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RESEARCH

New diagnostic approach to central hypothyroidism after traumatic brain injury in children and adolescents

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Abstract

Background: Pituitary lesions after traumatic brain injury (TBI) are frequent in children and adolescents, but the rate of post-TBI central hypothyroidism remains uncertain.

Objective: To identify the long-term incidence of post-TBI CH and the clinical and laboratory characteristics of this complication in children and adolescents.

Methods: The analysis included 31 patients with a history of TBI with at least 1 year of follow-up. Patients were evaluated at hospital admission and every 3 months thereafter. Assessments included clinical evaluation, brain CT and hormone assessments (basal fT4, IGF-1, cortisol and adrenocorticotropic hormone; insulin tolerance test/thyrotropin-releasing hormone test with TSH, growth hormone and cortisol measurement; and corticotropin-releasing hormone test, if indicated). The CH diagnosis was based on clinical and laboratory findings and a therapeutic trial with levothyroxine.

Results: Overall, five patients (16%) developed CH (3 with associated adrenal insufficiency). At 3 and 12 months, median fT4 values were lower in patients with CH compared with those without anterior pituitary dysfunction (n = 18; P = 0.01). Patients with CH received levothyroxine and progressed with clinical resolution and increased median fT4 (from 0.92 to 1.47 ng/dL) and IGF-1 (from −2.08 to −0.22 standard deviation scores (SDS)) levels. Temporary suspension of levothyroxine was accompanied by decreased median fT4 (1.02 ng/dL) and IGF-1 (−1.07 SDS) levels and reappearance of clinical symptoms, which resolved once levothyroxine was reinitiated.

Conclusions: The longer follow-up, valorization of clinical manifestations, nontraditional laboratory approach and therapeutic trial with levothyroxine in the present study revealed a higher rate of post-TBI CH in children and adolescents than that reported in the literature.

Keywords: traumatic brain injury; central hypothyroidism; GH; IGF-1; children; adolescents

Introduction

Traumatic brain injury (TBI) often results in anatomical and histological damage to the pituitary stalk and anterior pituitary gland (1, 2, 3) through various mechanisms (4). Post-TBI anterior pituitary dysfunction (APD) was first reported in 1918 (5) but was considered a rare complication until recently when Benvenga and

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coworkers reported an increased incidence of this complication after actively investigating its occurrence among patients with a history of TBI (6). Studies have shown varying rates of post-TBI APD in adults. Although studies in the pediatric population are less frequent, the available studies also report variable rates of occurrence (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21), highlighting a current challenge in establishing the best strategy to investigate the occurrence of post-TBI APD in this population (22). One particular concern is the lack of data related to the occurrence of central hypothyroidism (CH) after TBI in children and adolescents, as the clinical manifestations of hypothyroidism may be similar to those of neurological sequelae. Therefore, the identification and treatment of CH is fundamental for recovery after TBI. The lack of high-quality data related to this condition in the pediatric population is also troubling, given the critical role of the pituitary axis in the development of children and adolescents.

Based on these considerations, the primary aim of this study was to evaluate the rate of CH and the clinical characteristics and laboratory findings of this complication in a longitudinal cohort of children and adolescents with TBI. A secondary aim was to compare the hormone levels in this cohort with those in patients with a history of TBI but without APD.

Materials and methods

This was a prospective longitudinal study of children and adolescents aged 2–20 years, admitted to the School Hospital of the Pontifical Catholic University of Paraná (Curitiba, Brazil) between March 2007 and January 2009. The reason for admission was TBI with neurological manifestations with or without findings on brain computed tomography (CT). The only exclusion criterion was the previous use of medications with the potential to interfere with the hypothalamic–pituitary axis. Patients with a follow-up shorter than 1 year were excluded from the analysis due to a lack of data to properly diagnose or rule out APD.

