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Clinical Research Article

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Health-Related Quality of Life in Patients With Early-Detected Central Congenital Hypothyroidism

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Abstract

Context: Central congenital hypothyroidism (CH) requires lifelong medical treatment. The majority of children with central CH have multiple pituitary hormone deficiencies (MPHD), but in some cases central CH is isolated. Most pituitary hormone deficiencies are associated with impaired health-related quality of life (HRQoL). However, studies on HRQoL in central CH are lacking.

Objective: To evaluate HRQoL and fatigue in children and young adults with central CH, as well as parent perspectives.

Design: Nationwide cross-sectional study comparing HRQoL between early-detected central CH patients and unaffected siblings with the Pediatric Quality of Life inventory (PedsQL™) and PedsQL Multidimensional Fatigue Scale. Participants ≥ 8 years old filled in self-reports; parents of participants aged 3 to 18 years filled in parent reports. Isolated central CH patients, MPHD patients, and siblings were compared using a linear mixed model and Tukey's post hoc test.

Results: Eighty-eight patients and 52 siblings participated, yielding 98 self-reports and 115 parent reports. Isolated central CH patients (n = 35) and siblings showed similar scores on all subscales, both in the self-reports and parent reports. For MPHD patients (n = 53), self-reported scores were similar to those of siblings. Parent reported total

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HRQoL and fatigue scores were significantly poorer in MPHD patients compared with siblings (mean differences –10.2 and –9.4 points; $P < 0.01$), as were scores for physical functioning, social functioning and general fatigue.

Conclusion: Self-reported HRQoL scores in isolated central CH and MPHD patients were similar to siblings. However, parents reported significantly lower HRQoL and fatigue scores for MPHD patients, suggesting a difference in perceived limitations between MPHD patients and their parents.

Key Words: congenital hypothyroidism, central hypothyroidism, quality of life, fatigue, neonatal screening

Children with congenital hypothyroidism (CH) suffer from inborn thyroid hormone deficiency, for which lifelong treatment is necessary. In central CH, this is caused by insufficient hypothalamic-pituitary stimulation of the thyroid gland. While a third of central CH patients have no additional pituitary problems (referred to as isolated central CH), the majority of patients suffer from multiple pituitary hormone deficiencies (MPHD). Most of these patients exhibit growth hormone deficiency (GHD) or adrenocorticotropin (ACTH) deficiency (1). GHD, present in up to 96% of central CH patients with MPHD, requires daily subcutaneous injections with recombinant human growth hormone (GH) (2). ACTH deficiency, present in 78% to 88% of patients, requires multiple oral hydrocortisone dosages per day and continuous vigilance from both parents and child to prevent a potentially life-threatening adrenal crisis (2,3). In addition, gonadotropin deficiency can be present, which is associated with body image concerns and low self-esteem due to the differences in physical appearance between patients and peers (4). For all children with central CH, either isolated or within the framework of MPHD, frequent hospital visits and blood collections are required.

Health-related quality of life (HRQoL) has been described as "those aspects of self-perceived well-being that are related to, or affected by, the presence of disease or treatment" (5), but various definitions have been proposed (6). Knowledge on HRQoL in central CH patients will enable endocrinologists to provide early support for (psychosocial) problems encountered by patients and their parents. It also facilitates a holistic approach, which is promoted, for example, during the transfer from pediatric to adult care (7). Furthermore, it may contribute to patient/parent-physician communication becoming more patient-centered, which would improve patient/parent satisfaction (8). In children with central CH, especially those with MPHD, the previously mentioned "medical burden" is likely to result in an impaired HRQoL, but studies on HRQoL in children with central CH (with or without MPHD) are lacking, as was shown in a recent systematic review (9). Impaired HRQoL has been described in closely related patients groups like patients with (isolated) GHD or ACTH deficiency (10-12). In adult patients with central ACTH deficiency fatigue is a well-known problem, in addition to HRQoL impairment (12). There are a few studies on quality of life (QoL) that included adult patients with childhood-onset MPHD, but the groups are often small, and it is not always clear whether central CH was present in these patients (10,13,14).

