School attainments in children with congenital hypothyroidism detected by neonatal screening and treated early in life

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Abstract

Objective: Evaluation of school attainments in children with congenital hypothyroidism (CH) detected by neonatal screening and treated early in life.
Patients and methods: Text comprehension, mathematics, reading, writing and verbal and spatial memory, as indices of school learning, were evaluated in nineteen 5- to 10-year-old children with CH attending nursery or elementary school. L-Thyroxine substitution (starting dose 8–10 μg/kg body weight per day) was initiated at a mean age of 30 ± 10 days of life. The control group included 298 unaffected children matched with the CH children for age and school grade. Thirty per cent of controls were classmates of CH children. Intelligence quotients (IQ), language performances and motor development were evaluated in CH children at age 5 years, and were related to their school attainments. School performances of CH children were also compared with their neonatal serum thyroxine (T_4) concentration, and with the social–cultural level of the family.
Results: Four out of 19 (21%) children with CH, 3 in the nursery and 1 in the elementary school, displayed a generalized learning disorder. Symbol copy, geometric copy, phrase repetition, dictation writing and spontaneous writing were particularly defective in nursery school CH children, while orthographic error recognition was defective in elementary school CH children. School learning disorders in CH children were significantly correlated with a borderline-low IQ, poor language performances and a low social–cultural level of the family, but not with motor skills or neonatal T_4 concentration.
Conclusion: School attainments of early treated CH children were within the normal range in most affected cases. However, about 20% of CH children, most of them attending nursery school, showed a generalized learning disorder. Low IQ scores and poor language performances at age 5 years were associated with defective learning, mainly in CH children living in a poor social–cultural environment. In this subset of CH children, prompt initiation of speech and psychomotor rehabilitation therapy is recommended in order to prevent subsequent school learning disorders.

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Introduction

Several studies have reported normal global neuropsychological development in children with congenital hypothyroidism (CH) detected by neonatal screening and treated early in life (1–3). However, some of these CH children have subtle impairments in language abilities (3–5), neuromotor skills (5–7), behaviour (8, 9) and cognitive performances (4, 10–18). Such impairments might adversely affect school learning. Investigations of school attainments in CH children treated early in life have produced controversial results (19, 20). School performances were found normal by the New England Congenital Hypothyroidism Collaborative (19), but mild non-verbal learning disability (20) and mild impairment in educational attainments (21) have been found in other series of early treated CH children.

The present study was designed to assess school performances in a group of CH children detected by neonatal screening and attending nursery or elementary school when 5–10 years old. Comprehension, arithmetic, reading, writing, orthographic error recognition (OER) and verbal and spatial memory were evaluated. Learning attainments at school were related to the results of cognitive, language and motor tests performed at age 5 years. We also studied the influence on learning achievements of the severity of neonatal hypothyroidism and of the social–cultural level (SCL) of the family.

Materials and methods

Patients and controls

The CH group included 19 CH children (13 females, 4 males) detected by neonatal screening. All CH children were born at term, and none of them suffered from other perinatal disease. All children were born in iodine-sufficient urban areas of Tuscany. L-Thyroxine (L-T_4) substitution therapy (8–10 μg/kg body weight (BW) per day) was initiated at a mean ($\pm$ SD) age of 30 ± 10 days (range 17–50, median 31 days). Before starting therapy, serum T_4 concentration was $\leq 3\,\mu$g/dl ($\leq$40 nmol/l) in 13 CH children and $> 3\,\mu$g/dl ($>$40 nmol/l) (range 3.5–9.0 μg/dl, 45–116 nmol/l) in the remaining 6 children. Follow-up examination, including measurements of serum free thyroid hormones T_4 and tri-iodothyronine and thyrotrophin (TSH), was carried out every 3 months in the first year of life, and every 3–6 months thereafter. The initial dose of L-T_4 was adjusted taking into account the serum concentration of free thyroid hormones and TSH, with the aim of maintaining serum TSH in the normal range. Any elevation in the serum TSH concentration was promptly corrected by increasing the dose of L-T_4.