We collected the following data from patients during their hospital stay: chronological age, sex, pubertal status, cause of trauma, neurological and endocrine abnormalities, Glasgow coma scale (GCS) score at admission, brain CT findings, time until normalization of neurological abnormalities, duration of hospitalization and Glasgow outcome scale (GOS) on discharge (23). One of the authors, who is a pediatric endocrinologist (GMG), performed a clinical evaluation of all the patients and supervised blood drawing in their first 6 h of hospitalization for measurement of baseline values of free T4 (fT4), cortisol, adrenocorticotropic hormone (ACTH) and IGF-1.

Approximately 2–4 weeks after hospital discharge and trimonthly thereafter, the patients were reexamined by the same endocrinologist at the Service of Pediatric Endocrinology Prof. Romolo Sandrini of the Federal University of Paraná School Hospital (FUPSH, Curitiba, Brazil). These follow-up evaluations included clinical history taking, physical examination (including weight, height and body mass index (BMI)) and assessment of pubertal status (evaluation of Tanner stage in all patients and testicular volume measurement using Prader's orchidometer in boys) (24, 25). Height and BMI z-scores were calculated using Growth XP 2019 (www.GrowthXP.com) based on reference values established by the World Health Organization (WHO).

Fasting serum fT4 and IGF-1 levels were measured at 3-month intervals throughout the follow-up period. At the 3- and 12-month visits, the patients underwent an insulin tolerance test (ITT) combined with a thyrotropin-releasing hormone (TRH) stimulation test after 10- to 12-h fasting. During the tests, blood was drawn for measurement of fasting serum glucose, fT_4, TSH, cortisol, growth hormone (GH) and IGF-1 levels. Intravenous regular insulin 0.1 IU/kg (Novolin; Novo Nordisk Farmacêutica do Brasil Ltda, Brazil) and TRH 200 μg (Ferring Pharmaceuticals, Germany) were then administered, followed by repeat blood drawing at 20, 40 and 60 min for measurement of glucose, TSH, cortisol and GH levels. The reference values for peak and delta TSH values post-TRH were ≥9 μIU/mL and ≥7 μIU/mL, respectively (Supplementary Table 1, see section on Supplementary materials given at the end of the article) (26, 27, 28, 29, 30, 31). In case a low cortisol value (<18.0 μg/dL) was observed in one of the ITTs in the presence or absence of clinical signs suggestive of adrenal insufficiency, a corticotropin-releasing hormone (CRH) test was conducted with intravenous injection of corticorelin ovine triflutate 100 μg (Ferring Pharmaceuticals), with blood samples collected before and 10, 20, 30, 40, 60 and 90 min after the injection for measurement of cortisol and ACTH values. If injury to the hypothalamic–pituitary–gonadal axis was suspected, sex steroids were measured, and a gonadotropin-releasing hormone (GnRH) test (with measurement of luteinizing hormone levels) was obtained. Supplementary Table 1 shows the reference values and assays used for all tests.

The diagnosis of CH was established in the presence of three or more clinical signs consistent with hypothyroidism during follow-up, along with serum fT4 levels either within or below the lowest quartile of the reference value or >20% lower than baseline, each accompanied by clinical resolution and a fT4 increase of ≥20% during a therapeutic trial with levothyroxine (1.5–2.0 μg/kg/day).

The diagnosis of central adrenal insufficiency (CAI) was established in the presence of clinical signs consistent with adrenal insufficiency combined with a low peak cortisol in at least one of the ITTs and clinical resolution with a glucocorticoid (hydrocortisone or prednisone) administration. All patients with

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laboratory test results suggestive of CAI, even in the absence of clinical manifestations, were alerted about the risk of acute adrenal insufficiency in stressful situations.

The study protocol was approved by the Human Research Ethics Committees at FUPSH. The parents of all patients signed the informed consent form.

Statistical analysis

Quantitative variables are described as median (minimum–maximum) values or frequencies and percentiles. Due to the small number of cases in the group with CH, the comparison between two classifications of a single variable in relation to a quantitative variable was made using the nonparametric Mann–Whitney test. Associations between qualitative variables were tested using the chi-square or Fisher's exact test. *P* values <0.05 were considered significant.