The Dutch neonatal screening program for CH is thyroxine-based and detects not only primary CH but also central CH (15). Recently we have studied long-term outcomes of a 20-year cohort of early-detected central CH patients and reported on clinical, genetic, and cognitive outcomes (2,16). The aim of these studies is to explore potential benefits of early detection of central CH.

The aim of the current study was to compare HRQoL between early-detected central CH patients and healthy siblings. In addition to HRQoL, we compared the presence of fatigue and specific components of fatigue in both groups. For children up to 19 years old, parent reported scores were collected as well. We expected HRQoL to be significantly lower in patients compared with siblings, especially in MPHD patients due to the medical and psychosocial burden of the various pituitary hormone deficiencies.

Materials and Methods

Design, setting, and recruitment

HRQoL was a planned primary outcome in a nationwide study on the clinical characteristics and long-term outcomes of children with early-detected central CH (2,16). In short, we invited all central CH patients in the Netherlands who were detected by neonatal screening during the 20-year period between January 1, 1995 and January 1, 2015. Patients were asked to participate in 3 study parts: assessment of clinical characteristics (review of medical charts and a study visit); cognitive assessment (participation in an IQ test during the study visit), and a QoL assessment (online questionnaires). Patients could choose to participate in the cognitive or QoL assessment only; therefore, the number of participants slightly differs between the current study and the other study parts

(2,16). For both the cognitive and QoL assessment, 1 unaffected sibling was invited as control for each patient. All siblings had normal neonatal screening results for CH. Female siblings with an *TBL1X* or *IRS4* variants (ie, carriers) were excluded from the study to prevent inclusion of siblings with a milder phenotype of central CH. Male siblings with these variants were considered patients (16).

Clinical characteristics were derived from medical charts and a nationwide database on children with abnormal screening results for CH, maintained by the Netherlands Organization for Applied Scientific Research. This database also contains the pretreatment plasma free thyroxine (FT4) concentrations of all central CH patients born during the study period.

Patients were asked for participation through their treating physician; the complete recruitment process has been described previously (2). Informed consent was obtained from parents of children <19 years of age and from children ≥12 years of age prior to participation in the study. The medical ethical committee of the Amsterdam University Medical Center (location: Academic Medical Center) approved the study.

Outcome measurements

HRQoL was assessed in all participants using age-specific forms of the Dutch version of the Peds Quality of Life (PedsQL™) 4.0 inventory: generic core scales (17). The PedsQL measures 5 components of HRQoL: overall functioning, physical functioning, emotional functioning, social functioning, and role functioning. Role functioning refers to cognitive functioning at school, during study, or during work, depending on what is relevant for the age group. The PedsQL has been validated among large groups of children and parents/caregivers, and has been used in children with endocrine disease previously (18,19). In addition, it has been validated in young adults (18-30 years of age) (20).

The outcome score ranges from 0 to 100 points, with higher scores indicating a better HRQoL. In longitudinal studies, the minimal clinical important difference (MCID) is often used to evaluate changes in HRQoL scores. For the total HRQoL score of the PedsQL, MCIDs of 4.4 points (self-report) and 4.5 points (parent report) have been calculated (21). MCIDs for subscales vary from 6.6 to 9.0 in the self-report and from 6.9 to 9.7 in the parent report (21).

Fatigue was assessed with age-specific forms of the Dutch version of the PedsQL™ Multidimensional Fatigue Scale (22). This questionnaire provides a total fatigue score and divides fatigue into 3 components: general fatigue, sleep/rest fatigue, and cognitive fatigue. The outcome score ranges from 0 to 100 points with lower scores indicating more fatigue.

For participants below 8 years of age, parents filled in the parent report; participants aged 8 to 19 filled in the age-specific self-report and had their parents fill in the parent report, and participants ≥19 years of age filled in the age-specific self-report only. One parent, either father or mother, was asked to fill in the parent reports. Questionnaires were filled in online; participants could use a study-specific website based on the web-based application KLIK (Dutch abbreviation for "quality of life in clinical care") (23).

