CASE REPORT

Neuropsychological development in a child with early-treated congenital hypothyroidism as compared with her unaffected identical twin

Stefania Bargagna1, Luca Chiovato2, Daniela Dinetti1, Lucia Montanelli2, Cristina Giachetti1, Elisabetta Romolini1, Mara Marcheschi1 and Aldo Pinchera2

1Stella Maris Scientific Institute, Institute of Developmental Neurology, Psychiatry and Educational Psychology, and 2Institute of Endocrinology, University of Pisa, Pisa, Italy

(Correspondence should be addressed to Luca Chiovato, Institute of Endocrinology, University of Pisa, Viale del Tirreno 64, 56018 Tirrenia-Pisa, Italy)

Abstract

Objective: Neonatal screening for congenital hypothyroidism (CH) prevents the serious neuropsychological features of CH, but the question remains whether intelligence and motor skills of CH children treated early are completely normal.

Design: In this report we describe the rare case of two genetically identical twins, only one of whom was affected by CH due to thyroid agenesis. L-Thyroxine (9 µg/kg body weight/day) therapy was initiated at 27 days of age and was adequate throughout the follow-up.

Methods: Neuropsychological evaluation was performed on the twins in parallel from 3 months to 8 years of age.

Results: The CH twin (NB) did not show major neuromotor impairments but, compared with the unaffected twin (EB), she had a slight delay in postural/motor achievements and in language development that completely disappeared at 8 years of age. On standardised tests of intelligence, NB was indistinguishable from control children but, compared with her twin, she had lower IQ scores in most testing occasions up to 7 years of age (NB = 108 vs EB = 115). School achievements of NB did not significantly differ from those of her classmates but, compared with her twin, she scored worse in writing, mechanical reading, verbal memory, and possibly in arithmetic.

Conclusions: Because the twins were genetically and phenotypically identical, were raised in the same environment, and received a similar education, it is concluded that hypothyroidism in utero and in the first neonatal month was responsible for the lower neuropsychological achievements of the CH twin. While foetal hypothyroidism is at present unavoidable, earlier diagnosis and initiation of treatment in neonates with CH are important and highly recommended.

European Journal of Endocrinology 136 100–104

Introduction

Neonatal screening programmes for congenital hypothyroidism (CH) have been effective in preventing the serious neuropsychological features of this disease that were commonly observed before the advent of mass screening. Although neuropsychological follow-up studies in general have been favourable (1, 2), controversy exists as to whether intelligence levels of CH children treated early differ from those of control subjects. Many programmes report good psychometric outcomes (1, 3, 4), with intelligence quotients (IQ) similar to controls. Other follow-up studies show a mild decrease in IQs of infants with CH detected by neonatal screening as compared with controls (5–8). 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. False positive cases, siblings, matched or unselected normal children have been used as controls in studies of children with CH (1). However, identical twins of CH children would be a better control when complex functions such as intelligence are investigated (9). In this paper, we report two genetically identical twins one of whom was affected by CH due to thyroid agenesis. The CH twin was detected by neonatal screening and treated since the first month of life. Both twins were raised in the same family, and received a similar education. Their
neuropsychological development was studied parallel, and their motor skills, cognitive development and school achievements were compared.

**Patient and unaffected twin**

Two female dichorial twins were delivered by caesarean section after 38 weeks of gestation by a 31-year-old woman in her first pregnancy. The twin with congenital hypothyroidism (NB) weighed 2750 g and the unaffected twin (EB) 2500 g. Neither of the two suffered anoxia or any other neonatal disorder. In the first two weeks of life, NB showed umbilical hernia, feeding problems, hypotonia, prolonged jaundice and a large posterior fontanel. Neonatal screening on day 7 of age revealed a low thyroxine (T₄) level (20-5 nmol/l) and a high thyrotrophin (TSH) level (>100 mU/l). After recalling, serum tests on day 25 of age confirmed low total (T) T₄ (20-0 nmol/l) and free (F) T₄ (1-4 pmol/l) concentrations, associated with high TSH (>250 mU/l) levels. EEG showed slow amplitude potentials and a diffuse slowing. Therapy with L-thyroxine (L-T₄) (9 μg/kg body weight/day) was initiated at 27 days of age. By 58 days of life, her TT₄ level was up to 177-6 nmol/l (FT₄ = 15-4 pmol/l), and TSH level had decreased to 9 mU/l. The initial dose of L-T₄ was adjusted taking into account the increase in body weight and the results of FT₄, FT₃, and TSH in serum samples taken at 3, 4, 6, 9 and 12 months of age and every 3-6 months thereafter. At 3 months of age, the serum TSH level was normal (1-7 mU/l) and remained so throughout the treatment with L-T₄. Growth velocity of NB during L-T₄ treatment was normal and paralleled that of her unaffected twin. At 2 years of age, one month after discontinuation of L-T₄, a thyroid scan with technetium 99m revealed absent thyroid tissue in the neck and in ectopic position. Thyroid indices were again found to be abnormal: FT₄ < 2-5 pmol/l; TSH = 330 mU/l. A diagnosis of thyroid agenesia was formulated. Simultaneous tests on blood spot and serum samples obtained from EB during the first year of life showed normal results for T₄ and TSH.