Results

Of the 48 patients assessed at baseline, 17 were followed for less than 1 year and were excluded from further analysis. All 31 patients (chronological age 2.4–18.6 years) with follow-up longer than 1 year underwent comprehensive endocrine evaluations over 1–16 years. Of these, five (16.1%) developed CH ('CH group'), seven exhibited abnormalities in the GH–IGF-1 axis, and one developed isolated CAI. The remaining 18 patients had no APD ('non-APD group') (Table 1).

Baseline evaluation

At baseline, we observed no differences between the CH group and the non-APD group regarding epidemiological data, cause of trauma, loss of consciousness, GCS values, neurological manifestations (drowsiness, mental confusion, echolalia, amnesia, loss of consciousness, seizure, diplopia, otorrhagia, otoliquorrhea or rhinorrhea), CT imaging findings (cranial fracture, brain edema, cerebral hemorrhage, subarachnoid hemorrhage, extradural hematoma, pneumocephalus or midline deviation), time to neurological normalization, duration of hospitalization or GOS (Table 2). The results from the endocrine workup were also comparable between the groups, except for IGF-1 levels, which were lower in the CH group (P = 0.02) (Table 2).

Follow-up evaluation

During follow-up, the five patients in the CH group presented three or more of the following clinical signs of hypothyroidism: decreased physical activity, tiredness, fatigue, cold intolerance, mood changes, somnolence, memory impairment, decreased school performance, constipation or erectile dysfunction (Table 2). Serum fT4 values in the lowest quartile (0.80–1.10 ng/dL) were observed in four of these five patients at the 3-month follow-up visit and in all 5 at the 12-month follow-up visit. Notably, five of the 18 patients in the non-APD group also had fT4 values in the lowest quartile in the 3-month (n = 2) and 12-month (n = 3) follow-up assessments but had no clinical manifestations of hypothyroidism. In addition, three patients in the CH group (patients 1, 2 and 4 in Table 2) had a >20% decrease in fT4 levels relative to baseline during the first year of follow-up. Low (<0.8 ng/dL) fT4 levels during follow-up were observed in two patients in the CH group (patients 3 and 5) at 17 months and 9.2 years, respectively, after the TBI event.

During the TRH stimulation test, the delta TSH was <7 μIU/mL in two patients in the CH group (patients 2 and 3), and peak TSH values were <9 μIU/mL in one patient in the CH group (patient 2) and one patient in the non-APD group. Notably, three patients in the non-APD group, who had fT4 levels persistently normal and no manifestations of hypothyroidism, presented TSH values >25 μIU/mL during the test.

The GH peak during the combined ITT/TRH test was >30 ng/mL in three patients (patients 3, 4 and 5) in the CH group and in two patients in the non-APD group. In addition, three patients in the CH group (patients 1, 2 and 3) had IGF-1 values below −2 standard deviation scores (SDS) right before the therapeutic trial with levothyroxine; the remaining two patients in this group had IGF-1 values of −1.49 SDS (patient 4) and −0.69 SDS (patient 5) at the same time point.

All patients in the CH group were started on levothyroxine as a therapeutic trial between follow-up months 13 and 35. During levothyroxine treatment, the clinical symptoms of hypothyroidism resolved in all patients, and their fT4 levels increased (median increase from 0.92 to 1.47 ng/dL) (Table 2). During the follow-up period, levothyroxine treatment was interrupted in all patients, either at their own decision or at the request of their families. During levothyroxine interruption, the median serum fT4 levels decreased to 1.02 ng/dL and increased again to 1.37 ng/dL when levothyroxine was restarted. The maximum fT4 level during levothyroxine treatment was 1.77 ng/dL (Fig. 1). All patients remained on levothyroxine until their last recorded visit before the preparation of this article.

In the CH group, the median IGF-1 values at follow-up months 3 (−1.9 SDS) and 12 (−1.49 SDS) were comparable to those at baseline (−1.72 SDS). The median IGF-1 value increased (from −2.08 to 1.47 SDS) during levothyroxine treatment, decreased (−1.07 SDS) when levothyroxine was interrupted and increased again (0.67 SDS) when levothyroxine was reintroduced (Fig. 2).