Statistical analyses

Siblings were used as controls in this study. Siblings are considered an ideal control group to minimize the effects of confounding factors that are shared by siblings and patients, such as socioeconomic status. QoL in siblings of chronically ill children does not appear to differ from peers (24).

Since there are many differences in clinical characteristics between isolated central CH patients and MPHD patients, for example with respect to disease severity based on pretreatment FT4 concentrations, it was considered inappropriate to compare patients and siblings only (2). We thus compared scores between the 2 groups of patients and siblings, using a linear mixed model. The use of a linear mixed model allows paired analysis without excluding those patients for whom no sibling could be included. Endocrine status (ie, healthy, isolated central CH, or MPHD) was included as a fixed factor. The assigned code for each family was included as a random factor (intercept) in the model. Because age-specific forms and corresponding norms were used, age was not included in the model. Significant differences between the three groups were explored in a post-hoc analysis using Tukey's test. To decrease the probability of type I errors, we used a Bonferroni correction for multiple testing. We adjusted the *P*-value by dividing it by the number of domains tested; a P-value < 0.01 (0.05/5 and 0.05/4) was thus considered statistically significant for PedsQL and PedsQL Fatigue scores. R version 3.6.1 (2019-07-05) was used for statistical analysis, using packages lme4 and emmeans (25,26).

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Results

A total of 126 patients were available from the nationwide database on central CH, detected by neonatal screening during the 20-year study period (2). Since 1 patient was untraceable and 3 patients emigrated, 122 patients were considered eligible and were invited to participate in either study part. Eighty-eight patients (72%) agreed to take part in the QoL assessment. Fifty-two siblings were included in the sibling control group. For the remaining patients, there was no sibling (n = 20), the sibling was too young to participate (n = 5), the sibling or parents refused participation (n = 2), or the patient or parents did not allow communication with the sibling (n = 3). In 3 families, 2 siblings both had isolated central CH (caused by the same gene mutation), and no healthy siblings were available.

We obtained 41 parent reports of children below 8 years of age (25 patients/16 siblings), 74 self-reports and 74 parent reports of participants aged 8 to 19 (48 patients/27 siblings), and 24 self-reports of participants ≥19 years of age (15 patients/9 siblings). One patient of 9 years old did not fill in the self-report, and for 1 sibling of 14 years old the parents did not fill in the parent report.

The patient group consisted of 53 (60%) MPHD patients and 35 (40%) isolated central CH patients. Pretreatment plasma FT4 concentrations were measured at median ages of 13 and 14 days, respectively (Table 1), which is of importance because FT4 concentrations are known to differ from day to day during the neonatal period (27). Treatment was started shortly after abnormal CH screening results were reported (ie, before the age of 3 months) in 86 (98%) patients. Sociodemographic and clinical characteristics of participating patients and siblings are summarized in Table 1. No differences were found between participating patients and nonparticipants regarding sex, age, or type of disease (data not shown).

Health-related quality of life

Self-reports

Scores from the PedsQL self-report are shown for each group in Table 2. In isolated central CH patients, the self-reported total PedsQL and subscale scores did not differ from those of siblings. For MPHD patients, self-reported scores were somewhat lower compared with those of siblings, but these differences were not statistically significant.

Parent reports

In the parent reports isolated central CH patients scored similar to siblings on all subscales (Table 2). For MPHD patients, the parent reports showed significant differences with siblings regarding total score, physical functioning, and social functioning (Table 3). MPHD patients showed, on average, a 10-point lower total PedsQL score in the parent reports than siblings [95% confidence interval (CI) −15.9 to −4.4 points; $P < 0.001$). Large differences in the parent reports were also seen between MPHD patients and siblings for subscales physical functioning (mean difference −9.4 points, 95% CI −16.2 to −2.5 points; $P = 0.005$) and social functioning (mean difference −15.1 points, 95% CI −23.1 to −7.2; $P < 0.001$). MPHD patients also scored lower than isolated central CH patients regarding social functioning (Table 3).

