Cognitive and motor development in children with early-treated congenital hypothyroidism. A longitudinal study

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SUMMARY AND CONCLUSION

The goals of this thesis were to obtain detailed information on the level of cognitive and motor functioning of children with early-treated CH, and to estimate the relative effect of the cause of CH, initial T4 level at screening, and age at start of treatment on cognitive and motor outcome. These goals were accomplished by using two complementary approaches: a diagnostical approach, to establish the general level of cognitive and motor functioning (see *chapter 5*), and an experimental clinical approach, to determine possible mechanisms that may be responsible for the cognitive and motor deficits exhibited by these children (see *chapter 6 - 10*).

An overview of the most important anatomical, endocrinological and biochemical details, necessary for a better understanding of the psychological data, is given in *chapter 2*.

In *chapter 3* the role of thyroid hormones in fetal and neonatal brain development is considered. Thyroid hormone is important for all life processes but crucial for early brain development. Most neonates with severe hypothyroidism show no evidence of the condition at birth. However, in the absence of immediate treatment their condition will deteriorate progressively. For years this has erroneously been interpreted as evidence for the fact that T4 is unnecessary for normal fetal development. The presence of both T4 and receptors for T4 in the early fetal brain has thoroughly challenged this interpretation. In view of recent findings (e.g. transplacental T4 transfer; increased type II 5'-deiodinase), the explanation is not that thyroid hormones are unnecessary in fetal life, but rather that sufficient (maternal) T4 is available to minimize the impact of fetal hypothyroidism and thus that the most severe problems occur peri/postnatally. It follows that, a policy aimed at ensuring maternal euthyroidism during pregnancy and immediate treatment of the hypothyroid infant thereafter might strongly contribute to improved developmental prognosis in children born with CH.

A review of the literature on the developmental outcome in children born with CH is given in *chapter 4*. In the early seventies, before the onset of neonatal

screening, it was generally known that final outcome in CH was inversely related to the duration of the hypothyroidism. Treatment started within three months of age was found to be critical for children with CH, particularly for those with little functional thyroid activity. With the advent of radioimmunoassay techniques to measure thyroid hormone in blood, neonatal screening programmes were implemented all over the world. This offered the opportunity to set up prognostic therapy evaluation studies, which in turn resulted in more detailed information on the relationships between etiology, disease severity, age at onset of therapy, and ultimate prognosis. With the exception of the researchers of the New England Congenital Hypothyroidism Collaborative, who state that early and adequate treatment guarantees optimal outcome, the majority of studies agree that, despite early onset of treatment (within 3 weeks post partum), infants with very low screening T4 concentrations are highly vulnerable to the development of cognitive and motor problems. They have lower IQ's than controls and a broad range of more or less serious neuromotor deficits.

Diagnostic approach

In *chapter 5* the results of the diagnostic assessment are presented. Seventy two children with early-treated CH and 35 matched controls were studied at the ages of 7.5 and 9.5 years. Despite having received treatment at a mean age of 23 days post partum, children with low neonatal T4 concentrations (< 50 nmol/l), particularly those with thyroid agenesis, had significant motor problems and borderline IQ scores of 89 ± 12.6 at the age of 7.5 years, and 91.8 ± 13.8 at 9.5 years of age. Specific aspects of cognitive functioning (e.g. memory, language) seemed relatively undisturbed. The longitudinal data indicated that the detrimental effects on cognitive and motor development, at least in children with severe CH were long lasting. Children with thyroid agenesis were especially likely to have substantial motor problems and borderline intelligence scores as late as 9.5 years of age. Finally, significant correlations between age at start of therapy and both motor and intelligence scores indicated that any delay in start of treatment should be avoided.

