Psychological consequences of congenital hypothyroidism: Cognitive, motor and psychosocial functioning
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Summary of the thesis (English)
Summary in English

In the Netherlands approximately 70 children are diagnosed with (permanent) congenital hypothyroidism (CH) each year. About 90% of them has permanent CH of thyroidal origin (CH-T), caused by a total or partial absence of thyroid hormone, as a result of a congenital anatomical or biochemical defect of the thyroid gland. Because thyroid hormone is essential for development of the central nervous system, especially during prenatal life and the first years after birth, these children are at risk for brain damage and subsequent cognitive and motor deficits. Moreover, thyroid hormone plays an important role in metabolism. Therefore, lifelong treatment with thyroxine (T4), starting as early as possible, is of utmost importance. The aim of neonatal CH screening programs is to prevent cerebral damage through early initiation of T4 supplementation. To optimize the effect of early treatment on cognitive and motor outcome in CH patients, heelpuncture timing and treatment modalities have been adapted several times since the introduction of the nationwide screening in The Netherlands in 1981.

In this thesis, the results of our study entitled “Effect evaluation of the neonatal screening in The Netherlands” are described with focus on (1) cognitive and motor consequences of CH and the effect of the changes in timing and treatment modalities on cognitive and motor outcome over the years, and (2) psychosocial functioning of children and young adults with CH, including health related quality of life (HRQoL), developmental tasks, and self-esteem. Furthermore, all outcomes were analyzed in relation to severity and to treatment variables, such as timing of initiation of T4 supplementation and initial T4 dose. Three nationwide cohorts of patients with CH have been included (1981-82; tested at 21.5 years of age; 1992-93, tested at the age of 10.5 years and 2002-04, tested at ages of 1 and 2 years).

In Chapter 1, the general introduction, the medical and psychological aspects of CH are illustrated. A short introduction is given on the thyroid gland, thyroid hormones, the role of thyroid hormone in fetal brain development, CH and neonatal screening. Furthermore, psychological consequences of CH are described. Main findings of previous studies on cognitive and motor deficits in children with CH are summarized. Several studies on the effect of the screening and early treatment have shown that most children with CH achieve scores for intelligence within the normal range, however those with severe CH often show, significant deficits in mean IQ scores despite early treatment. Thus, even in patients with CH who receive early treatment, intellectual, motor and neurocognitive deficits have been reported. In addition, next to negative effects on general cognitive functioning children with CH are also at risk for learning disabilities particularly in math and learning to read, hearing impairment and visual problems and subtle and specific neurocognitive impairments, such as memory and attention problems. Besides general cognitive impairments, deficits in motor functioning are commonly seen in children with CH. These deficits were observed in fine motor skills, gross motor skills
and static balance. Despite the important results obtained in terms of standardization of screening procedures and improvements in time and dose at starting treatment, controversy exists in literature worldwide on the effect of these changes on the development of the child.

Over the years, much has been reported about the cognitive and motor development of children with CH while little is known about social-emotional functioning of patients growing up with CH. Psychosocial functioning of young adults and children with CH, such as Health Related Quality of Life (HRQoL), developmental tasks (Course of Life [CoL]) and self-esteem has not been studied thoroughly. Nevertheless, detailed knowledge on these topics can be highly relevant for optimizing support of children with CH.

The **first part** of this thesis presents the results of the cognitive and motor outcome in three different cohorts of patients. All outcomes were analyzed in relation to treatment variables.

In **Chapter 2** the results are presented of the intellectual and motor outcome of young adults from the 1981-1982 cohort with congenital hypothyroidism diagnosed by neonatal screening. In this cohort 70 patients with thyroidal CH were tested at a mean age of 21.5 years; 49 of them were previously tested at 9.5 years. Their median age of start of treatment was 28 days (range 4-293). Young adults with CH scored significantly lower on the Full Scale IQ score (95.8) than the norm population (100), as measured with the Wechsler Adult Intelligence Scales (WAIS-III). Furthermore, CH patients had significant worse total motor scores (7.8) than the norm population (3.2), as measured with the Movement ABC. Both intellectual and motor outcome were most impaired in patients with severe CH: mean full scale 91.3, mean total motor impairment score 9.8. In the group that was tested previously at the age of 9.5 years, no significant change in IQ scores from childhood to adulthood was found and for the majority of patients motor score classification remained the same. Initial T4 concentration (a measure of the severity of CH) was correlated with IQs and motor scores. There was no correlation found between starting day of treatment and IQs and motor scores.

**Chapter 3** describes the intellectual and motor outcome of 10 year old children with CH born in 1992-1993, in whom treatment was initiated at a median age of 20 days (range 2-73 days). For the total CH-T group the mean Full Scale IQ score (97.3), measured with the Wechsler Intelligence Scale for children (WISC), was not significantly different from the population mean (100). However, in patients with severe CH the mean Full Scale IQ score (93.7) was significantly lower compared to the norm population. In all three severity subgroups significant motor problems were observed, as measured with the Movement ABC, but most pronounced in the severe CH group. These results were compared with those obtained from patients born and screened in 1981-82, examined at the age of 9.9 years of age, in whom T4-supplementation was initiated significantly later. Essentially, findings from 10-year old children born in 1992-1993 were similar to those10-year old children of the 1981-1982 cohort. Apparently, advancing initiation of T4-supplementation from 28 to 20 days after birth did not result in improved
cognitive or motor outcome in CH-T patients.

