

Studies on neurodevelopmental issues in children

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Summary

Preventive Youth Health Care in the Netherlands has a history of more than a century. As part of the Youth Health Care system, all children living in the Netherlands receive free preventive medical assessments, from birth through adolescence. Research on neurodevelopmental issues in children in the field of the Youth Health Care is not quite common. However, research on brain-behavioral relations and neurodevelopment in children does have large potentialities using the infrastructure of Youth Health Care, especially regarding longitudinal cohort studies. In this respect it has become quite a challenge for Youth Health Care to contribute to research on neurodevelopmental issues in children, taking into account the achievements of neurosciences in the last decades. First, it is important to gain deeper understanding of the complex processes underlying normal development in children in relation with the ratio of risk-bearing factors and protective factors of the child and his environment. Secondly, research on neurodevelopmental delays or disorders in children is important in elucidating the prevalence, etiology, course and potential therapeutic interventions. Thirdly, more research on neurodevelopmental disorders is needed focused on the interference with respectively the impact on learning and social functioning of the child. Finally, research on neurodevelopmental issues in children is of great importance for the field of the Youth Health Care in attaining evidence based methods for early detection and preventive measures in case of developmental delays or disorders.

The present thesis contemplates to contribute in the knowledge on neurodevelopmental issues in children and to elucidate the added value of interdisciplinary co-operation within the context of research and care in the domain of neurodevelopmental disorders in children. Therefore, the general objective of this thesis was to emphasize the connection between neurodevelopmental research and Youth Health Care. In the context of this general intention, this thesis was focused on the following specific objectives within the domain of neurodevelopment in children:

- (1) to assess the relationship between acid-base status at birth and short-term and long-term neurodevelopmental outcome, in terms of general movements at birth respectively at age of 3 months, mental and motor development at age of 9 months respectively 18 months, and neurological, cognitive and behavioral functioning at age of 4 years;
- (2) to determine effects of medication treatment in children with ADHD in terms of information processing and behavioral functioning;
- (3) to monitor medication treatment in children with ADHD, focusing on the neurobiological substrate of ADHD in relation to neurodevelopmental outcome; and
- (4) to indicate the practical implications of the multidimensional aspects of neurodevelopmental issues. Two studies of this thesis deal with the predictive value of acid-base status at birth on later cognitive development at pre-school age. As such it concentrates on the first four years of development and the possible role of acidosis for development of later attention problems and cognition. Subsequently, three studies are presented on the effects of medication in a group of school-aged children with ADHD. The specific aim of these three studies was to demonstrate the influence of medication on the brain mechanism of ADHD respectively on learning and behavioral outcome: the neurobiological substratum of ADHD is discussed. A case study on the risks of medication for ADHD in a child with cerebral palsy is described. Finally, the multidimensional aspects of neurodevelopmental issues are discussed in an article where Youth Health Care, Child Neurology and Child Neuropsychology are brought together.

In **chapter 1** the background, the general objective and the aims of the thesis are described in terms of neurodevelopment and health of children. Introductory remarks enclose a description of the preventive Youth Health Care in the Netherlands, in particular assignment, function and working methods of Youth Health Care practice. Brain-behavior relations are supposed to be the most important theoretical frameworks in children with

neurodevelopmental disorders. As such Child Neurology and Child Neuropsychology are closely allied disciplines, which are brought together with Youth Health Care in a field of action for the studies in this thesis.

Chapter 2 describes a study on the relationship between acid base status and quality and quantity of General Movements (GMs) at birth and quality of GMs at age three months and motor, cognitive and behavioral functioning at the age of four years. Quality and quantity of general movements were assessed in full-term infants at birth and at the age of three months. At the age of four years in a group of 44 children outcome on motor, cognitive and behavioral functioning was measured, with a main focus on evaluation of neuromotor behavior. In this sample of infants with a large variation in umbilical artery pH and without severe neonatal neurological abnormalities, acid-base status at birth and quality of GMs at three months of age is not predictive for motor milestone achievement, cognitive and behavioral functioning at four years, but these parameters are related to a less optimal condition of the nervous system. The latter finding has, however, limited clinical significance. The results of this study are discussed from a clinical point of view, especially with concern to the prognosis for development in children with a history of perinatal acidosis of different degree.

The aim of the study presented in **chapter 3** was to further investigate the relationship between acid-base status at birth and long-term neurocognitive and behavioral outcome using an extended sample size. Based on analysis of data collected at the age of nine months, 18 months and four years, a group of 66 children was prospectively evaluated, with special reference to information processing capacities at the age of four years. In particular this study was focused on the values of initial umbilical artery pH and base excess as predictors of neurocognitive and behavioral outcome at early school age as well as possible gender differences. This study revealed only significant positive correlations between initial umbilical artery pH and mental and motor development at the age of 18 months. At the age of four years no significant correlations could be found between initial umbilical artery pH values and mental processing, language reasoning and visual motor integration on the age of four years. Finally no relation was found between pH values at birth and behavioral outcome at four years. In conclusion, acid-base status at birth in full-term infants, without clinical evidence of perinatal hypoxic-ischemic encephalopathy, is a poor predictor of long-term neurocognitive and behavioral outcome in children.

