje af is, vind ik het ook jammer dat dit onderzoek zijn einde nadert. Het was namelijk een prachtig (maar zeer ambitieus) project. Ik ben bijzonder trots op wat ik samen met de mensen om mij heen bereikt heb. Ik hoop dat er nog velen zullen volgen die zich sterk willen maken om de geneeskunde voor de meervoudig gehandicapte kinderen verder op de rails te zetten.

Voor dit soort grootschalig onderzoek (speciaal in een pioniersfase) is niet alleen een enorme interne motivatie noodzakelijk maar zijn ook mensen om je heen onmisbaar om je te inspireren, te prikkelen en te steunen. Daarom wil ik enkele mensen met naam noemen.

Om te beginnen mijn eerste promotor Prof. Dr. Evenhuis. Heleen, ik ben blij dat ik de eerste stappen van de leerstoel mee heb mogen maken, en eraan heb kunnen bijdragen. Ik heb bijzonder veel bewondering voor je interne motivatie, en de manier waarop je ondanks tegenslagen altijd je eigen plan kan trekken en je doel in het oog kan houden.

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Corine als co-promotor en projectleider onderzoekslijn “comorbiditeit bij kinderen met ernstige meervoudige beperkingen”. Na een lastige start bij de leerstoel (waarbij iedereen verschillend beeld van jouw functie als post-doc had), heb je je draai goed kunnen vinden. Met je aanstelling in het Sophia is er nu een start gemaakt met de brug tussen twee werelden: ziekenhuis en leerstoel. Ik hoop dat de onderzoekslijn die we met dit onderzoek gestart zijn, het vervolg zal krijgen die het verdient. Ik ben onze samenwerking zeer op prijs gaan stellen, alsmede je grote inzet en bereikbaarheid. Ik ga ervan uit dat wij na dit schrijven nog regelmatig zullen samenwerken.

Prof. Dr. J.C. de Jongste, Prof Dr. A.J. van der Heijden en Dr. E.W. Steyerberg dank voor uw snelle beoordeling van het manuscript en Prof. Dr. S. Thomas, Prof. Dr.

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Elsbeth, Rob, Michiel & Ymie: Laat de wereld zien waar de leerstoel voor staat! Veel succes.

Annelies, bedankt voor je inzet en de vele, vele kilometers die we samen afgelegd hebben.

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(Roparun), Luc Zimmerman (discussies over geneeskunde) en Jan van Lierop (coverfoto).

Verder alle (oud-)collega's van de huisartsgeneeskunde die ik niet bij naam genoemd heb. Iedereen van de AVG-opleiding, ik ben benieuwd welke plaats AVG's in de geneeskunde jullie gaan innemen, veel succes!

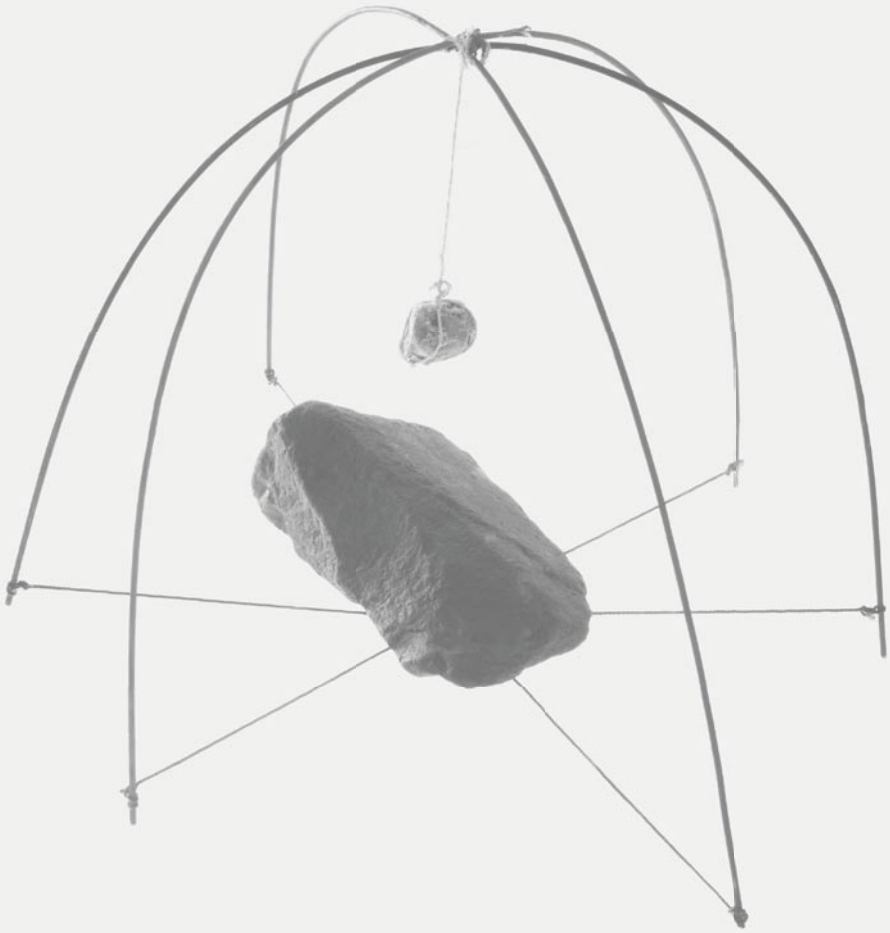
Echter mijn grootste dank gaat uit naar alle kinderen, ouders en begeleiders die aan het onderzoek meegewerkt hebben. Zonder jullie was het allemaal niet mogelijk! Hopelijk zal u ook in de toekomst het belang van onderzoek in blijven zien, en kan deze tak van de geneeskunde een inhaalslag maken zodat de medische zorg voor meervoudig gehandicapten in Nederland een hoger niveau kan bereiken.