Evaluation of school learning attainments

Four CH children (DS, GF, SS, BM), aged 5 years, attended the nursery school, and 15, aged 6–10 years, attended the elementary school, three (CB, NF, FB) in the 1st grade, three (ET, NM, AS) in the 2nd grade, six (NB, EB, FG, PL, MG, AD) in the 3rd grade and three (DD, AF, SP) in the 4th grade class.

The following learning tests were administered to nursery school children: (i) school maturity test (22) (subtests: symbol comparison, symbol copy, picture connection for semantic aspects, quantity, picture choice, picture copy, geometric picture copy, phrase repetition, summary, picture description); (ii) alphabetic knowledge evaluation test (23) (independent letter recognition, presented letter recognition, letter copy, postponed letter copy, dictated writing); (iii) spontaneous writing evaluation test (23); and (iv) digit span verbal memory and cube spatial memory tests (24).

Elementary school children received the following learning tests: (i) comprehension test (25); (ii) objective arithmetical performance test (26); (iii) reading and writing tests; (iv) OER test (23); and (v) digit span verbal memory and cube spatial memory tests (24).

Informed consent was obtained from parents, teachers and the school board. Anonymity was maintained. An Italian language methodology was used for language tests. School learning assessment took into account current Italian school curricula and was calibrated for Italian children.

The control group included 298 children (141 females, 157 males). Sixteen attended the nursery school and 282 the elementary school, 51 in the 1st grade, 50 in the 2nd grade, 81 in the 3rd grade and 100 in the 4th grade class. Thirty per cent of controls included classmates of CH children, the remaining control children attended paired classes of the same grade.

Evaluation of cognitive and neuro–motor development

CH children were evaluated at age 5 years with the Griffiths intelligence scale (27), the modified Touwen neuro–motor examination (28) and several language tests (Bortolini–Fanzago language articulation test (29), language comprehension and spontaneous speech tests (30)). The following items were evaluated: intelligence quotient (IQ), language performance (language) and motor skills (motor). According to the DSM-IV (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders) (31), a semiquantitative score (0–2) was attributed to language performances (0 = expressive language disorder with simplified/limited varieties of grammatical structures and phonological errors; 1 = phonological disorder; 2 = normal language) and motor skills (0 = coordination disorder with clumsiness and delays in achieving developmental motor milestones; 1 = mild clumsiness; 2 = normal motor development).

The SCL of the family was assessed taking into account the parents' school-leaving qualifications, their current job and social position. A semiquantitative score (0–3) was assigned to SCL, with 0 indicating the worst and 3 indicating the best.

Data analysis and statistics

Differences in learning achievements between CH children and controls attending nursery school were analyzed by *t*-test (two-tail). A z-score (deviation from the control mean expressed in units of standard deviation) was calculated for each performance of CH children. For elementary school children we calculated individual z-scores for each performance compared with control children in the same grade. We thus obtained a table with 7 columns (corresponding to performances) and 15 rows (corresponding to individual patients). The column means were used to test the hypothesis that a specific area was generally defective in CH children, whereas the row means were used to test for the existence of overall performance heterogeneity among CH children. The significance of the values observed was obtained by comparison with a normal density having zero mean and S.D. $= 1/n$ (n being the number of averaged scores). Pearson correlation coefficients were computed to evaluate relationships between learning achievements and each of the following variables: intelligence (IQ), language, motor, SCL of the family, pretreatment serum T_4 concentration and age at starting treatment.

Results

Nursery school children

Table 1 shows the results of learning tests in the 4 CH children and in the 16 controls. CH children had significantly lower scores ($P < 0.01$) in five tests: symbol copy, geometric copy, picture copy, phrase repetition and spontaneous writing. Although at a lower significance level ($P<0.05$), CH children had worse scores in four additional tests: independent recognition, presented letter recognition, dictation writing and verbal memory.