Experimental clinical approach

The ability to sustain attention over a prolonged period of time was studied in *chapter 6*. A computer-paced and a self-paced continuous performance task were used in which the performance decrement over time, expressed in response speed, response variability and number of errors, was the main dependent variable. The findings indicated that children with low neonatal T4 levels (< 50 nmol/l) had problems remaining attentive over time in both tasks. Their task efficiency (response variability and number of errors) deteriorated more rapidly as a function of time than that of controls. From a clinical point of view this finding needs to be given serious consideration, since a difficulty in sustaining attention may interfere with performance at school or at work.

Since motor skills seem to be primarily affected in children with early-treated CH, four experimental studies were set up to investigate the mechanisms underlying CH motor problems.

In *chapter 7* we examined the drawing performance of these children in terms of motor programming and motor control, under speed and accuracy instructions. The data indicated that, at the age of ± 7.5 years, drawing performance of children in the low T4 group was characterized by long preparation times, a high level of fluency, short movement times and short pause durations. Moreover, at high speed, these children made longer strokes, with greater variation than the control subjects. Three alternative explanations were proposed:

1) Longer reaction times and increased pause durations under speed instructions in the low T4 children might be evidence of some programming difficulty in these children.

2) The findings seemed to reflect an immature open loop motor control strategy in which children's movements were largely based on motor preprogramming with little attention being given to visual control during execution. Such a strategy is considered to be characteristic of five year old children. Therefore, the low T4 children may be suffering from a developmental delay in motor development.

3) Fine motor performance of the low T4 children may have been the result of a "noisy" motor system and/or the inability to reduce the effects of neuromotor noise on movement outcome.

Based on the explanation in the previous study that the longer reaction times in the low T4 group might be due to difficulties in movement preprogramming, we analysed the extent to which a number of specific cognitive processes preparing for motor action, i.e. stimulus identification, response preparation and response inhibition, are involved in the motor deficits displayed by CH children (see *chapter 8*). For this purpose a variant of Sternberg's response bias task was applied. There were two response conditions: in the baseline condition a yes/no frequency of 50% : 50%; in the response bias condition a yes/no frequency of 30% : 70%. The outcome of the study showed that children with early-treated CH, particularly those with low neonatal T4 concentrations, had slower and more variable reaction times. However, their slower and more variable way of responding could not be attributed to the cognitive preparation of a motor response, e.g. stimulus identification, response preparation, and response inhibition. Rather, it was argued that slowness and variability in responding may have been associated with a less efficient motor execution system.

One of the main themes in this thesis is the possible role of a neocerebellar timing deficit in the etiology of motor problems in children with early-treated CH. The following arguments support to this idea:
1) The finding that in humans sufficient maternal thyroid hormone is available to conserve normal fetal brain development, implies that functions most affected by lack of T4 will be those that develop peri/postnatally.
2) The neocerebellum, which is mainly responsible for coordination and timing aspects of motor performance, undergoes its major development, and thus a period of high sensitivity to T4, during early neonatal life.
3) In the absence of maternal T4, thyroid deficiency between birth and onset of treatment can cause neocerebellar impairment, which may lead to motor coordination and timing problems.
4) Delayed onset of treatment is related to clear signs of cerebellar ataxia and dysmetria.

Chapter 9 describes an experiment in which CH children performed unimanual rhythmic tapping. Based on the idea that the neocerebellum is involved in "computing" the timing requirements necessary for motor control, the Wing and Kristofferson model of repetitive movements was chosen as an analytic tool to

identify the source of the supposed timing deficit. The model postulates two independent processes which are involved in periodic behaviour: a timekeeper (clock) that determines when a response should be emitted, and an implementation (motor delay) process, that executes the command. Wing and Kristofferson proposed that both the motor delay and the clock variance could be estimated from the total 'intertap' variance. To overcome certain estimation problems it was decided to modify the model by explicit incorporation of a drift parameter and by the estimation of clock and motor delay variances using exact rather than approximate values for the expected values of the relevant statistics. Results of the modified analysis revealed that for children with early-treated CH the motor delay variance was four times higher than for the controls, while the clock variance did not differ. It was concluded that motor problems in early-treated CH were not associated with impaired neocerebellar timing, but seemed to be associated with deficits in peripheral mechanisms, involved in motor execution.