Fatigue

Self-reports

For fatigue, no significant differences were seen between MPHD patients, isolated central CH patients, and siblings in the self-reported scores (Table 4).

Parent reports

For isolated central CH patients, there was no difference in the parent reported fatigue scores when compared with siblings. The parent reports of MPHD patients, however, showed a significantly lower total fatigue score, compared with siblings (Table 4). MPHD patients scored an on average 9.4 points lower total fatigue score (95% CI −16.6 to −2.5, $P = 0.005$). For the subscale general fatigue, parent reported scores for MPHD patients were significantly lower as well, with a mean difference of −11.0 points (95% CI −18.4 to −3.6, $P = 0.002$) (Table 5).

Discussion

In this study on HRQoL in early-treated central CH patients, self-reported scores for HRQoL and fatigue did not significantly differ from siblings for both isolated central CH patients and MPHD patients. These results imply that self-reported HRQoL is not affected in patients with early-treated central CH, and that, overall, both isolated central CH and MPHD patients perceive few limitations in their functioning compared with siblings. It should be noted that self-reported scores of MPHD patients appeared on average lower than those of siblings, especially for social functioning and role functioning, but these differences were not statistically significant. Yet, due to the small sample size of the current study, we cannot rule out minor differences in self-reported HRQoL between MPHD patients and siblings.

While parent reported HRQoL scores for isolated central CH patients were similar to those of siblings, parent reported HRQoL scores for MPHD patients were significantly

Table 1. Sociodemographic and clinical characteristics of participating patients with central congenital hypothyroidism and siblings

	MPHD (n = 53)	Isolated central CH (n = 35)	Siblings (n = 52)
Age in years, median (range)	9.8 (4.0-22.6)	13.0 (4.1-24.0)	12.9 (3.3-29.7)
Male, n (%)	37 (70)	32 (91)	27 (52)
Neonatal hospital admission, n (%)	46 (87)	11 (31)	13 (25)
Hospital admissions during childhood, n (%)			
0	23 (43)	26 (74)	46 (88)
1	13 (25)	5 (14%	5 (10)
≥2	17 (32)	4 (11)	1 (2)
Pretreatment FT4 concentration (pmol/L), mean ± SD[a]	8.7 ± 2.1	10.4 ± 2.4	NA
Age in days at first FT4 measurement, median (range)	13 (2-135)	14 (5-58)	NA
Additional pituitary hormone deficiencies, n (%)			
ACTH deficiency	45 (85)	NA	NA
GH deficiency	50 (94)	1 (3)[b]	NA
Gonadotropin deficiency[c]	18 (34%)	NA	NA
MRI pituitary findings (n = 50/n = 19)			
Pituitary stalk interruption syndrome[d]	44 (88)	0 (0)	NA
Septo-optic dysplasia	2 (4)	0 (0)	NA
No abnormalities	4 (8)	19 (100)	NA
Genetic variants in isolated central CH (n = 32)			
IGSF1	NA	15 (53)	NA
IRS4	NA	5 (16)	NA
TBL1X	NA	5 (16)	NA
TSHB	NA	1 (3)	NA
TRH-R	NA	1 (3)	NA
No genetic variant identified	NA	3 (9)	NA
Parental characteristics			
Paternal age in years at birth, median (range)	33.8 (24.0-56.2)[n = 52]	33.0 (26.1-48.9)	31.9 (22.6-43.2)[n = 51]
Maternal age in years at birth, median (range)	30.6 (21.7-41.1)	30.5 (20.9-40.3)	31.2 (20.3-43.3)
First child	30 (57)	17 (49)	23 (44)
Parental paid employment, n (%)			
Yes	40 (75)	31 (89)	43 (83)
No	1 (2)	2 (6)	2 (4)
Unknown	12 (23)	2 (6)	7 (13)
Single-parent household, n (%)			
Yes	5 (14)	2 (6)	1 (2)
No	36 (63)	30 (86)	44 (85)
Unknown	16 (28)	3 (9)	7 (13)
Reporting parent in participants <19 years old, n (%)			
Father	4 (10)	9 (28)	11 (26)
Mother	37 (90)	23 (72)	32 (74)