In order to measure the global learning performance of individual CH children, we calculated the z-score of single tests, and then the mean of z-scores of all tests for each CH child (Table 2). Three out of four CH children had significantly lower performances compared with the controls, and two of them (DS, SS) belonged to the lower 0.002 tail of the population.

Elementary school children

For each learning test of individual CH children we calculated a z-score, compared with the mean performance observed in grade-matched control children. Results are summarized in Table 3 with 7 columns (performances in learning tests) and 15 rows (individual CH children).

The grand-total mean ($z = -0.090$) was not significantly different from zero ($P = 0.46$). However, one CH child (PL) had a significantly lower ($P < 0.05$) mean z-score. The analysis of mean z-scores (means of performances in all CH subjects) indicated that OER (mean $z = -1.768$, $P < 0.038$) is a defective area, while other performances are within the normal range.

The frequency distribution of z-scores of all learning performances in CH children did not show gross deviation from the z-score distribution of normal children.

Distribution of learning performances among all CH children

CH children attending nursery and elementary school in any class grade were grouped together taking into account their individual mean z-scores (Fig. 1). Three CH children attending the nursery school (DS, SS, BM) had mean z-scores lower than 2 S.D. from the mean of controls.

Correlation of individual learning performances with other variables

Table 4 shows the mean z-scores of learning tests in individual CH children compared with IQ, language and motor scores evaluated at age 5 years, with the SCL of the family, with neonatal serum T_4 levels, and

Table 1 Results of learning tests in the 4 children with CH attending nursery school and in 16 control children.

Performances	Mean (± S.D.) CH children	Controls	*t*	*P*
School maturity test (22)				
Total score	21.25 ± 5.19	35.56 ± 6.89	2.732	0.014
Symbol comparison	3.25 ± 2.06	4.56 ± 1.40	1.078	NS
Symbol copy	0.75 ± 0.96	4.38 ± 1.41	3.477	0.003
Picture connection (semantic)	3.75 ± 2.63	5.63 ± 1.09	1.191	NS
Quantity	3.25 ± 4.72	3.88 ± 2.99	0.245	NS
Picture choice	1.75 ± 2.00	2.38 ± 1.15	0.549	NS
Picture copy	2.00 ± 1.15	3.69 ± 1.40	2.025	0.058
Geometric copy	0.25 ± 0.50	2.25 ± 1.81	4.600	0.001
Phrase repetition	0.25 ± 0.50	2.13 ± 1.02	3.589	0.002
Summary	3.50 ± 1.91	3.94 ± 2.43	0.418	NS
Picture description	2.56 ± 1.00	2.94 ± 1.24	0.768	NS
Alphabetic knowledge evaluation test (23)				
Independent recognition	3.25 ± 4.55	15.94 ± 7.24	2.732	0.014
Presented recognition	5.00 ± 1.83	15.06 ± 0.87	2.607	0.018
Copy	19.00 ± 2.63	20.69 ± 1.03	1.460	NS
Postponed copy	18.75 ± 4.24	20.50 ± 7.22	1.125	NS
Dictation writing	4.00 ± 5.74	15.00 ± 13.68	2.864	0.010
Spontaneous writing	3.50 ± 1.00	23.13 ± 0.73	3.452	0.003
Verbal memory	3.25 ± 0.50	4.19 ± 1.05	2.462	0.024
Spatial memory	2.50 ± 5.97	3.50 ± 7.85	1.554	NS

with the age of life (days) at starting L-T_4 treatment. IQ scores of CH children were within the normal range (85–133). Language was normal in six CH children, while mild or specific disorders were observed in nine and four children respectively. Motor was unaffected in nine CH children, while a mild or marked motor disorder occurred in seven and three CH children respectively. Neonatal serum T_4 concentration was $\leq 3\,\mu g/dl$ in 13 CH children and $> 3\,\mu g/dl$ in the remaining 6. The SCL of the family was high (3) in two CH children; medium–high (2) in five, medium–low (1) in seven and low (0) in five. Table 5 shows the correlation coefficients between the mean z-scores of learning tests in CH children and the other variables. There was a significant correlation of learning z-scores with IQ ($r = 0.67$, $P < 0.002$), language ($r = 0.55$, $P < 0.02$) and the SCL of the family ($r = 0.46$, $P < 0.05$). No significant correlation was found with

Table 2 Mean scores and mean z-scores of school learning tests of children with CH attending nursery school.

