INVITED COMMENTARY

Congenital hypothyroidism: treat children but don't forget their parents

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Congenital hypothyroidism (CH), detected in 1:3500 to 1:4000 newborns world-wide, is one of the most common preventable causes of mental retardation if treated early (1). In the 1970s neonatal screening programmes were started to guarantee detection and treatment from the first weeks of life. Prior to the onset of screening, when clinical diagnosis was commonly delayed, the neurodevelopmental prognosis in CH children was poor. A clear inverse relationship was evident between age at start of treatment and intelligence quotient (IQ), the worst outcome (75% with IQs < 80) being observed in those infants diagnosed at the ages of 6 and 9 months (2). Screening programmes have been extremely successful in the detection and early treatment of infants with CH, and in preventing the serious neuropsychological sequelae of this condition. Although neuropsychological follow-up studies in general have been favourable, slightly lower IQs compared with unaffected controls have been reported, particularly in the most severely affected infants (1, 2). Some follow-up programmes report good psychometric outcomes, with IQs similar to controls (3–5) and no apparent impediment in school performances (3). Other reports indicate a mild decrease in IQs of CH infants in spite of early substitution treatment (6–9). The latter studies also report poorer motor skills (6, 10, 11), defective language abilities (12) and learning problems in school (13). A 1996 meta-analysis of literature data, which included 675 patients and 570 controls in North America and Europe, showed a trend toward lower IQs and slightly poorer motor skills in CH patients compared with controls (14). Pooling of data showed a significant deficit of the mean IQ of 6.3 points (95% confidence interval: 4.7–7.8). A common problem of these studies is the difficulty in controlling for appropriate modulating influences of neuropsychological development such as genetic background, socio-economic status, cultural level of the family and education burden. While false positive cases, siblings, matched or unselected normal children have been used as controls (14), unaffected identical twins raised in the same family would be the best control when complex functions such as intelligence are investigated. Two genetically identical twins,

one of whom had thyroid agenesis and the other who was unaffected were described in this Journal in 1997 (15). In spite of early (4th week of life) and adequate L-thyroxine (L-T₄) therapy (9 µg/kg per day), the CH twin showed IQ scores that were in the normal range but lower compared with the unaffected twin. At the age 7 of years the deficit in total IQ scores was 7 points (108 vs 115), a figure similar to that estimated in the meta-analysis of literature data.

Several risk factors for the eventual outcome of the neuropsychological development in early-treated CH have been evaluated. These include: (i) pretreatment serum T₄ concentration; (ii) neonatal skeletal maturation; (iii) aetiology of CH; (iv) age at start of treatment; (v) starting L-T₄ dose; (vi) adequacy of substitution treatment in the first 2 years of life and even afterwards; (vii) socio-economic class of the family. Most follow-up studies found a significant correlation between cognitive development and pretreatment serum T₄ (4, 6, 8–10, 16). In a multicentre survey in the UK (16), the relationship between IQ and serum T₄ level at diagnosis was discontinuous with a threshold of 3.3 mg/dl (42.8 nmol/l). Below this level, a 10-point IQ deficit was observed as compared with control subjects of similar social class. Above this threshold, children were unlikely to suffer more than a 5-point deficit. A skeletal development at the time of diagnosis ≤ 36 weeks of gestation (12) or an area of the knee epiphysis < 0.05 cm² (9) were both found to be associated with significantly lower IQs compared with control groups. Overall, the severity of foetal-neonatal hypothyroidism, defined by skeletal maturation at diagnosis and/or pretreatment serum T₄, is the most important independent risk factor for the eventual neuropsychological outcome (14), partly due to an effect on brain development determined prenatally. Small amounts of maternal T₄ pass the placenta (17), but it is difficult to believe that this limited maternal supply of T₄ is sufficient in most cases of severe CH. In keeping with these observations, several studies found that children with severe CH due to thyroid agenesis achieve significantly lower IQs compared with hypothyroid children with thyroid ectopy who display some degree of residual thyroid function (6, 10, 18).

Treatment variables also play a role in the cognitive development of children with CH. The duration of neonatal hypothyroidism that occurs between delivery and the restoration of euthyroidism with therapy depends on both the age at starting treatment and the initial dose of L-T₄. T₄ half-life appears to be shorter in the neonate, so that maternally transferred T₄ levels fall rapidly (17). A significant negative correlation between age at start of treatment and neuropsychological outcome was found in early follow-up studies reporting the initial results of screening programmes (19). Development quotient scores of infants treated later than 50 days of age were below the normal mean (19). No such relationship has been reported in more recent surveys (9, 16), probably due to a general improvement in the screening procedures which resulted in earlier diagnosis and treatment of CH in the majority of affected children. Depending on the initial dose of L-T₄, neonatal serum T₄ and thyrotrophin (TSH) levels may take several weeks to rise to the normal range. In the US (20) higher starting doses of L-T₄ (10–15 µg/kg per day) have been used to treat children with CH than in Europe (5, 16, 21) and have been associated with a shorter time to achieve euthyroidism. The Quebec group (9) reported that infants with severe CH, defined by low serum T₄ levels and retarded skeletal maturation, who had been treated with an initial dose of L-T₄ of 6 µg/kg per day beginning at a mean age of 5 weeks had a mean IQ at the age of 12 years that was 15 points lower than that of infants with less severe CH. In a subsequent study by the same group (22), infants with severe CH were treated at a median age of 14 days with a starting dose of 12.1 µg/kg per day (median). At 18 months of age these severely affected CH children had a development quotient similar to that of infants with less severe hypothyroidism, who served as controls (22). The authors concluded that earlier treatment with a higher starting dose of L-T₄ eradicated the gap in IQ scores between children with severe CH and those with the moderate form of the disease. It is worth emphasising that in this study the mean serum T₄ concentration of infants treated with a higher dose of L-T₄ was supraphysiological in the first few months of life, while serum tri-iodothyronine (T₃) levels were within the normal range at all times. Clinical signs of thyroid hormone excess or unduly advanced bone maturation were not observed in the Quebec study, but evidence from other reports suggests that higher starting doses of L-T₄ lead more commonly to behaviour problems reflecting anxiety, social withdrawal and poor concentration (2, 7). Thus, in the absence of randomised controlled studies comparing the effects on long-term outcome of the higher and lower doses of L-T₄, the use of initial dosages greater than 8–10 µg/kg per day should probably be restricted to those CH infants with extremely low (<3 mg/dl) pretreatment serum T₄. Suboptimal treatment in the first and second year of life (3, 8), a time-period when the brain is critically dependent on T₄ for normal development, may also