Questions on parental paid employment and single-parent households were included in the questionnaires for participants <19 years of age only.
[a]Reference interval for plasma FT4 concentration at day 13 to 15 of life: 15.3-26.5 pmol/L (27).
[b]Partial growth hormone deficiency was diagnosed in one patient with *IGSF1* deficiency syndrome.
[c]Outcome of the hypothalamus-pituitary-gonadal axis was not yet known in 29 MPHD patients (55%).
[d]MRI features compatible with pituitary stalk interruption syndrome are hypoplasia or aplasia of the anterior pituitary; a thin, interrupted or absent pituitary stalk and (partial) posterior pituitary ectopy.
Abbreviations: CH, congenital hypothyroidism; MPHD, multiple pituitary hormone deficiencies.

lower compared with siblings, and this also applied to parent reported fatigue scores. This indicates a difference in how parents and MPHD patients perceive HRQoL and symptoms of fatigue. Differences between self- and parent reports in pediatric HRQoL scores are not uncommon, and it is known that information provided by these reports is not entirely equivalent (28).

Based on studies on HRQoL in adult patients with various pituitary hormone deficiencies, we expected HRQoL to be affected, especially in MPHD patients.

Table 2. PedsQL scores for patients with central congenital hypothyroidism and siblings, divided by disease type and type of report

	MPHD	Isolated central CH	Siblings	*P*-value LMM[a]
Self-report scores: PedsQL domain	n = 33	n = 29	n = 36	
Total score	79.8 (75.6-84.0)	82.7 (78.2-87.3)	84.4 (80.3-88.4)	0.25
Physical functioning	86.5 (82.4-90.7)	87.5 (83.0-92.0)	89.0 (85.0-93.0)	0.63
Emotional functioning	76.5 (70.4-82.6)	79.0 (72.4-85.5)	79.4 (73.6-85.3)	0.76
Social functioning	80.6 (75.2-85.9)	90.8 (85.0-96.6)	87.9 (82.9-93.0)	0.02
Role functioning	71.7 (65.8-77.5)	70.9 (64.6-77.3)	78.5 (72.9-84.1)	0.06
Parent proxy-report scores: PedsQL domain	n = 41	n = 32	n = 42	
Total score	77.0 (72.9-81.2)	83.7 (78.9-88.4)	87.2 (83.2-91.2)	<0.001
Physical functioning	83.9 (79.2-88.6)	88.1 (82.7-93.5)	93.2 (88.6-97.8)	<0.01
Emotional functioning	71.3 (65.7-76.8)	77.0 (70.7-83.4)	78.3 (72.9-83.6)	0.10
Social functioning	75.3 (69.8-80.9)	88.8 (82.4-95.2)	90.4 (85.0-95.8)	<0.001
Role functioning	74.1 (68.1-80.1)	78.3 (71.4-85.2)	82.3 (76.4-88.2)	0.08

Data are given as estimated marginal means (95% confidence interval).
[a]*P*-values are derived from the linear mixed model for each domain and represent the comparison across 3 groups.
Abbreviations: LMM, linear mixed model; MPHD, multiple pituitary hormone deficiencies; PedsQL, Peds Quality of Life 4.0 Inventory.

