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Clinical Research Article

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Cognitive and Motor Outcome in Patients with Early-Detected Central Congenital Hypothyroidism Compared with Siblings

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Abbreviations: CH, congenital hypothyroidism; FSIQ, full-scale intelligence quotient; FT4, free thyroxine; MPHD, multiple pituitary hormone deficiencies; PSIS, pituitary stalk interruption syndrome; SOD, septo-optic dysplasia; TBG, thyroxine-binding globulin; TSH, thyrotropin.

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Abstract

Context: Early treatment of primary congenital hypothyroidism (CH) prevents irreversible brain damage. Contrary to primary CH, outcome studies on central CH are scarce. Most patients with central CH have multiple pituitary hormone deficiencies (MPHD); these patients are also at risk for neonatal hypoglycemia.

Objective: To assess cognitive and motor outcome in patients with early-treated central CH detected by the Dutch neonatal screening.

Methods: In this cross-sectional study, primary outcome full-scale intelligence quotient (FSIQ) was measured in patients with MPHD and patients with isolated central CH born between January 1, 1995, and January 1, 2015, with siblings as controls. Secondary outcomes were intelligence test subscales and motor function. Linear mixed models were used to compare both patient groups and siblings, followed by post hoc tests in case of significant differences.

Results: Eighty-seven patients (52 MPHD; 35 isolated central CH) and 52 siblings were included. Estimated marginal means for FSIQ were 90.7 (95% CI 86.4-95.0) in patients with MPHD and 98.2 (95% CI 93.0-103.5) in patients with isolated central CH. While patients with

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MPHD scored lower FSIQs than siblings (mean difference –7.9 points, 95% CI –13.4 to –2.5; $P = .002$), patients with isolated central CH did not. Processing speed was lower in both patient groups than in siblings (mean differences –10.5 and –10.3 points). Motor difficulties occurred significantly more often in patients (33%) versus siblings (5%; $P = .004$).

Conclusion: In early-treated central CH, FSIQ is comparable with siblings in patients with isolated central CH, while patients with MPHD have a significantly lower FSIQ. This may be explained by disease-specific consequences of MPHD, such as neonatal hypoglycemia and more severe hypothyroidism.

Key Words: congenital hypothyroidism, central hypothyroidism, congenital hypopituitarism, neonatal screening, cognitive outcome, IQ

Thyroid hormone is essential for normal pre- and postnatal brain development. Since early treatment of children with congenital hypothyroidism (CH) prevents irreversible brain damage (1), this condition has been included in many neonatal screening programs worldwide since the 1970s. When treated early, the cognitive outcome of children with primary CH improves substantially. This has been extensively reported in previous literature, and the majority of early-treated patients now obtain normal or near-normal IQ scores (2, 3). The objective of most neonatal screening programs is to detect primary (thyroidal) CH, the most common form of CH (4). Central CH, caused by insufficient hypothalamic–pituitary stimulation of the thyroid gland, is much less common, with a prevalence of 1:16,000 (5). While it fulfills the criteria for disease screening, central CH is only rarely included in neonatal screening programs (4, 6).

Counterarguments for central CH screening are the presumed mild character of the hypothyroidism, and the assumption that patients are detected early enough by clinical signs of multiple pituitary hormone deficiencies (MPHD). MPHD are present in the majority of patients with central CH (7). In previous studies, both arguments were disproved: more than half of patients with central CH have moderate to severe hypothyroidism, and clinical detection usually occurs far beyond the neonatal period (8-10). In a recent study among patients with early-detected central CH, including patients with isolated disease as well as patients with MPHD, we found that the diagnosis was seldom made based on clinical signs, even though 66% of these patients had been hospitalized in the first week of life (11). Instead, 95% were diagnosed only after the notification of an abnormal neonatal screening result. This emphasizes that clinical diagnosis is neither straightforward nor reliable.