Phenotypic similarity prompted us to investigate whether the two dichorial twins were genetically identical. Human leukocyte antigens (HLA) class I (HLA A 2, 3; HLA B 35, 51) and class II (HLA DR 11, 12; HLA DR 52, HLA DQ7) were common to both twins. At 'finger-print DNA test' by polymerase chain reaction the twins were identical for all 16 polymorphisms studied (ABO, RH, HP, GC, PI, ACP, PGM, ESD, APOB, YNZ22, D1S80, TH01, VWA, FES, F13A1, DQA1). The probability of not being genetically identical was estimated to be lower than 1/10⁵.

**Mother**

Thyroperoxidase antibody (TPOAb = 1:102400) was found in sera of both twins during the first month of life, and progressively decreased in titre until disappearance at 9 months of age. Thyroglobulin antibody (TgAb) was negative. The mother was diagnosed as having a previously unrecognised, asymptomatic autoimmune thyroiditis with a small goitre and high titres.

---

**Table 1** Neuromotor scores (standardised Touwen neurological examination) measured at 3, 5 and 8 years of age in NB (twin with congenital hypothyroidism) and EB (unaffected twin) compared with control children (C; mean ± s.d.).

<table>
<thead>
<tr>
<th></th>
<th>NB</th>
<th>EB</th>
<th>(n = 11)</th>
<th>C</th>
<th>NB</th>
<th>EB</th>
<th>(n = 14)</th>
<th>C</th>
<th>NB</th>
<th>EB</th>
<th>(n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance</td>
<td>4</td>
<td>6</td>
<td>8±4 ±1·0</td>
<td>6</td>
<td>7</td>
<td>9±6 ±0·8</td>
<td>10</td>
<td>10</td>
<td>9±8 ±0·4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal coordination</td>
<td>1</td>
<td>3</td>
<td>6±1 ±1·8</td>
<td>2</td>
<td>7</td>
<td>7±8 ±0·4</td>
<td>8</td>
<td>8</td>
<td>7±8 ±0·7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross motor</td>
<td>4</td>
<td>5</td>
<td>6±4 ±1·5</td>
<td>7</td>
<td>7</td>
<td>7±2 ±0·6</td>
<td>8</td>
<td>8</td>
<td>7±7 ±0·8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor</td>
<td>2</td>
<td>4</td>
<td>6±3 ±2·8</td>
<td>5</td>
<td>7</td>
<td>8±8 ±1·3</td>
<td>10</td>
<td>10</td>
<td>9±7 ±0·9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>8</td>
<td>8</td>
<td>8±6 ±2·2</td>
<td>10</td>
<td>10</td>
<td>9±6 ±0·9</td>
<td>10</td>
<td>10</td>
<td>9±9 ±0·5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated movements</td>
<td>7</td>
<td>7</td>
<td>9±0 ±1·7</td>
<td>8</td>
<td>8</td>
<td>10±6 ±0·6</td>
<td>12</td>
<td>12</td>
<td>10±6 ±0·8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>46</td>
<td>54</td>
<td>63±3 ±10</td>
<td>58</td>
<td>66</td>
<td>72±8 ±3·1</td>
<td>78</td>
<td>78</td>
<td>75±5 ±3·1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1** Postural and motor achievements in NB (twin with CH) (■) and EB (unaffected twin) (○) in the first 2 years of life. HH = holding up of head; LS = sitting by herself for a sufficiently long period; S = standing; W = walking.
of circulating TPOAb. Her thyroid function was normal. TSH-receptor antibodies (TRAb) with TSH-blocking activity (10) were not found in the mother’s serum and in sera drawn from twins during the first month of life.

Methods

In vitro assays

Commercial kits were employed for the following determinations: TT4 and TT3 (ARIA II, Beckton Dickinson, Milan, Italy); FT4 and FT3 (FT4 Kit and FT3 Kit, Technogenetics, Milan, Italy); TSH (Delfia hTSH, Pharmacia, Turku, Finland); TPOAb and TgAb (Micromsome Test Kit and Thyroid Test Kit, Fujizoki, Tokyo, Japan); TRAb (TRAK radioreceptor assay, BRAHMS, Berlin, Germany). A bioassay was used to search for TSH-blocking antibodies (10).