In *chapter 10* the supposed neocerebellar timing deficit was investigated from a clinical perspective by concentrating on the clinical signs of movement disorders following neocerebellar injury, e.g. dysmetria and dysdiadochokinesia. Children were instructed to produce sequences of fast continuous line drawings with a pen between predefined target circles on an XY-digitizer. Movements were analysed in terms of movement time, pause duration, overshoots, undershoots, velocity and force. The data showed that motor performance of children with thyroid agenesis was characterized by overshoots, high velocity, short movement times and a large initial force impulse. The only finding in favour of a neocerebellar timing deficit was the increased number of overshoots, while the other findings were not in line with a neocerebellar explanation. It was concluded that children with thyroid agenesis seem to be characterized by a deficient motor execution system. In terms of the Van Galen model this means that children may suffer from a noisy motor system and/or are less able to apply effective stiffness control through muscle co-contraction in order to minimize motor noise to an adequate level.

In *chapter 11* we obtained detailed information on the behaviour at home and at school of a group of children with early-treated CH. Two standardized

questionaires were used: the Groningen Behaviour Checklist Family situation and the Groningen Behaviour Checklist School situation. Behavioural comparisons were made between various CH subgroups, as well as between CH patients and matched controls. For differential diagnostic reasons CH children were also compared with children with early-treated PKU and children with signs of ADHD. At cluster level it appeared that CH children were more "introverted" than controls. Moreover, PKU children had less favourable scores than CH children on the clusters "negative task orientation", "positive task orientation" and "social negativity." Finally, CH children scored lower than the ADHD children on "negative task orientation" and "social negativity" and higher on "positive task orientation." At scale level, CH children were more "clumsy" than both the controls and the PKU patients. The thyroid agenesis children showed more signs of "clumsiness" than the other CH subgroups. Since "introversion" is typically associated with clumsiness, and since CH children were found to be more "clumsy" than the controls, it seems plausible to suggest that CH motor problems strongly contribute to CH "introversion".

CONCLUSION

In the diagnostic part of the study we showed that early and adequate treatment does not guarantee optimal outcome in all children with hypothyroidism. It appeared that low neonatal T4 concentration, and thyroid agenesis in particular, make a child highly vulnerable to the development of both intelligence and motor problems. This may be seen as evidence for the fact that these CH patients have some neurological damage at the time of referral, arising from exposure to very low T4 levels prenatally or during the interval between birth and referral. In view of this, a delay between birth and onset of treatment of 23 days in children with severe hypothyroidism may be considered too long to provide optimal protection against the occurrence of neurological impairment after birth. A more definite conclusion with respect to this matter awaits additional research, which should be aimed at measuring the effects of a minimal delay between birth and onset of treatment on cognitive and motor outcome in these children.

This study has been one of the first to identify possible cognitive and motor

deficits in CH on the basis of what is known about the early neurological development of children born with thyroid deficiency and to apply advanced experimental psychological measurement techniques to describe such deficits. Two important findings were made. The first concerns the finding that CH children have difficulty maintaining attention over time, which may have important implications for their performance at school or at work. The second concerns the more elementary finding that CH motor problems are probably related to (peripheral) processes associated with motor execution and/or motor control rather than to (central) processes associated with motor programming and/or motor timing. It seems as if children with CH suffer from a dysfunction in applying effective stiffness control through muscular co-contraction.

Considering the effectiveness of the experimental clinical approach in detecting the origins of CH cognitive and motor deficits, future research should be aimed at the elaboration of the above findings. For instance, including direct measurement of muscle activity (EMG analysis) would allow an examination of the relationship between agonist and antagonist activity in fast repetitive movements, a notion that is considered to be critical for cerebellar function. Further, including quantitative measures of motor noise and limb stiffness would allow an investigation of the amount of motor noise and the quality of motor noise management through stiffness control in CH children.