While most screening programs are thyrotropin (TSH)-based, central CH detection requires a thyroxine (T4) or free T4 (FT4) measurement. Since 1995, the Dutch neonatal screening program has consisted of a 3-step approach, with T4 measurement as the first step in all neonates, TSH measurement in the lowest 20% of T4 concentrations, and thyroxine-binding globulin (TBG) measurement in the lowest 5%. This approach effectively detects primary and central CH. TBG measurement prevents false-positive results due to TBG deficiency (5). Failure to detect central CH early is especially worrying for patients with MPHD. In our previous study 96% of patients with MPHD had growth hormone deficiency, and 88% had central adrenal insufficiency (11). With these hormone deficiencies, patients with MPHD are at risk for severe hypoglycemia and thus for brain damage and cognitive impairment (12, 13).

The most important argument in favor of screening for central CH remains an expected improvement in cognitive outcome after early treatment (6). In a recent systematic review, we showed that sufficiently large studies on cognitive outcome in patients with central CH are lacking (14). We identified 6 studies that measured full-scale intelligence quotient (FSIQ), including 30 patients in total (27/30 MPHD). FSIQs were shifted towards lower values with 10% of patients having an FSIQ <70 (below –2 SD in the general population) but the included studies were small, heterogeneous, and possibly suffered from selection bias, so that results should be interpreted with caution (14).

The objective of the current study was to assess cognitive and motor outcome in a 20-year cohort of patients with early-detected central CH, including both patients with isolated central CH and patients with MPHD. Primary outcome was FSIQ; secondary outcomes were intelligence test subscales, motor function, and attending special education.

Materials and Methods

Participants

All patients with central CH detected by neonatal screening in The Netherlands are registered in a national database maintained by the Netherlands Organization for Applied Scientific Research. Permission to access the database was obtained from the Privacy Committee of the Dutch CH Screening Board. We selected patients born between January 1, 1995, and January 1, 2015. The starting year was in accordance with the last modification of the neonatal screening program, that is, adding TBG as the third

measurement (5). The end date ensured patients would be ≥3 years old, which is considered the youngest age to reliably conduct the selected intelligence tests (15).

Patients were recruited through their current treating physician (11). Patients with a severe syndrome were included or excluded based on their ability to complete an intelligence test; this was mainly judged based on their ability to communicate. Patients with the following syndromes were excluded: Kabuki syndrome, KAT6A syndrome, trisomy 15, muscle–eye–brain disease, and severe septo-optic dysplasia (SOD). One patient with a mild phenotype of SOD was included (11).

For each included patient 1 unaffected sibling of at least 3 years old, sharing both biological parents with the patient, was included as control. In case of multiple siblings, the sibling with the smallest age difference was included, with preference given to older siblings over younger siblings. In families with 2 eligible patients, both were included as patients. Whereas male patients with isolated central CH caused by (X-linked) *TBL1X* or *IRS4* variants were included, female siblings with these variants, namely carriers, were not. This is because carriers are reported to have lower plasma FT4 concentrations, and it remains unclear whether this represents disease or reflects an altered individual "set point" (16).

Demographic and clinical data collection

Medical charts were obtained to collect clinical data, and parents completed an online sociodemographic questionnaire. FT4 measurement was performed in all patients within a time span of 90 days before or after the cognitive assessment. Genetic testing was performed in patients with isolated central CH as part of our previous study (11). As reported in this previous study, we did not perform genetic testing in patients with MPHD because of an anticipated low mutation yield, especially in patients with nonsyndromic MPHD (11, 17).