HRQoL in isolated central hypothyroidism has only been reported in 1 previous study on adult patients with isolated central CH due to *IGSF1* deficiency syndrome. In line with our results, HRQoL scores in these patients were similar to healthy controls (29). While the burden of treatment in isolated central CH is limited to 1 daily dosage of thyroid hormone, the burden of additional pituitary hormone deficiencies can be considered more extensive. ACTH deficiency requires multiple dosages of hydrocortisone each day with the necessity of increasing the daily dosage in case of illness to prevent a life-threatening adrenal crisis. Furthermore, while the currently used dosage schemes try to mimic the physiological cortisol rhythm, patients will only achieve a pale imitation of the natural rhythm (30). It is, therefore, not surprising that lower HRQoL has been reported in adults with ACTH deficiency: compared with matched controls, patients showed lower scores for all domains except bodily pain (12). This also applies for GHD patients, in whom studies have shown that young adults with childhood-onset disease experience difficulties in psychosocial functioning, and report lower scores for HRQoL subscales general health perception, physical functioning, and role limitation due to physical health (10,11,31) An association between HRQoL and final height is often lacking, suggesting that other factors play a role in the lower HRQoL scores in these patients (11). Injection pain on a daily basis is an important burden to GH administration and has been reported by 39% to 54% of patients and 48% of caregivers (32,33). Patients who do not consider injections to be painful are mostly adults, suggesting that children are more likely to experience discomfort from GH therapy (33). Studies on QoL in isolated gonadotropin deficiency, also referred to as congenital hypogonadotropic hypogonadism (CHH), are scarce in pediatric patients. However, it is well acknowledged that a lack of pubertal development and "not being in line" with peers is associated with psychosocial problems (4,34). Studies show that adults with CHH report a lower HRQoL compared with healthy controls and experience depressive symptoms more often than healthy, nonpsychiatric controls (35-37). Although hormonal replacement therapy attempts to mimic the physiological situation, it has been suggested that the patients' biochemical situation might still not be satisfactory, like in patients with ACTH deficiency (36).

In conclusion, studies in patients with various specific pituitary hormone deficiencies show lower HRQoL scores for each group separately. By inference, lower HRQoL scores in pediatric MPHD patients might be expected. This assumption is supported by an adult study performed by Kao et al, who studied QoL in 92 adult patients with childhood-onset MPHD (13). Of these, 19 patients had congenital hypopituitarism. QoL scores were lower in patients compared with controls, but the patient group mainly consisted of cancer patients, and subgroup data on patients with congenital hypopituitarism could not be reviewed separately (13).

An encouraging finding of the current study is that self-reported HRQoL in pediatric MPHD patients appears to be similar to that of siblings; this finding might be related to the early detection of patients. Since all included patients were detected by neonatal screening and have received

Table 3. Post-hoc analyses for differences in PedsQL scores between isolated central CH patients, MPHD patients, and siblings

Parent proxy-report scores: PedsQL domain	Mean change in score	Standard error	Lower limit of 95% CI	Upper limit of 95% CI	*P*-value
Total score					
Isolated central CH *vs* siblings	−3.5	2.6	−9.8	2.8	0.39
MPHD *vs* siblings	−10.2	2.4	−15.9	−4.4	<0.001
MPHD *vs* isolated central CH	−6.7	3.1	−13.9	0.6	0.08
Physical functioning					
Isolated central CH *vs* siblings	−5.1	3.3	−12.9	2.8	0.27
MPHD *vs* siblings	−9.3	3.0	−16.6	−2.1	0.008
MPHD *vs* isolated central CH	−4.2	3.6	−12.7	4.3	0.47
Social functioning					
Isolated central CH *vs* siblings	−1.6	3.6	−10.3	7.1	0.90
MPHD *vs* siblings	−15.1	3.3	−23.1	−7.2	<0.001
MPHD *vs* isolated central CH	−13.5	4.1	−23.3	−3.6	0.004

Post-hoc analyses are only reported for domains that showed a significant difference between groups in the linear mixed model.
Abbreviations: CH, congenital hypothyroidism; CI, confidence interval; MPHD, multiple pituitary hormone deficiencies; PedsQL, Peds Quality of Life 4.0 Inventory.

treatment from a very young age, patients might have grown accustomed to their treatment. In addition, while a "diagnostic odyssey" including incorrect diagnoses and a delay in care is frequently reported in late-detected CHH patients, we can assume that none of our patients had such an experience due to early detection (4).