Chapter 4 reports on a prospective study on the effects of medication treatment in a group of 37 children with ADHD, comparing clonidine to methylphenidate medication. Information processing and behavioral functioning were systematically assessed before and eight weeks after medication was started. The results of medication monitoring comparing clonidine to methylphenidate showed significant different effects as well as similar effects on information processing and inhibition control in behavior. It was found that methylphenidate had significant positive effects on spatial reasoning and aggressive behavior. The difference in effect on aggressive behavior between methylphenidate and clonidine was statistically significant. Both types of medication in children with ADHD without neurological dysfunction can effectively improve information processing and inhibition control in behavior. This study also demonstrated that neuropsychological assessment is not only an important tool to establish the treatment diagnosis of ADHD, but it is also a useful instrument to objectively evaluate the effect of medication.

Chapter 5 presents a study on imaging of brain dopamine transporter and receptor activity in six boys with ADHD. Single-photon emission computed tomography (SPECT) was used to monitor methylphenidate treatment. Imaging by SPECT was performed before starting treatment with methylphenidate and SPECT was repeated after three months. An extensive neuropsychological assessment was also performed before and three months after treatment. The results on SPECT were studied in relation to baseline and follow-up neuropsychological findings. Three months after initiation of treatment with methylphenidate a down-regulation of the post-synaptic dopamine receptor was found with a maximum of 20% and a down-regulation of the dopamine transporter with a maximum of 74.7% in the striatal system. This corresponded with a positive clinical response evaluated by neuropsychological questionnaires and tests. These findings indicated that dopamine transporter imaging by SPECT might be used to monitor psychostimulant treatment in children suffering from ADHD.

Chapter 6 deals with the potential long-term effects of chronic methylphenidate treatment. In this study, single-photon emission computed tomography (SPECT) was used to investigate possible long-term alterations in the

cerebral dopamine system after cessation of treatment with methylphenidate in five children with ADHD. Three months after initiation of treatment with methylphenidate, a reduction of the dopamine transporter in the striatal system was observed. Methylphenidate was administered for a period of 9 to 20 months. Follow-up with single-photon emission computed tomography after withdrawal of methylphenidate medication showed an increase of dopamine transporter activity comparable with pretreatment values. The observed up-regulation of dopamine transporter activity might support the assumption that methylphenidate does not lead to permanent damage of the nigrostriatal dopaminergic pathways. Single-photon emission computed tomography (SPECT) was used to investigate possible long-term alterations in the cerebral dopamine system after cessation of treatment with methylphenidate in five children with ADHD.

Chapter 7 describes a case report in order to discuss the possible proconvulsant effect the role of clonidine, focusing on the role of the alpha-2-adrenoreceptors. Clonidine is used as second line medication for the treatment of attention deficit hyperactivity disorder in children. Clonidine is an imidazoline derivate and acts as an agonist on alpha-2 adrenergic receptors. Product information concerning clonidine reports seizures only after overdosage of clonidine and prescription of clonidine is up till now not contraindicated in patients with known epilepsy. Attention deficit hyperactivity disorder in 9-year-old girl with cerebral palsy was treated with clonidine. Two weeks after initializing treatment with clonidine, the girl was transferred to emergency room because of a secondarily generalized convulsive status epilepticus. Within the spectrum of pharmacological interventions for the management of ADHD in school-aged children the role of clonidine is changing. Special caution is warranted in administration of clonidine for the treatment of attention deficit hyperactivity disorder in children with a prior history of seizures or with electroencephalographic abnormalities in absence of seizures.

Chapter 8 reports the experiences on a transmutal consultation hour for children with behavioral-neurological developmental disorders, in particular ADHD. In this project the lines between the finding place (school or family) and secondary health care are very short for case finding by the youth health care physician. Children have already been pre-examined according to a standard protocol before they are presented to secondary health care consultants at the joint consultation. In addition, the consultants can consult directly with the youth health care physician if necessary. The examination results are discussed not only directly with the parents, but the youth health care physician will always also pass on the information (with the parents' permission) to the school. This implies that the immediate consequences of the examination results for educational support at school are discussed and that tailored advice is provided. Once treatment has started, the same short lines of communication are used to include the school's experiences with the child in the evaluation. This procedure appeared to be extremely pragmatic in practice, especially due to the 'bridging function' of the youth health care physician between secondary health care and schools, and the youth health care physician's intermediate position in the health care chain both at the start and the end of secondary health care.

Finally, in **Chapter 9** the findings as presented in the preceding chapters are combined and discussed. Recommendations for further research and implications on future course of action are presented in this chapter. The presented studies have clearly demonstrated the significance of an interdisciplinary approach in neurodevelopmental disorders, relating brain structure, function, neuropsychological dysfunctions, social and school functioning from an age dependent perspective. Combining assessment on neurological diagnostics (neuroimaging), neurocognitive outcome, and follow-up by Youth Health Care in children treated for ADHD, three dimensions are brought together by integrating the triad 'structure - function - learning'. Youth Health Care services play a key role in the network of numerous professionals and institutions concerning early detection, referral and prompting interventions in children with developmental disorders.