Outcome assessment

Cognitive function

Cognitive assessment was performed at the study hospital (Amsterdam UMC, location AMC; 74 patients/47 siblings) or upon request at the patients' local hospital (13 patients/5 siblings) between June 2017 and December 2019. Tests were performed in the morning by a pediatric neuropsychologist (J.P.M.), a physician (J.C.N.), or a psychology student trained by the pediatric neuropsychologist. Although assessors were not involved in clinical care for the patients, they were not formally blinded for the participants' disease status: participants were not asked to conceal their disease status but were also not encouraged to talk about it. We used the most recent Dutch Wechsler scales available at the start of the study: the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL) for participants <6 years, the Wechsler Intelligence Scale for Children (WISC-III-NL) for participants 6 to 16.9 years old, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL) for participants ≥17 years. When a participant underwent a Wechsler test within the previous 12 months (n = 4), the first score was obtained rather than retesting, to prevent an inflated score due to a practice effect (18). The mean population norm score for FSIQ, as well as for subscales, is 100 with a SD of 15.

By design, reported subscales differ between the used intelligence tests. WPPSI-III- and WISC-III–specific subscales are verbal and performance IQ. WAIS-specific subscales are verbal comprehension, perceptual reasoning, and working memory. Processing speed is reported in all tests, except for the WPPSI in participants under 4 years of age. Attendance of special education was assessed through a questionnaire. In The Netherlands, education for children with learning disabilities is mostly integrated in regular education, but special education is available for children with severe learning disabilities or other special needs.

Motor function

Parents were asked to complete the Motor Assessment Battery for Children-2 (MABC-2) checklist, developed to screen 5- to 13-year-old children in primary education for motor difficulties (19). The numerical outcome is compared with an age-specific norm score, using the 85th and 95th percentile as cut-offs to differentiate between normal ("green"), and abnormal scores ("orange" if >85th percentile or "red" if >95th percentile). MABC-2 scores >85th percentile were considered abnormal, that is, indicative for motor difficulties.

Data on age at attainment of motor milestones (sitting, standing and walking independently) and need for physical therapy for delayed motor development were collected from medical charts and by consulting parents.

Statistical analysis

Clinical characteristics were compared between patient groups (MPHD vs isolated central CH) using the chi-squared test or Fisher's exact test for dichotomous variables, and the Student's t test for normally distributed continuous variables. For non-normally distributed continuous variables the Mann–Whitney U test was used. Primary outcome FSIQ and continuous secondary outcomes were compared between the 2 patient groups and siblings using a linear mixed model based on maximum likelihood estimation. A linear mixed model accounts for the fact that patient and sibling data are not independent,

and facilitates the use of data from all patients, regardless of the presence of an eligible sibling. A random intercept was constructed for each family. Endocrine status (MPHD, isolated central CH, or healthy) was included as a fixed factor. Since all tests yielded age-specific norm scores, age was not added to the model. By using a sibling control group, confounding factors shared by patients and siblings were controlled for. Significant differences identified through linear mixed models were explored in post hoc analysis using Tukey's range test. To assess the association between severity of hypothyroidism and FSIQ, pretreatment FT4 concentration was added to the FSIQ model. In a separate analysis, the FT4 concentration during the IQ assessment was added to model for FSIQ as well, to determine whether the current FT4 concentration affected FSIQ. The fit of these models was compared with the model for FSIQ with the likelihood ratio test. Pearson's correlation coefficient was calculated to assess the relationship between pretreatment FT4 and FSIQ, and FT4 and processing speed. Proportions of dichotomous outcomes were compared using McNemar's test. Proportions of abnormal MABC-2 scores were compared using the z-test for partially paired samples, as the MABC-2 checklist is validated for ages 5 to 13 only, thus rendering a partially paired sample (20). The level of statistical significance was set at $P < .05$. Analyses were performed with RStudio version 3.6.1 (2019-07-05), using packages lme4, emmeans, partiallyoverlapping and ggplot (20, 21).

Ethical aspects

The study protocol was approved by the ethics committee of Amsterdam UMC, location AMC. All participants gave their informed consent. Written permission was obtained from all patients ≥12 years and from both parents (where applicable) for patients younger than 18 years.

Role of funding source

Support for this investigator-initiated study was provided by Pfizer (tracking number WI219179). Pfizer was not involved in patient recruitment, data collection, data analysis, or preparation of the manuscript. Pfizer reviewed the manuscript prior to submission for publication.