The differences observed between the self- and parent reported scores in MPHD patients are intriguing. Several explanations are possible for these differences. First, parents or caregivers are usually responsible for medical tasks such as medication storage, timely medication administration, and increasing hydrocortisone dosages in case of stress or illness. The younger the patient is, the greater the parents' responsibility is, although many parents will continue to feel responsible well into adulthood. This might have resulted in differences between the parent reports, which were completed for patients aged 3 to 18 years old, and self-reports, which were filled in by patients aged 8 to 23 years old. In addition, studies in children with epilepsy have shown that children are far less concerned with the future compared with their parents, who report both present and future concerns (38). In general, children and parents might draw on different values regarding the chronic disease, resulting in differences in HRQoL between the 2 types of measurement (39,40). Third, it has been described that agreement between the patient and proxy report is large for subscales relying on "concrete information", such as physical functioning, while levels of agreement are moderate for more abstract subscales like emotional and social functioning (41). Finally, it has been hypothesized that a correlation exists between the overall parental view of a child's progress and the outcomes of various questionnaires. This hypothesis suggests that the parents' overall view is (partly) responsible for the intercorrelation seen between parental questionnaires that aim to evaluate different domains (42). In other words, when a parent report is used to measure the child's HRQoL, outcomes might be associated with respondent-related factors such as an overall view.

Although the patients' and parents' perception of HRQoL might differ, both are important in clinical care (28). The parent's HRQoL perception will often determine the use of healthcare facilities, as children are dependent on their parents or caregivers for a consultation (43). In addition, there are many situations in which the clinician will not be able to obtain a self-report, and it is important to take into account the parents' perception of the child's HRQoL as well. When we evaluate the differences between MPHD patients and siblings observed in the current study using their respective MCID, all differences can most certainly be considered of clinical importance.

We would like to highlight the clinical importance of the subscale social functioning. Although self-reported scores for social functioning did not differ significantly between groups, the mean scores presented in Table 2 show that both MPHD patients and their parents observe a difference with siblings regarding social functioning. Social functioning refers to the ability to function in a social community, ie, to get along with peers and make friends. The current study suggests that MPHD patients are likely to experience problems in this domain, and clinicians should thus actively inquire about patients' social functioning. Impaired social functioning may be related to not feeling in line with peers (eg, due to frequent hospital visits or the need for an increased dose of hydrocortisone in case of stress).

Table 4. PedsQL Fatigue scores for patients with central congenital hypothyroidism and siblings, divided by disease type and type of report

	MPHD	Isolated central CH	Siblings)	*P*-value LMM
Self-report scores: PedsQL Fatigue domain	**n = 33**	**n = 29**	**n = 36**	
Total fatigue	72.8 (67.6-78.1)	78.6 (72.9-84.3)	76.0 (71.0-81.0)	0.30
General fatigue	78.9 (73.3-84.6)	81.9 (75.8-88.0)	82.0 (76.5-87.4)	0.67
Sleep	71.0 (64.5-77.6)	75.7 (68.5-82.8)	72.4 (66.1-78.6)	0.59
Cognitive fatigue	67.8 (60.7-75.0)	78.6 (70.8-86.4)	74.0 (67.2-80.7)	0.10
Parent proxy-report scores: PedsQL Fatigue domain	n = 41	n = 32	n = 42	
Total fatigue	76.6 (71.8-81.4)	83.7 (78.2- 89.2)	86.0 (81.4-90.6)	0.003
General fatigue	76.9 (71.9-82.0)	85.2 (79.5-91.0)	87.9 (83.0-92.8)	0.001
Sleep	80.9 (75.8-85.9)	85.8 (80.0-91.6)	87.5 (82.5-92.5)	0.12
Cognitive fatigue	72.2 (64.9-79.5)	80.0 (71.6-88.4)	82.0 (74.8-89.1)	0.09

Data are given as estimated marginal means (95% confidence interval).
Abbreviations: LMM, linear mixed model; MPHD, multiple pituitary hormone deficiencies; PedsQL Fatigue, Pediatric Quality of Life Multidimensional Fatigue Scale.