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Table 1 Baseline and follow-up data of patients with TBI, grouped according to the development of central hypothyroidism (CH group) versus the absence of anterior pituitary dysfunction (non-APD group). The data are shown as median (minimum–maximum) values or frequency (percentage).

	CH group (*n* = 5)	Non-APD group (*n* = 18)	*P* values
During hospital stay			
Age at TBI (years)†	14.3 (7.3–17.2)	9.3 (2.4–17.8)	0.06
Sex			0.12
Male*	4 (80%)	6 (33%)	
Female*	1 (20%)	12 (67%)	
Sexual maturation			0.14
Complete*	4 (80%)	12 (67%)	
Incomplete*	1(20%)	6 (33%)	
Cause of TBI			NF
Traffic accident	3 (60%)	9 (50%)	
Same level or elevated fall	1 (20%)	7 (39%)	
Others	1 (20%)	2 (11%)	
Loss of consciousness at TBI*	4 (80%)	8 (44%)	0.32
Glasgow score on admission*			0.70
Mild (13–15)	4 (80%)	11 (61%)	
Moderate (9–12)	0 (0%)	5 (28%)	
Severe (3–8)	1(20%)	2 (11%)	
Days until neurological normalization†	2 (2–4)	2 (2–10)	0.64
Days of hospitalization†	8 (4–14)	4 (3–17)	0.06
Brain CT			NF
Normal*	3 (60%)	6 (33%)	
Abnormal*	2 (40%)	12 (66%)	0,64
Brain alterations*	2 (40%)	9 (50%)	0,34
Cranial fracture*	1 (20%)	9 (50%)	0,62
GOS on hospital discharge*			0.59
Optimal recovery (5)	4 (80%)	17 (94%)	
Moderate disability (4)	0 (0%)	1 (6%)	
Severe disability (3)	1 (20%)	0 (0%)	
During follow-up after hospital discharge			
Duration of follow-up (years)†	10.2 (2.8–12.5)	4.8 (1.0–11.2)	0.11
Free T4 (ng/dL)			
Hospital admission†	1.15 (0.91–1.67)	1.3 (0.88–1.67)	0.20
Hospital discharge†	1.19 (0.98–1.61)	1.32 (0.88–1.67)	0.33
3-month visit†	1.01 (0.97–1.08)	1.23 (0.97–1.46)	0.01
12-month visit†	0.96 (0.82–1.11)	1.17 (0.83–1.47)	0.01
TSH (μIU/mL) during TRH stimulation test			
3-month visit†			
Before TRH	2.1 (1.2–7.6)	2.5 (0.7–4.3)	0.82
Peak after TRH	12.9 (7.9–17.8)	16.4 (9.1–37.0)	0.18
12-month visit†			
Before TRH	1.7 (1.1–2.3)	2.2 (0.9–2.3)	0.12
Peak after TRH	12.4 (10.0–19.8)	15.7 (8.5–46.3)	0.10
GH (ng/mL) during ITT/TRH stimulation test			
3-month visit†			
Peak after ITT/TRH	19.2 (7.0–40.0)	8.4 (2.5–36.1)	0.10
12-month visit†			
Peak after ITT/TRH	24.2 (9.4–40.0)	6.7 (2.9–40.0)	0.02
IGF-1 (SDS)			
Hospital admission†	−1.72 (−2.98 to −0.64)	−0.42 (−1.90–1.10)	0.02
3-month visit†	−1.90 (−2.34 to −0.63)	−0.27 (−2.19–1.77)	0.02
12-month visit†	−1.49 (−2.44 to −0.69)	−0.57 (−2.22–1.12)	0.04

GH, growth hormone; GOS, Glasgow outcome scale; NF, not feasible; non-APD group, group without anterior pituitary dysfunction; SDS, standard deviation score; and TRH, thyrotropin-releasing hormone.
*Chi-square test or Fisher's exact test. †Nonparametric Mann–Whitney test.