Neuropsychological evaluation

Neurodevelopmental assessment was performed by the standardised Touwen neuropsychological examination (11). Cognitive abilities were assessed by psychometric scales: Brunet-Lézine test from birth to 2 years of age, Terman-Merrill scales from 2 to 6 years of age; Wechsler Intelligence Scales Children Revised (WISC-R) at 7 years of age. Psychometric tests were performed at 3, 6, 9, 12, 18 and 24 months, and at 3, 5 and 7 years of age. The Bortolini–Franzago phonological evaluation (12), tests for comprehension (from 6 to 8 years of age) and repetition (at 8 years of age) of grammatical phrases were used to assess language development and speech abilities. For the above tests, 34 age-matched female children served as controls. To evaluate school achievements, twins were assessed for arithmetic, reading comprehension, writing, mechanical reading, verbal memory and spatial memory at the age of 8 years while attending the primary school in parallel but separate classes. Testing occurred in the twins’ school and their anonymity was maintained as best as possible. Control classmates were recruited by obtaining permission from the school board and parents. Teachers were ‘blinded’ as to the child with CH. Results of the twins’ performances were expressed as Z-scores, i.e. the individual result calculated as s.d. from the mean of classmates. The twins have been living in a favourable environment, a middle-class family of good socioeconomic status. The mother is a teacher with a university degree, and the father is an accountant with a high school degree. Informed consent was obtained from parents. The study had ethical committee approval.

Results

Major impairments in neurodevelopmental development were not observed in the CH twin (NB) (Fig. 1, Table 1). In the first 2 years of life, NB showed a 2- to 3-week delay in postural and motor achievements with respect to her unaffected twin (EB). NB achieved holding up the head at 4 months, sitting at 7 months–15 days, standing at 11 months–15 days, and walking at 18 months of age. At 3 and 5 years of age, total neuromotor scores in NB were significantly lower (< 2 s.d. from the mean) than in control children. At both ages, NB performed significantly worse in distal coordination, balance and fine motor performances. Less marked differences in motor skills were evident in NB compared with EB. When she was 8 years old, NB showed a clear improvement in total and selective neuromotor scores which no longer differed from those of EB or of control children. Total IQ scores of NB were always within the normal range of tests, and increased from 93 at 3 months to 108 at 7 years of age (Tables 2, 3). IQ scores of NB did not significantly differ from those of control children. As compared with her unaffected twin, NB had lower IQs

Table 2 Scores for development quotient (DQ) on the Brunet-Lézine test observed in NB (twin with CH) and EB (unaffected twin) at 3, 6, 9, 12, 18 and 24 months of age. Normal values (N) for DQ at different ages are shown as means ± s.d. Scores for intelligence quotient on Terman-Merrill scales in NB and EB at 3 and 5 years of age are also shown. Results in control children (C) are given as means ± s.d., n = 24 at 3 years; n = 23 at 5 years.

<table>
<thead>
<tr>
<th>Development quotient</th>
<th>Intelligence quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
</tr>
<tr>
<td>NB</td>
<td>93</td>
</tr>
<tr>
<td>EB</td>
<td>100</td>
</tr>
<tr>
<td>N</td>
<td>102 ± 11.2</td>
</tr>
<tr>
<td>C</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3 Scores for Intelligence Quotient (IQ) on WISC-R observed in NB (twin with CH) and EB (unaffected twin) at 7 years of age. Results in control children are given as means ± s.d., n = 20.

<table>
<thead>
<tr>
<th></th>
<th>NB</th>
<th>EB</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>108</td>
<td>115</td>
<td>105 ± 10.5</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>105</td>
<td>112</td>
<td>105 ± 9.8</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>111</td>
<td>115</td>
<td>106 ± 10.1</td>
</tr>
</tbody>
</table>
Language development was slightly delayed in both twins as compared with the normal pattern. NB showed babbling at 8 months, the first words at 15 months, word combinations at 24 months, and the first simple phrase at 30 months. She had a slight delay in most language achievements with respect to EB, but this gap never exceeded 2 weeks. At 4 years of age, NB still displayed some phonological disorder and her language expression was poorer than that of EB until 5 years of age. At 8 years of age, speech articulation and language performances of NB were adequate and did not differ from those of her unaffected twin. School achievements of NB were judged adequate by her teachers who excluded any degree of learning disability. She did not significantly differ from classmates for scores in any test of school performance (Fig. 2). Compared with her unaffected twin, NB scored worse in writing, mechanical reading, verbal memory, and possibly in arithmetic. Attention problems were not reported by parents or teachers. As compared with her unaffected twin, parents reported greater impulsivity and a hyperkinetic behaviour in NB from the age of 18 months up to 5 years.