CH children (initials)	**Mean**	**z**	***P***
DS	0.269	−3.235	0.001
CF	0.491	−1.350	0.089
SS	0.319	−2.814	0.002
BM	0.389	−2.217	0.013

Table 3 Learning tests of children with CH attending elementary school. For each learning test of individual CH children we calculated a z-score, compared with the mean performance observed in grade-matched controls. Results are summarized with 7 columns (performances in learning tests) and 15 rows (individual CH children). The grand-total mean ($z = -0.090$) was not significantly different from zero. One CH child (PL) had a significantly lower ($P = 0.05$) mean z-score. The analysis of mean z-scores (means of performances in all CH children) indicated that OER is a defective area, while other performances are within the normal range.

CH children (initials)	**Comprehension**	**Arithmetic**	**Reading**	**Writing**	**OER**	**Verbal memory**	**Spatial memory**	**Mean z-score**	***P***
CB	−1.391	0.248	−0.159	−0.175	−0.023	0.096	0.123	−0.484	0.314
NF	0.746	−0.732	−0.125	−0.363	−0.637	0.096	0.123	−0.526	0.299
FB	1.173	1.718	−0.169	1.201	1.205	0.096	0.123	2.021	0.978
ET	−0.225	−0.753	0.819	−0.930	−0.905	1.438	0.074	−0.182	0.428
NM	−0.225	−0.577	−0.092	0.680	−0.905	0.261	0.074	−0.296	0.384
AS	0.329	0.483	−0.168	0.680	−0.905	1.438	3.400	1.987	0.977
NB	0.824	−0.452	0.424	−0.591	0.213	−1.366	2.122	0.444	0.671
EB	0.824	0.671	−0.271	−0.166	0.741	−0.489	0.760	0.783	0.783
FG	0.096	−0.115	−0.558	0.685	−0.315	−0.489	0.760	0.024	0.510
PL	−0.147	0.446	−1.402	−1.441	−2.956	0.387	0.760	−1.645	0.050
MG	0.339	−0.340	−0.375	0.260	−0.844	−1.366	−0.601	−1.106	0.134
AD	−0.147	1.008	0.004	0.260	−0.844	−0.489	−0.601	−0.306	0.380
DD	0.824	0.692	−0.152	−0.108	0.674	0.247	—	0.889	0.813
AF	−1.958	−0.025	−0.007	0.612	−2.021	0.247	0.587	−0.969	0.166
SP	−1.262	−0.466	−0.225	0.612	0.674	−1.386	−0.508	−0.968	0.166
Mean z-score	−0.051	0.466	−0.634	0.184	−1.768	−0.330	1.923	−0.090	0.464
Mean *P*	0.480	0.679	0.263	0.573	0.038	0.371	0.973	0.464	—