negatively affect the neuropsychological outcome of CH children. Using linear multiple regression analysis and controlling for socio-economic status and pretreatment serum T₄ concentration, a follow-up study in Norway (8) found that at 2 years of age 19% of the variance in mental development scores was due to treatment variables (combinations of serum T₄ and TSH during the first year and bone age at 1.5 years). At 6 years of age, 35% of the variance in verbal IQ could be attributed to treatment variables: initial L-T₄ dose, mean serum T₄ concentration in the first year and a combined measure of serum T₄ and TSH during the second year (8). Even at the age of 15 or 16 years improvement in thyroid control by adequate substitution treatment was associated with a significant improvement in psychometric test scores (23). The socio-economic state of the family also has a significant impact on mental development (16, 19). This is evident both in infants with severe CH and in those with less severe hypothyroidism (16).

In this issue of the *European Journal of Endocrinology* Salerno *et al.* (24) report the intellectual outcome at 12 years of age of 40 children with CH detected by neonatal screening and treated at a mean age of 28 days with a standard initial dose of L-T₄ (25 µg/day; 6.8 ± 1.8 µg/kg per day). Similar to some previous studies (3–5) the mean full-scale IQ score of CH children did not significantly differ from that of their siblings used as controls. However, the mean performance IQ was significantly lower, suggesting minimal brain damage. Within the performance score, the items significantly affected were picture completion, block design and object assembly, which are considered to have a high spatial loading. Thirteen patients (32%) in the present cohort showed definitely low IQ scores (<80), significantly lower than those found in other patients and in unaffected siblings. Confirming the results of previous reports, low IQ scores were associated with a lower pretreatment serum T₄ concentration (4, 6, 8–10, 16), thyroid agenesis (6, 10, 18), less adequate treatment, probably due to poor compliance from the second year of life onwards (3, 8, 23), and lower familial IQs (10). In our opinion these findings again emphasise the need for earlier initiation of treatment (within the first 2 weeks of life) and for a higher starting dose of L-T₄, with the goal of shortening the duration of postnatal hypothyroidism. A specific effort is also recommended to improve the adequacy of L-T₄ substitution and to ameliorate compliance to treatment. As suggested by the New England Congenital Hypothyroidism Collaborative (23), hormonal values should be monitored monthly as well as 2 weeks after any change in L-T₄ dosages at least during the first year of life. Monitoring should then be continued three or four times a year through adolescence. The measurement of serum TSH, free T₄ and possibly free T₃ is recommended, and the dose of L-T₄ should be adjusted to maintain serum TSH concentrations in the normal range (18).

A new aspect of the present paper is the careful

evaluation of the parental attitude to their children's disease. Most previous studies on early-treated children with CH report cognitive, motor and linguistic development, but do not specifically address the affective relationship between parents and affected children. Congenital diseases such as CH may result in a sense-of-guilt in the parents and in frustration due to the loss an idealised 'perfect' child. CH is a chronic disease associated with the need for continuous medical therapy and frequent monitoring. It is also a latent disease, because CH manifests with few clinical signs that are nicely controlled by substitution therapy but might result in impaired growth, neurologic deficits or mental retardation later in life. Parental worries and anxiety consequent to the birth of a baby with a congenital, chronic and possibly invalidating disease might be projected on the child, producing emotional distress, poor self-confidence and an anxious or depressed behaviour (25). In the Salerno *et al.* study (24), interviews with parents of CH children showed that the diagnosis of CH, the perspective of endless treatment, and the need for frequent assessments had deleterious effects on their psychological well-being. Three educational-affective attitudes were identified in the parents: (i) 38% of them showed appropriate coping with the emotional distress and a good attitude toward rearing the child and toward the therapeutic programme; (ii) the majority (51%) reacted with anxiety resulting in overstimulation of the child and strict compliance to therapy; (iii) a small minority (11%) completely refused the disease showing poor attention to the emotional well-being of their child and poor compliance to treatment. The three types of personality profiles were distributed equally between children with low or normal IQs, indicating that their influence on poor cognitive performances was minor. Interestingly enough the fact that overstimulation and control were the most frequent parental attitudes might explain why in the present study CH children with normal IQs performed better than their siblings on the verbal tests. While the latter finding might be reassuring for the cognitive outcome of CH children, the high frequency of incorrect psychological attitudes observed in parents strongly suggests that the follow-up of CH children should include an evaluation of the parent-child affective relation. Psychological counselling of parents might be mandatory in most families of CH children.

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