Results

From the nationwide database, 133 patients with central CH were identified, of whom 7 were excluded because of a severe syndrome (11). Of the remaining patients, 3 had emigrated, 1 was untraceable, and 35 declined participation in the cognitive assessment, yielding 87 patients and 52 siblings, originating from 84 families. One patient with mild SOD was included; 3 patients with severe SOD and 1 patient with mild SOD and severe visual impairment were excluded. No siblings were excluded because of a severe syndrome. From 3 families, 2 patients (and no siblings) were included.

Table 1 summarizes the perinatal and sociodemographic characteristics of participants, which were comparable between patients and siblings. A male predominance was seen among patients; this was not unexpected since isolated central CH is associated with X-linked genes (16, 22). Characteristics of both patient groups are summarized in Table 2, which includes the genetic etiology of isolated central CH for 27 out of 35 cases (15 *IGSF1*, 5 *IRS4*, 5 *TBL1X*, 1 *TRHR*, 1 *TSHB*).

Table 1. Perinatal and sociodemographic characteristics of participating patients with central congenital hypothyroidism (CH) and sibling controls

	Patients (n = 87)	Siblings (n = 52)
Male (%)	68 (78)	26 (50)
Age (years)	11.5 (7.6-17.9)	12.7 (7.9-15.6)
Gestational age (weeks)	40.1 (38.4-41.4)	39.5 (38.0-40.8)$^{(n = 50)}$
Birthweight (g)	3391 ± 666	3201 ± 666$^{(n = 50)}$
Birthweight SDS	–0.14 ± 1.2	–0.14 ± 1.1$^{(n = 50)}$
Apgar score <6 at 5 minutes of age	5 (6)	1 (2)
Maternal education[a]		
Lower	22 (25)	12 (23)
Intermediate	31 (36)	22 (42)
Higher	30 (35)	14 (27)
Not specified	4 (5)	4 (8)
Paternal education[a]		
Lower	23 (26)	13 (25)
Intermediate	25 (29)	16 (31)
Higher	28 (32)	17 (33)
Not specified	11 (13)	6 (12)
Paid parental employment		
Yes	63 (72)	41 (79)
No	10 (12)	4 (8)
Not specified	14 (16)	7 (14)

Numbers represent n (%), median (interquartile range) or mean (± SD).
Abbreviation: SDS, standard deviation score.
[a]The level of education was classified as lower, intermediate or higher following the classification of Statistics Netherlands (CBS): "lower education" contains primary education, lower vocational education and general secondary education at junior level, "intermediate education" contains general secondary education at senior level and intermediate vocational education, and "higher education" comprises higher professional education and university education.

FT4 concentration was within target range in 80 patients (92%), above the upper limit of the reference interval in 5 patients (23-25.9 pmol/L) and below the lower limit in 2 patients (8.4 and 10 pmol/L).

Cognitive outcome

Mean FSIQ was 93.8 ± 17.9 in all patients with central CH and 99.2 ± 14.0 in siblings (Fig. 1). Patients and siblings were compared using linear mixed models, taking into account the patient's endocrine status (MPHD or isolated central CH). Mean FSIQ in patients with MPHD was 90.7 (95% CI 86.4-95.0), compared with 98.2 (95% CI 93.0-103.5) in patients with isolated central CH, and 98.6 (95% CI 94.5-102.8) in siblings (Table 3). Post hoc analysis showed that patients with MPHD scored 7.9 points lower than siblings (95% CI –13.4 to –2.5, $P = .002$), and 7.5 points lower than patients with isolated central CH (95% CI –15.1 to 0.01, $P = .05$; Table 4). Adding pretreatment FT4, as indicator of severity of hypothyroidism, to the model did not improve the fit of the model ($P = .18$). If assessed outside of the model, a weak positive correlation between pretreatment FT4 and FSIQ was found (r = 0.22; $P = .04$). Adding the FT4 concentration measured at the time of the assessment to the model for FSIQ did not improve the model fit ($P = .88$).