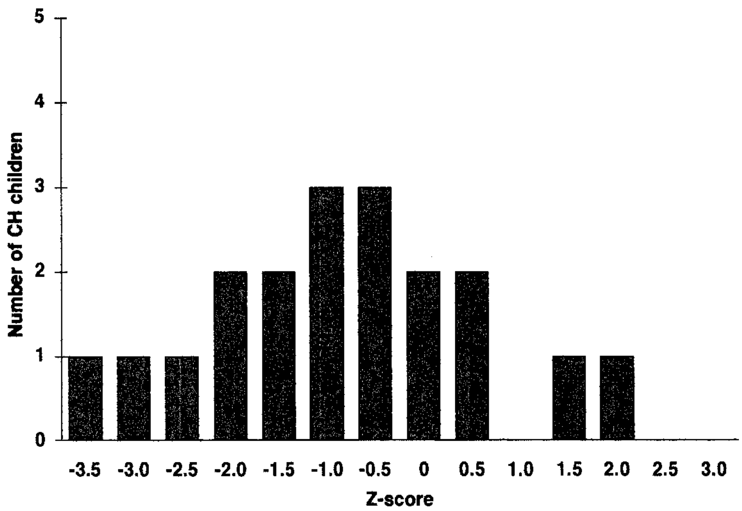

Figure 1 Distribution of mean z-scores of learning tests in children with CH attending nursery or elementary school in any class grade.

Table 4 Mean z-scores of learning tests (Learn) in individual children with CH compared with IQ, language (Lang) and motor skills (Motor) scores evaluated at 5 years of age, SCL level of the family, neonatal serum T_4 concentration and the age of life (days) at starting L-T_4 treatment.

CH children (initials)	**Learn**	**IQ**	**Lang**	**Motor**	**T_4** (μg/dl)	**SCL**	**Days**
DS	−3.235	85	0	0	7	0	36
SS	−2.814	95	0	1	1	1	20
BM	−2.217	100	1	2	1	1	21
PL	−1.645	97	1	1	6	0	46
GF	−1.350	91	0	0	1	1	23
MG	−1.106	104	1	1	1	0	30
AF	−0.969	108	2	2	2	0	23
SP	−0.968	103	1	2	5	1	17
NF	−0.526	95	1	1	1	1	24
CB	−0.484	113	2	2	1	3	19
AD	−0.306	99	1	1	1	2	50
NM	−0.296	97	0	0	1	3	31
ET	−0.182	123	2	2	9	1	36
FG	0.024	103	1	1	3	1	32
NB	0.444	108	2	2	1	2	32
EB	0.783	128	2	2	1	2	50
DD	0.960	133	1	1	4	0	23
AS	1.987	103	2	2	3	2	34
FB	2.021	122	1	2	1	2	40

Table 5 Correlation coefficients between the mean z-scores of learning tests in children with CH and IQ, language (Lang), motor skills (Motor), SCL level of the family, neonatal serum T_4 concentration, and age in days (days) at starting L-T_4.

	r	***P***
IQ	0.671	<0.002
Lang	0.547	<0.02
SCL	0.459	<0.05
Motor	0.439	NS
T_4	−0.319	NS
Days	0.300	NS

neonatal serum T_4 concentration ($r = -0.32$, NS) and the age in days at starting L-T_4 ($r = 0.30$, NS). Global learning performances did not significantly differ in CH children with neonatal $T_4 \leq 3\,\mu$g/dl compared with those with a neonatal $T_4 > 3\,\mu$g/dl.

Discussion

Learning disorders are manifested as significant difficulty in acquiring and using the skills of listening, oral production, reading, writing, reasoning and mathematics (32). Global learning difficulty patterns usually present a less severe picture compared with selective learning disorders (dyslexia, dysgraphia, dyscalculia) and are usually transient, provided that appropriate teaching support is undertaken. In Italy, the prevalence of learning disorders in the whole child population is around 3.4% (33). This prevalence does not include children with relational pathologies or sensorial deficits. School learning is dependent on the integrity of the basic neuropsychological mechanisms that are anchored to the neurobiological substrate. In this regard, phonological and morphosyntactic aspects of speech, and fine and gross motor skills are particularly relevant for the acquisition of reading, writing and arithmetic. The SCL of the family is an additional factor influencing school learning (34). An educated family background and continuous stimulation by parents can make progress at school easier, and can favour learning.

In some follow-up programmes for CH, global IQs of children treated early in life do not differ from those of control children (1, 3). Other follow-up studies report a mild decrease in global IQs compared with controls (10–18). Differences in motor and psychometric subtests have also been reported. These include language deficits (4–6), lower scores in tests involving motor speed, balance and fine or gross motor functions (5–7), and reduced verbal and memory abilities (16).