Ook had ik de steun van mijn vrienden in de afgelopen jaren niet willen missen. Ik heb de meeste van jullie minder gezien en gesproken dan me lief is, maar wellicht kunnen we dat nog goed maken.

Jeroen, jouw liefde, jouw rust, jouw balans en jou vertrouwen hebben mijn wereld voorgoed veranderd. Je bent voor mij onmisbaar.

Van kleins af aan heb ik geleerd dat het belangrijk is om het beste uit jezelf te halen, altijd je beste been voor te zetten en om te vertrouwen dat jij zelf in staat bent om situaties te verbeteren. Ik had dit alles nooit kunnen doen zonder het gezin waarin ik opgegroeid ben en de onvoorwaardelijke steun en liefde van mijn ouders.

About the Author / Over de Auteur



ABOUT THE AUTHOR

Rebekka Veugelers was born on August 25, 1977 in Vlissingen, the Netherlands. She passed secondary school (HAVO, 1994) and pre-university education (VWO, 1996) at the St Willibrord college, Goes. She started her study in medicine at the Erasmus University Rotterdam in September 1996. During the academic year 1999-2000 she was a board member of one of the students' societies of Rotterdam ("Vice Praeses Senaat" at the "Rotterdamsch Studenten Gezelschap"). In 2001 she received her doctoral degree in medicine after a final project at the Chair of Intellectual Disability Medicine, department of General Practice at the Erasmus MC ("Feasibility of the Rotterdam Activity Monitor in children with severe multiple disabilities"). From 2001 to 2005 she conducted a study on risk factors of recurrent pneumonias and malnutrition in children with severe motor and intellectual disabilities at this Chair. Among other things, this study resulted in this thesis. From 2002 to 2004 she was chairman of the Rotterdam PhD council and representative in the Dutch PhD council. As part of her PhD-training she obtained her Master of Science degree in Clinical Epidemiology at the Netherlands Institute of Health Sciences (NIHES) in 2005. Currently she has resumed her medicine study with her practical years (co-schappen). In 2007 she hopes to graduate as a Medical Doctor.

OVER DE AUTEUR

Rebekka Veugelers werd op 25 augustus 1977 geboren in Vlissingen. Zij behaalde haar HAVO (1994) en VWO (1996) diploma's aan het St Willibrord college te Goes. In 1996 startte zij met haar studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Het studiejaar 1999-2000 bekleedde zij een bestuursfunctie bij een van de Rotterdamsche Studenten Verenigingen ("Vice Praeses Senaat" bij het "Rotterdamsch Studenten Gezelschap"). In 2001 rondde ze haar doctoraal geneeskunde af met een afstudeeronderzoek bij de Leerstoel Geneeskunde voor Verstandelijk Gehandicapten, afdeling Huisartsgeneeskunde van het Erasmus MC ("de toepasbaarheid van de Rotterdamse Activiteiten Monitor bij kinderen met ernstige meervoudige beperkingen"). Van 2001 tot 2005 hield zij zich bezig met het opzetten en uitvoeren van een onderzoek op naar risicofactoren van recidiverende lage luchtweginfecties en ondervoeding bij kinderen met ernstige motorische en verstandelijke beperkingen bij deze leerstoel. Dit resulteerde o.a. in

dit proefschrift. Van 2002 tot 2004 was zij voorzitter van de Promovendi vereniging Rotterdam, en afgevaardigde voor de Landelijke Promovendi vereniging. In 2005 behaalde ze haar Master of Science diploma in de Klinische Epidemiologie aan het Netherlands Institute for Health Sciences (NIHES). Momenteel heeft zij haar studie Geneeskunde hervat, en loopt haar co-schappen. Zij hoopt in 2007 haar arts-diploma te behalen.