An FSIQ <85, that is, <–1 SD in the general population, was seen in 28 (32%) patients versus 8 (15%) siblings ($P = .05$). Eight patients (9%), but no sibling controls, had an FSIQ <70, <–2 SD in the general population ($P = .04$).

Processing speed was significantly lower in both patient groups when compared with siblings, with a similar difference in patients with MPHD and patients with isolated central CH, scoring on average 10.5 and 10.3 points lower than siblings (Table 4). Among patients, a weak correlation between pretreatment FT4 and processing speed was seen (r = 0.22; $P = .04$).

Ten patients (11%) and 4 siblings (8%) attended special education. Patients with MPHD attended special education more frequently than patients with isolated central CH (9/52 vs 1/35, $P = .04$). Only 6 out of 9 patients with MPHD in special education had a participating sibling; pairwise analysis showed no significant difference between patients and siblings ($P = .68$). Comparisons of primary and secondary outcomes between groups did not change when patients with a FT4 concentration outside the target range during the cognitive assessment were excluded. FSIQ and additional subscales did not differ between patients with and without a participating sibling (data not shown).

Table 2. Disease characteristics of patients with multiple pituitary hormone deficiencies (MPHD) and isolated central congenital hypothyroidism (CH)

	MPHD patients (n = 52)	Isolated central CH patients (n = 35)	*P* value
Pretreatment FT4 (pmol/L)	8.8 ± 2.0	10.4 ± 2.3	<.001
CH severity			
Mild (FT4 ≥ 10 pmol/L)	16 (31)	22 (63)	.006
Moderate (FT4 5-10 pmol/L)	35 (67)	12 (34)	.005
Severe (FT4 < 5 pmol/L)	1 (2)	1 (3)	1
Age at treatment initiation (day of life)	17 (14.8-21.5)	21 (16-28)	.10
FT4 concentration during assessment			
Within RI	47 (90)	33 (94)	.70
Above upper limit of RI	5 (10)	0 (0)	.08
Below lower limit of RI	0 (0)	2 (6)	.16
Additional pituitary hormone deficiencies			
Growth hormone deficiency	50 (96)	1 (3)[a]	NA
Adrenocorticotropin deficiency	46 (88)	NA	NA
Neonatal hypoglycemia	28 (55)[(n = 51)]	5 (15)[(n = 34)]	<.001
Lowest glucose level (mmol/L)	1.2 ± 0.8[(n = 26)]	2.1 ± 0.5	.02
Gonadotropin deficiency	19 (79)[b]	NA	NA
MRI pituitary findings in patients with MPHD			
Pituitary malformation within the spectrum of PSIS	46 (88)		
No abnormalities	3 (6)		
MRI not performed or failed	3 (6)		
Gene variants in patients with isolated central CH			
IGSF1		15 (43)	
IRS4		5 (14)	
TBL1X		5 (14)	
TRHR		1 (3)	
TSHB		1 (3)	
No gene variants identified		6 (17)	
Genetic analysis not performed		2 (6)	

Numbers represent n (%), mean (± SD) or median (interquartile range). Malformations within the PSIS spectrum include anterior pituitary hypoplasia, an interrupted pituitary stalk and an ectopic posterior pituitary.

Abbreviations: FT4, free thyroxine; MRI, magnetic resonance imaging; PSIS, pituitary stalk interruption syndrome.

[a]Partial growth hormone deficiency in one patient with *IGSF1* deficiency syndrome.

[b]n = 24 with final outcome available, 28 not known yet.