In Chapter 4 we studied cognitive and motor outcome from 95 children with CH-T born in 2002-2004 at 1 and 2 years of age. These children, who were screened and treated according to national recommendations and current practice, had subtle deficiencies in mental developmental index scores (MDI) as measured with the Bayley scales of Infant Development (BSID-II-NL), at two years of age. This was most prominent in children with severe CH-T. The mean mental developmental index scores (MDI), of the severe, moderate and mild CH-T group at 1 year of age and the moderate and mild CH-T groups at 2 years of age were similar to the population mean. Furthermore, children with CH-T had motor problems at 1 and 2 years of age, irrespective of severity of hypothyroidism. In all three severity subgroups significant lower psychomotor developmental index scores (PDI) scores as measured with the BSID-II-NL were observed. No correlations were found between starting day of treatment and developmental outcome. An effect of initial disease severity was observed only on MDI, whereas all disease-severity groups were equally affected on PDI. Initial T4 concentration and initial T4 dose were weak predictors for developmental outcome.

In the second part of the thesis, the psychosocial consequences of CH are reported. The aim of chapter 5 was to describe the HRQoL, Course of life (CoL) and self-esteem- mean scores and percentages at risk in 69 young adults with CH, born in 1981-1982. CH patients are more often at risk for HRQoL impairment and reported lower HRQoL on several domains (cognitive functioning; sleeping; pain; daily activities; vitality; aggressiveness; depressive moods) compared to healthy adults. Patients reported a lower self-esteem and had a delayed course of life on the domain of social development compared to the norm population. With respect to the milestones of social development, a significant lower percentage of CH patients compared to the comparison group had been a member of a sports club for at least one year during primary school and secondary school. The sociodemographic outcomes and their final educational level until now did not differ from that of the normal population. There were no significant differences between the severity groups for HRQoL, CoL and self-esteem.

In chapter 6 the HRQoL and self-worth in 10-year old children with CH diagnosed by neonatal screening have been studied. The results show that having CH has a negative impact on several aspects of HRQoL and self-worth. Significant differences in mean scores were shown in all domains of the TACQoL except for physical functioning. 10-year-old children with CH born in 1992-1993 experienced worse HRQoL than the norm population with respect to cognitive, motor and social functioning, negative moods and autonomy. In addition, a greater percentage of children with CH, especially patients with severe CH, appeared to be at risk for impaired HRQoL as well as for impaired self-worth with respect to school performance and athletic performance. Lower IQ was only significantly associated with worse cognitive HRQoL. Severity, age at onset therapy, initial T4 dose and motor skills were not significantly associated
with HRQoL and self-worth.

The purpose of chapter 7 was to explore HRQoL in the third cohort of investigated children with CH at two years of age and to compare the results to those of the general (healthy) population. Furthermore, the study examined the influence of severity of CH on HRQoL. Although HRQoL in most domains appeared similar to the Dutch norm population, this study demonstrated that children with severe CH have a lower HRQoL on two of the twelve scales of the TAPQoL: motor functioning and communication. Furthermore, the regression analyses in the present study demonstrated that worse scores on the MDI and PDI were related to lower HRQoL regarding communication, and worse scores on the PDI were related to lower HRQoL regarding motor functioning. Thus, the parent's perception of motor and cognitive functioning, as measured with the TAPQoL, equates with objective findings.

In the final chapter 8, main findings of the results of the preceding chapters are discussed and reflections of the main findings are given. Four key messages were formulated:

1. For children and adults with severe CH, cognitive deficits are a consequence.
2. Deficits in motor functioning are prominent in most children and adults with CH.
3. Impact of treatment factors on cognitive and motor outcome after the implementation of the Dutch neonatal screening program is only limited.
4. Children and adults with CH are at risk for psychosocial problems.

Next, limitations of the studies were considered and recommendations for follow-up research were provided as well as implications of this study for clinical practice. Three important recommendations for clinical practice were formulated:

- Be aware of possible consequences of CH and provide relevant information.
- Monitor and screen patients with CH.
- Refer to targeted care if necessary.

In conclusion, this thesis shows that although the development of children with CH is considerably improved by early treatment as a result of neonatal screening, they are still at risk for motor and cognitive problems. This applies especially for children with severe CH. Fine-tuning of treatment and timing does not seem to further improve the positive effect of the screening program. This is probably due to the prenatal hypothyroid state or the thyroid hormone deficiency in early life.

Results of this thesis also show that CH has a negative impact on several aspects of HRQoL, developmental milestones (CoL) and self-esteem. Patients reported more problems with cognitive, motor and psychosocial functioning. This is a source of concern that deserves attention. Therefore awareness of psychological consequences among health care physicians, screening, monitoring and referring of patients to targeted care is of utmost importance.