Elementary school performances, both global and in different subtests, were found normal by the New England Congenital Hypothyroidism Collaborative (19). However, Rovet *et al.* (20) reported mild non-verbal learning disability in some children with CH. Recently, less satisfactory scores for educational attainments, behaviour and motor skills were reported in CH children with more severe neonatal hypothyroidism ($T_4 \leq 3\,\mu$g/dl, 40 nmol/l) compared with less affected CH children (neonatal $T_4 > 3\,\mu$g/dl, 40 nmol/l) (21).

While differences for reading were small, deficits in mathematics were statistically significant (21).

In the present study a more detailed analysis of learning attainments was performed by evaluating not only reading and mathematics, but also abilities in writing, OER and verbal and spatial memory. Four (21%) CH children (three attending nursery school and one elementary school) experienced a learning disorder. This prevalence was greater than that expected in the general Italian child population. Learning disorders were more prevalent and marked in younger CH children attending nursery school. In these children symbol copy, geometric copy, phrase repetition and spontaneous writing were particularly defective. Independent letter recognition, presented letter recognition, dictation writing and verbal memory were less affected. The low number of children attending nursery school does not allow definitive conclusions to be drawn. It cannot be excluded that by pure coincidence our study grouped together cases with concomitant disadvantages due to severity of CH and low SCL family condition. As an alternative explanation it could be hypothesized that an improvement of learning performances does occur with increasing age in CH children. Indeed, global learning performances of older CH children attending elementary school did not significantly differ from those of control children. Only OER was significantly lower in CH children attending elementary school compared with controls.

Learning performances in the whole study group were significantly correlated with IQ and language scores at 5 years of age, and with the SCL of the family. CH children with learning disorders had borderline-low IQ scores ranging from 85 to 100, and severe to moderate language defects. A similar relationship with borderline-low cognitive level and poor language performances has been reported for learning disorders observed in the general population (35–38). A low SCL of the family also negatively affected learning attainments in our CH children. This may result from an insufficient supply of stimuli during the development or from difficulty in providing care for the child with resulting neglect in the affective–relational sphere (39).

The neonatal concentration of serum T_4 before starting L-T_4 replacement was apparently unrelated to subsequent school attainments in this group of CH children. Although in our (18, 40) and others' (14, 15, 17, 41, 42) experience, a low neonatal T_4 level is a risk factor for a defective neuropsychological development, in the present study the degree of neonatal thyroid hormone deficiency was not found to be a major variable influencing school learning. In this regard, our results do not completely agree with the recent observation that a low neonatal T_4 is associated with less satisfactory scores for educational attainments (21). This might be due to the fact that in our study the two CH children (DS and PL) with a learning disorder but a neonatal $T_4 > 3\,\mu g/dl$ were brought up in families with a particularly low SCL.

In our CH children, substitution treatment was initiated at age 17–50 days (median 31 days) with a starting dose of L-T_4 ranging from 8 to 10 $\mu g/kg$ BW per day. Correction of thyroid function, as assessed by a total serum T_4 concentration greater than 10 $\mu g/dl$ (19), was achieved between 30 and 80 days of life. Higher doses of L-T_4 (range 8.6–16.9, median 12.1 $\mu g/kg$ BW per day) started at an earlier age (range 12–35, median 14 days), have been reported to prevent any psychomotor abnormality in CH children with severe CH assessed at 18 months of age (43). The question of whether the school attainments of CH children treated earlier and with a higher dose of L-T_4 are entirely normal remains to be answered by the follow-up of this cohort of children.

In conclusion, our study indicates that the evaluation of IQ and language performances in CH children at the age of 5 years may alert one to the risk of subsequent occurrence of learning disorders. This is particularly true in CH children living in families with a low SCL. All CH children with borderline-low IQ and/or defective language should receive a careful neuropsychological observation associated with appropriate speech therapy and educational treatment in preschool years aimed at improving their school learning potential.

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