Motor outcome

The MABC-2 checklist was completed for 39 patients (24 MPHD, 15 isolated central CH) and 21 siblings, and indicated motor difficulties in 5 patients with isolated central CH (33%), 8 MPHD patients (33%), and 1 sibling (5%). Motor difficulties were seen more often in patients than

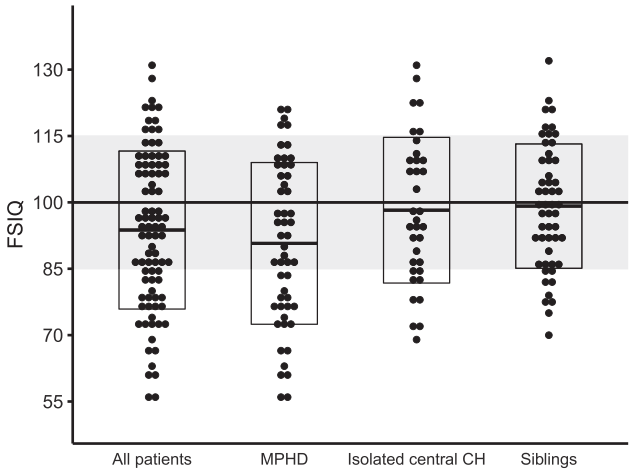

Figure 1. Distribution of full-scale IQ among 87 patients with central congenital hypothyroidism (CH), comprising 35 with isolated central CH and 52 with multiple pituitary hormone deficiencies (MPHD), compared with sibling controls (n = 52). Boxes represent mean full-scale IQ with upper and lower box limits representing ± 1 SD.The horizontal black reference line displays mean full-scale IQ in the general population, with the grey area representing ± 1 SD.

in siblings (P = .004). In addition, delayed motor development requiring physical therapy was present in 30 patients (34%) and 10 siblings (19%; P = .03). Because not all parents could remember when motor milestones were reached, data on motor milestones are not available for all patients. Milestone "walking independently" was reached significantly later by patients than siblings; this age difference was mainly caused by the difference between patients with MPHD and siblings (Table 4).

Discussion

The Netherlands has a long history of neonatal screening for both primary and central CH. In this study, which included the largest group of patients with early-treated central CH to date, we show a normal FSIQ in patients with isolated central CH, but a significantly lower FSIQ in patients with MPHD than in siblings. It remains unknown what these outcomes would be without neonatal detection, but it is likely that neonatal screening prevents prolonged thyroid hormone shortage and its consequences on brain development. In patients with MPHD, early diagnosis also prevents the consequences of additional pituitary hormone deficiencies, such as ongoing hypoglycemia, and thus aggravation of cognitive impairment. The current study cannot answer the question whether neonatal screening for central CH prevents cognitive impairment. To further investigate the role of early detection, studies on cognitive outcome in patients with late-detected central CH are necessary.

There are several possible explanations for the observed lower FSIQs in patients with early-detected MPHD; the

Table 3. Cognitive and motor outcomes in patients with multiple pituitary hormone deficiencies (MPHDs) and patients with isolated central congenital hypothyroidism (CH), compared with healthy siblings

	Estimated marginal means (95% CI)			
Outcome	MPHD patients (n = 52)	Isolated central CH patients (n = 35)	Siblings (n = 52)	*P* value
Mean FSIQ	90.7 (86.4-95.0)	98.2 (93.0-103.5)	98.6 (94.5-102.8)	.002
Processing speed	91.2 (86.9-95.6)	91.4 (86.1-96.7)	101.7 (97.4-106.0)	<.001
WPPSI/WISC: Verbal IQ[a]	97.2 (91.9-102.5)	102.9 (97.0-108.9)	96.3 (91.6-101.0)	.11
WPPSI/WISC: Performance IQ[a]	89.1 (84.2-94.0)	96.1 (90.6-101.6)	99.9 (95.6-104.2)	<.001
WAIS: Verbal comprehension[a]	94.4 (87.9-101.0)	101.4 (91.0-111.9)	104.0 (95.4-112.6)	.07
WAIS: Perceptual reasoning[a]	91.0 (82.2-99.7)	98.0 (84.4-111.7)	103.5 (93.2-113.9)	.02
WAIS: Working memory[a]	94.9 (87.1-102.8)	95.6 (83.1-108.1)	104.5 (93.6-115.3)	.21
Milestone: sitting independently (months)[a]	8.9 (8.2-9.7)	8.5 (7.6-9.4)	8.3 (7.5-9.0)	.29
Milestone: standing (months)[a]	11.7 (11.0-12.5)	11.0 (10.0-11.9)	10.6 (9.8 – 11.4)	.07
Milestone: walking independently (months)[a]	15.9 (15.0-16.7)	14.9 (13.9-16.0)	14.3 (13.4-15.2)	.02

