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Summary
Chapter 1: Introduction and outline

Theme of this thesis is the diagnostic evaluation of developmental delay (DD). DD is an aspecific symptom of many different pathological conditions. When a child presents with DD it is very important to determine the cause, because of the repercussions an etiologic diagnosis can have with respect to medical treatment and genetic counselling. In this thesis, DD is defined as a delay in psychomotor development. This delay may be caused by an underlying condition, but this can not always be determined. Potentially DD results in limitations in functioning in everyday life.

The work presented in this thesis is based on the results of the diagnostic evaluation of a large (n=639) cohort of patients presenting with DD. This diagnostic evaluation was done by a dedicated multidisciplinary team. Unique features of this team were:

- the activity of an interdisciplinary trained physician to guide the diagnostic process;
- a relatively extensive package of screening investigations (table 2.1) in case no diagnosis could be made otherwise.

The expertise of the team members primarily concerned the fields of clinical genetics, child neurology, paediatrics (specifically inborn errors of metabolism), child psychiatry, and ophthalmology.

Chapter 2: The ABC of diagnosing the etiology of developmental disability: a cohort-based algorithm

In this chapter, we describe the results of diagnostic evaluation of the cohort of 639 patients. We assessed the role of several aspects of the diagnostic workup in the multidisciplinary team. What is the role of clinical experts, and which investigations should be done on a screening basis? A diagnosis could be made in 172 (26.9%) patients. Most prevalent diagnoses were chromosomal aberrations (50.6%), inborn errors of metabolism (17.4%) and other monogenic conditions (11.0%).

Regarding clinical expertise: 32.0% of diagnoses were recognized at the first visit by the interdisciplinary trained physician. Another 14.5% of diagnoses was first recognized in the later phase of multidisciplinary evaluation.

Regarding screening investigations: 53.5% of diagnoses were based on screening investigations (table 2.1). Almost all screening investigations proved useful in our cohort. An overview of the relevance of the respective elements, on the basis of the literature and our experience is provided.

A proposal for a simple flowchart, consisting of three steps, for diagnostic evaluation of DD is given in figure 2.1.
Chapter 3: Magnetic resonance imaging and proton magnetic resonance spectroscopy of the brain in the diagnostic evaluation of developmental delay

Cerebral Magnetic Resonance Imaging (MRI) of the brain is frequently done in the diagnostic evaluation of DD. It’s main power is to visualise the dysfunctioning organ. More recently, in vivo Proton Magnetic Resonance Spectroscopy (1HMRS) has become available, enabling quantification of several metabolites in the brain. Abnormalities found with MRI or 1HMRS may or may not help physicians to establish a truly etiologic diagnosis. We assessed the role of MRI and 1HMRS in the first 109 patients from our cohort who underwent cerebral MRI/MRS. Although abnormalities were noted in the vast majority (80 à 90%) of patients, MRI and/or 1HMRS really contributed to an etiological diagnosis in only 10 (9%) patients, all of whom were scanned because of neurological features. In these 10 patients, 1HMRS was diagnostic in one patient and of additional value to MRI findings in 3 patients.

We conclude that MRI and 1HMRS may contribute to the diagnostic evaluation of DD, especially if applied specifically to patients with neurological signs, whereas its role is very limited in children without them.

Chapter 4: Quantitative multivoxel proton spectroscopy of the brain in developmental delay

When interpreting results of investigations in patients, it is an absolute necessity to compare them with the results of normal individuals. This is especially the case when the changes are quite subtle. In the field of 1HMRS in patients with DD, only a few pathognomonical entities exist, among which cerebral creatine deficiency. However, an inconsistent pattern of decreased or increased levels of metabolites was reported in patients with DD, leading to speculations on the pathophysiology of DD. Most studies included very few patients and controls.

We compared the 1HMRS results of 88 patients with DD who could not be diagnosed in our team, with 48 neurodevelopmentally normal controls. These patients and controls were assigned to five age-groups. The relative levels of choline, creatine, N-acetyl aspartate, and glutamate/glutamine in 24 voxels containing white matter and 12 voxels containing gray matter were quantified in an operator-independent manner and expressed in proportion to the total metabolite peak area in the volume of interest. White matter choline in DD showed less decrease with age. Mean choline levels, compared with mean control levels, increased from 99 to 111% with increasing age. This was statistically significant in the highest age groups (P = 0.015 [7 < yr ≤ 12.8] and P = 0.039 [ > 12.8 yr]). Other metabolites did not show clear alterations. The pathophysiological origin and significance may relate to myelination and maturation of the white matter, but this cannot be proven.
Chapter 5: Clinical, biochemical and neuroradiological studies in a child with a treatable disorder of creatin biosynthesis

In chapter 5a we describe the results of treatment of a patient with guanidino acetate methyltransferase deficiency. The biochemical hallmarks of this disease are accumulation of guanidinoacetate (GAA) and deficiency of creatin (Cr). Treatment with oral Cr supplementation resulted in partial normalization of cerebral (measured with magnetic resonance proton spectroscopy) and plasma levels of Cr and GAA. Addition of high dose ornithine to the treatment led to further normalization of plasma GAA, while cerebral Cr and GAA did not improve further.

In chapter 5b, we describe the developmental course of this boy. There was a remarkable difference between clinical observation and formal testing. Clinical observation seemed to indicate relatively isolated expressive language deficiency, leading to suspicion of cerebral Cr deficiency, but formal testing after establishing the diagnosis indicated a rather harmonic, global DD. This highlights the importance of considering Cr deficiency as possible cause of DD.

In chapter 5c, we describe the proton spectroscopy results at the time of diagnosis. A novel finding was that GAA levels were higher in grey matter than in white matter, pointing at the possible relevance of cerebral Cr synthesis.

Chapter 6: Clinical metabolic expertise, rather than metabolic screening, is required to diagnose most inborn errors of metabolism in children with developmental delay

In the first 372 patients from the cohort with developmental quotients lower than two standard deviations below the mean, we assessed the diagnostic yield of screening metabolic investigations, and the diagnostic yield of targeted investigations that could be initiated after clinical metabolic expertise.

16 (4.3%) patients were diagnosed with an inborn error of metabolism (IEM). The diagnostic yield of targeted metabolic investigations after clinical multidisciplinary expertise (14 patients) greatly exceeded the diagnostic yield of screening metabolic investigations (2 patients). The crucial symptoms indicating the respective IEM had not always been noted before referral. Therefore, clinical expertise regarding inborn errors of metabolism is warranted in all undiagnosed patients with a developmental delay, also in patients whose screening laboratory investigations are non-diagnostic.
Chapter 8: Conclusions and future directions

In this chapter we discuss the findings in the preceding chapters with respect to future developments in the field of diagnostic evaluation of DD. Guidelines for the diagnostic evaluation of DD should be updated regularly. On the basis of our results and experience we think that future guidelines should promote that every patient with DD:

- is exposed to concerted multidisciplinary expertise (including clinical genetics, paediatrics – including inborn errors of metabolism, child neurologist);
- is tested with appropriate screening investigations (table 2.1) when a diagnosis cannot be made otherwise.

Future developments are: the application of whole exome sequencing; the development of diagnostic algorithms for patients with possible energy metabolism defects; further research on the use of investigations in the cerebrospinal fluid; the embedding of diagnostic evaluation of DD in the healthcare system.