Table 5. Post-hoc analyses for differences in PedsQL fatigue scores between isolated central CH patients, MPHD patients, and siblings

Parent proxy-report scores: PedsQL Fatigue domain	Mean change in score	Standard error	Lower limit of 95% CI	Upper limit of 95% CI	*P*-value
Total score					
Isolated central CH *vs* siblings	−2.3	3.1	−9.7	5.2	0.75
MPHD *vs* siblings	−9.4	2.9	−16.2	−2.5	0.005
MPHD *vs* isolated central CH	−7.1	3.6	−15.6	1.4	0.12
General fatigue					
Isolated central CH *vs* siblings	−2.6	3.4	−10.7	5.5	0.72
MPHD *vs* siblings	−11.0	3.1	−18.4	−3.6	0.002
MPHD *vs* isolated central CH	−8.3	3.8	−17.4	0.7	0.08

Analyses are only reported for domains that showed a significant difference between groups in the linear mixed model.
Abbreviations: CH, congenital hypothyroidism; CI, confidence interval; MPHD, multiple pituitary hormone deficiencies; PedsQL Fatigue, Pediatric Quality of Life Multidimensional Fatigue Scale.

Strengths of the current study include the size of the patient group and the fact that isolated central CH and MPHD patients participated in the study in their "natural occurring ratio" (44). Moreover, the instrument used to measure HRQoL has been well-established in pediatric patients. A limitation of the current study is that not all eligible central CH patients agreed to participate in the QoL assessment. Because responders might differ from nonresponders (ie, in perceived limitations in daily life), we cannot exclude some degree of nonresponse bias. Several measures were taken to prevent nonresponse bias in this study by including as many respondents as possible: all eligible patients received a personalized invitation for the study by email and telephone, and questionnaires were made easily accessible on a visually appealing website. Despite these efforts, we were not able to include the entire group of eligible patients. Still, we consider the participation rate of 72% to be high for this cohort, which included patients who received their diagnosis over 23 years ago. Another limitation regards the size of the subgroups: although the group of central CH patients was large, subgroups of MPHD patients and isolated central CH patients were rather small. This also applies to the subgroups with various genetic variants among the isolated central CH patients (see Table 1). Important to note is that although siblings present a good control group, their QoL may be affected by the presence of a family member with a chronic illness. A systematic review on HRQoL in siblings of chronically ill children showed that HRQoL is not affected uniformly but is associated with the type of chronic disease and disease severity (45). For example, QoL is reduced in siblings of pediatric cancer patients, while siblings of patients with

type 1 diabetes, cystic fibrosis, or asthma scored similar to or higher than peers (24,46,47). Because central CH is not an acute life-threatening disease like cancer, we considered siblings an appropriate control group for the current study.

In addition, due to the cross-sectional design of the study, no conclusions can be made regarding the relationship between early detection of central CH and absence of HRQoL impairment in the self-reports. Finally, since the current study was performed in the Netherlands, all but 1 of the included patients were born in the Netherlands. This study thus mainly reflects the HRQoL perception of patients and parents who receive medical care for central CH in the Dutch healthcare system; the generalizability of the results to other countries may be limited.

In a review on QoL in young adults with primary CH, Léger concluded, "the impact of CH is clearly not uniform" (48). This also seems to be the case for early-detected central CH. In our study both isolated central CH patients and MPHD patients report HRQoL scores similar to siblings, showing no negative effect on QoL in this early-detected patient group. The lower parent reported scores for total HRQoL, physical functioning, and social functioning in MPHD patients, compared with siblings, might be caused by differences in perception between patients and parents, with parents focusing more on future concerns than children.

We hypothesize that early detection and treatment may have contributed to the normal self-reported HRQoL scores in early-detected central CH patients. To test this hypothesis, a comparison with HRQoL scores in late-detected central CH patients is necessary. If the results of this comparison are in support of our hypothesis, this is an extra argument for neonatal screening for central CH.

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Additional Information

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