Discussion

In some screening programmes for CH, global IQs of children treated early in life do not differ from those of control children (1, 3, 4). Other follow-up studies report a mild decrease in global IQs compared with controls (1, 5–8). Differences in motor and psychometric subtests have also been reported. These include:

- language deficits (6, 13),
- lower scores on tests involving motor speed (13),
- worse balance and fine or gross motor functions (6),
- and reduced verbal and memory abilities (14).

School performances were found normal by the New England Congenital Hypothyroidism Collaborative (15), but recently Rovet et al. reported a mild nonverbal learning disability in some children with CH (16). Thyroid agenesis as a cause of CH (6, 8), low (<25·7 nmol/l) serum T₄ and/or a markedly retarded bone age at diagnosis (5, 6, 14) identify those infants who are the most severely hypothyroid and are at risk of a worse neuropsychological outcome. In the above follow-up studies, false positive cases, siblings, matched or unselected normal children were used as controls, but none of them shares with CH infants the same genetic background. When complex functions such as intelligence are investigated, identical twins would represent a better control. Identical twins eliminate variables bound to genetic factors, and correlation coefficients as high as 0·75–0·87 have been reported in intelligence levels of monozygotic twins (17). Much lower figures have been found in dizygotic twins (0·53) and siblings (0·49). Identical twins raised in the same family also minimise differences due to socio-economic and cultural aspects of the environment (9). The constraints of therapy and medical follow-up in the child with CH, as well as differences in parental behaviour between twins, are of course unavoidable and must be borne in mind.

In the present paper we report the rare case of two genetically identical twins, one of whom was affected by CH due to thyroid agenesis. A similar occurrence was described in 1955 (18), but in the pre-screening era the affected twin did not receive adequate therapy until 4 years of age and at 5 years old, the CH twin was mentally retarded with an IQ (86) that was 58 points lower than that of the unaffected twin. Our twin with CH was started on L-T₄ treatment at 27 days of age, and by 58 days her serum TT₄ was greater than...
154 nmol/l. When 3 months old, her serum TSH was in the normal range and remained so throughout the follow-up. Despite being severely hypothyroid in the neonatal period (serum TT4 < 25-7 nmol/l), our CH twin had no major neuromotor impairment, and minor deficits in motor skills and delays in postural achievements disappeared with increasing age. A slight delay in language development with respect to her unaffected twin also disappeared with time. While NB was indistinguishable from control children on standardised intelligence tests, her global and verbal IQs were lower compared with her unaffected twin. In view of the high concordance in IQ levels between genetically identical twins, this difference in IQ scores, although modest, may be relevant. It is conceivable that in the affected twin CH was responsible for achieving an intelligence level lower than that expected from her genetic background. This finding is in keeping with those follow-up studies showing that, despite early treatment, children with severe CH are at risk of having lower IQs than controls (5-8). School achievements in our CH twin were adequate, but some performances were worse than those displayed by her unaffected twin. This again is in keeping with the observation (16) that children with severe CH may be at risk of minor learning disability.

The lesson from this rare pair of identical twins is reassuring for the neuropsychological prognosis of children with CH diagnosed by neonatal screening, but also confirms that starting treatment within 1 month of birth may not completely normalise intelligence. This failure may be due to foetal hypothyroidism, delay in the initiation of L-T4 in the first month after birth, or inadequate therapy during the first 2-3 years of life (1, 2). The last possibility is not pertinent to our case, since adequate treatment was offered to our CH twin from the 27th day of life onwards. Limited amounts of maternal T4 cross the placenta (19), but it is difficult to believe that this limited maternal supply of T4 is sufficient in most cases of severe CH. With the present modality of screening for CH, some degree of foetal hypothyroidism is therefore unavoidable. Neonatal hypothyroidism in the time between delivery and restoration of euthyroidism may also be responsible for decreased IQ scores in children with CH. Earlier diagnosis and initiation of treatment (within the first 2 weeks of life) in neonates with CH are, therefore, important and highly recommended.

Acknowledgements

The authors are grateful to Prof. R Domenici (Dipartimento di Biomedicina Sperimentale Infettiva e Pubblica, University of Pisa) for performing the DNA finger-print analysis.

References


Received 11 July 1996
Accepted 10 October 1996