Data are presented as mean ± SD, median (range) or n (%). *P* values derived from linear mixed models, except when indicated otherwise.

Abbreviations: CI, confidence interval; FSIQ, full-scale intelligence quotient; WAIS, Wechsler Adult Intelligence Scales; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

[a]Subscales with different numbers of participants (patients/siblings) due to use of age-appropriate tests: processing speed (85/50); verbal and performance IQ (60/42) and WAIS subscales (26/10). Motor milestones with different number of participants (patients/siblings) due to missing data: sitting (63/37); standing (70/36) and walking independently (83/45).

Table 4. Post hoc analyses for differences in full-scale IQ, performance IQ, processing speed, and motor milestone walking independently among patients with multiple pituitary hormone deficiencies (MPHDs), patients with isolated central congenital hypothyroidism (CH), and siblings

	Mean change in score	Standard Error (SE)	Lower limit of 95% CI	Upper limit of 95% CI	*P* value
Full-scale IQ					
Isolated central CH vs siblings	–0.4	2.8	–7.0	6.3	1
MPHD vs siblings	–7.9	2.3	–13.4	–2.5	.002
MPHD vs isolated central CH	–7.5	3.2	–15.1	0.02	.05
Processing speed					
Isolated central CH vs siblings	–10.3	3.2	–17.9	–2.8	.004
MPHD vs siblings	–10.5	2.8	–17.0	–3.9	<.001
MPHD vs isolated central CH	–0.1	3.4	–8.3	8.0	1
WPPSI/WISC: Performance IQ					
Isolated central CH vs siblings	–3.8	3.0	–11.0	3.5	.43
MPHD vs siblings	–10.8	2.8	–17.5	–4.1	<.001
MPHD vs isolated central CH	–7.0	3.6	–15.5	1.5	.13
WAIS: Perceptual reasoning					
Isolated central CH vs siblings	–5.5	7.4	–24.0	13.1	.74
MPHD vs siblings	–12.6	5.3	–26.2	1.1	.08
MPHD vs isolated central CH	–7.1	7.9	–26.4	12.3	.64
Motor milestone: walking independently (age in months)					
Isolated central CH vs siblings	0.7	0.7	–0.9	2.2	.56
MPHD vs siblings	1.6	0.6	0.2	3.0	.02
MPHD vs isolated central CH	0.9	0.7	–0.7	2.6	.37

Abbreviations: WAIS, Wechsler Adult Intelligence Scales; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

first is the presence of additional pituitary hormone deficiencies in patients with MPHD. Untreated growth hormone deficiency and central adrenal insufficiency can cause neonatal hypoglycemia which was indeed frequently documented (see Table 2). This may have resulted in neurological deficits, such as impaired executive function and visual motor function (13). A second explanation may be found in the degree of hypothyroidism. Based on the pretreatment FT4 concentration 69% of patients with MPHD had moderate to severe hypothyroidism, opposed to only 37% of patients with isolated central CH. Previous studies in patients with primary CH have shown a relationship between pretreatment (F)T4, and FSIQ or obtained educational level (23-25). In general, cognitive outcomes are normal in patients with early-treated mild or moderate primary CH while developmental problems may occur in patients with severe primary CH, despite early treatment (2, 3, 6, 24). However, pretreatment FT4 concentration was not significantly associated with FSIQ in the linear mixed model. This might be due to the small group sizes or various ages in days at which FT4 was measured, but may also indicate that the degree of hypothyroidism is not the main reason for the lower FSIQs in patients with MPHD. A third explanation for the lower FSIQs may be sought in the pituitary anomalies seen in almost all patients with MPHD, specifically, features of pituitary stalk interruption syndrome (PSIS; Table 2). PSIS, a midline brain anomaly, is considered to be at the mild end of the holoprosencephaly spectrum. Developmental delay in PSIS has not been studied extensively but has been described in some patients (26, 27). Since we studied early-treated patients it is possible that the cognitive impairment may be due partly to the brain anomaly itself.

FSIQ, verbal IQ, and performance IQ in patients with early-treated isolated central CH were similar to siblings. So far, FSIQ has only been reported in a few patients with isolated central CH; in our previous systematic review patients with isolated central CH were underrepresented, highlighting the need for further studies on cognitive outcome in this condition (14, 28). In addition, Joustra et al. examined executive functioning and memory, but not FSIQ, in 15 adult patients with *IGSF1* deficiency syndrome. Patients performed worse than controls on executive functioning tasks, while their memory function was normal (29). Whether early detection and treatment contributed to the normal FSIQs among our patients with isolated central CH is likely, but hard to prove with certainty. Obtaining a late-treated group of such patients is difficult; not only due

to the low prevalence of the disease, but also because many of them may not be clinically detected at all.

Processing speed and motor function

Processing speed is an FSIQ component which measures the speed with which relatively simple visual motor tasks are performed (30). The lower processing speed in both patient groups compared with siblings was especially remarkable for patients with isolated central CH, who have an otherwise normal cognitive outcome. A lower processing speed has also been reported in patients with early-detected primary CH, although not consistently (2, 31). Since thyroid hormone plays an important role in the differentiation of oligodendrocytes before and after birth, a lower processing speed may be due to impaired myelination, even in early-treated patients (31). Because both groups were affected similarly, we hypothesize there is a relationship between processing speed and hypothyroidism, while there is little effect of the presence of additional pituitary hormone deficiencies. The correlation with pretreatment FT4 indicates that severity of hypothyroidism does affect processing speed. Because a weak correlation was found, we hypothesize that other factors besides severity, such as the presence of hypothyroidism per se, affect processing speed to a larger extent.

Motor difficulties were present more often in patients with central CH than in siblings. Our data are similar to those found in patients with primary CH, who exhibit motor deficits despite early detection (14, 23, 24). Early postnatal hypothyroidism affects cerebellar development, and this mechanism is thought to be the origin of motor deficits in primary CH (32). Our results suggest that motor function might be affected in a similar way in central CH.

This study has several strengths. We present cognitive testing results of the largest group of patients with central CH studied to date. Almost all patients with MPHD had PSIS, creating a homogeneous group of patients, and almost all patients with isolated central CH had a genetically confirmed diagnosis. By using a nationwide cohort, selection bias was minimized compared to a single center study, and the included siblings represent an ideal control group. A limitation of our study was that the checklist used to assess motor outcome was only suitable for a part of the patients. This led to a relatively small group for whom motor outcome could be reported. In addition, the use of a checklist is considered less reliable than an objective motor assessment. In the interest of time, we did not perform such an assessment, but based on our findings we would suggest including it in future studies. The exclusion of syndromic patients from cognitive testing can be considered both a strength and a limitation. While this creates a more homogeneous patient group, and rules out syndromes as a cause of cognitive impairment, it leaves cognitive outcome in syndromic patients unexplored.

To date, central CH is the only pituitary hormone deficiency accessible for neonatal screening, which can be performed cost-effectively (5). Comparison of cognitive outcome in early and late-detected patients will provide the final answer to the question whether screening for central CH should be implemented worldwide. This will require international collaboration in order to collect a sufficiently large group of late-detected patients. For a comparable study group of patients with MPHD, studies will preferably focus on patients with MPHD with PSIS, which could be achieved by setting up an international registry for this rare disorder.

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Additional Information

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