Table 2 Clinical, imaging and laboratory findings at baseline and during follow-up in five patients with CH secondary to TBI.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Male	Male	Female
Findings at the TBI event					
Age (years)	7.3	14.9	15.9	16.2	17.2
Sexual maturation at 1st visit*	Prepubertal	T4, P4	Complete	T10, P4	Complete
Cause of TBI	Same-level fall	Traffic accident (bicycle)	Traffic accident (motorcycle)	Traffic accident (bicycle)	Traffic accident (motorcycle)
Loss of consciousness after injury	Yes	Yes	Yes	Yes	Yes
Findings at hospital admission					
GCS score	14	13	8	13	13
Clinical and neurological manifestations	Projectile vomiting	Lacunar amnesia	Somnolence, disorientation	Somnolence, mental confusion, echolalia, vomiting	Disorientation, vomiting, right otorrhagia
Brain computed tomography findings at hospital admission	Normal	Normal	Hemorrhagic injury in the left frontotemporal area, edema, subarachnoid hemorrhage, subdural hematoma along the cerebral falx	Normal	Fracture of the right temporal bone, extradural hematoma in the right parietal region, bilateral frontotemporal hemorrhage
fT4 values, ng/dL	1.63	1.22	1.15	0.91	0.97
IGF-1 values	−2.11	−0.64	−1.72	−1.51	−2.98
Cortisol values	41	15.5	49.1	24.4	16
ACTH values	135	8	135	12	<5
Findings at hospital discharge					
Time to normal neurological evaluation (days)	2	2	60	2	2
Duration of hospitalization (days)	4	8	14	6	11
GOS score at hospital discharge	5	5	3	5	5
Findings at follow-up					
fT4 values, ng/dL					
Month 3	1.08	1.01	1.00	0.97	1.05
Month 12	1.11	1.01	0.93	0.96	0.82
Before treatment	1.08	0.92	0.72	0.93	0.82
At LT4 start	1.49	1.11	1.47	1.40	1.54
At LT4 interruption	1.08	1.02	0.98	1.20	0.89
At LT4 reinitiation	1.77	1.21	1.28	1.37	1.65
IGF-1 values, SDS					
Month 3	−1.9	−0.63	−2.2	−1.15	−2.34
Month 12	−2.44	−0.72	−2.16	−1.49	−0.69

(Continued)

Table 2 Continued.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Before treatment	−2.44	−2.08	−2.16	−1.49	−0.69
At LT4 start	−0.84	0.86	−0.22	−0.6	1.08
At LT4 interruption	−1.47	−0.66	−0.59	−1.76	−0.40
At LT4 reinitiation	−0.09	1.54	−0.16	0.67	0.69
Start of clinical manifestations of hypothyroidism (months after TBI)	9	6	12	12	10
Clinical manifestations of hypothyroidism	Decreased school performance and physical activity, somnolence	Decreased school performance, fatigue, cold intolerance, memory impairment	Erectile dysfunction (normal testosterone level and normal LH response to the GnRH test), fatigue, cold intolerance	Fatigue, memory impairment, constipation	Memory impairment, somnolence, fatigue, cold intolerance
Start of LT4 (months after TBI)	16	35	17	14	13
LT4 dose (μg/kg/day)	2.0	2.0	2.0	1.5	2.0
Outcome	Clinical resolution with LT4 treatment; suspended LT4 21 months after TBI (parents' decision) with reappearance of symptoms; resumed LT4, with clinical resolution; poor LT4 adherence throughout; developed symptoms of adrenal insufficiency (syncope) at follow-up year 9, after a second TBI, with peak cortisol on ITT of 16.5 μg/dL	Missed appointments for 13 months after TBI; clinical resolution with LT4 treatment; suspended LT4 (patient's decision) and had reappearance of clinical manifestations while off LT4; developed clinical manifestation of adrenal insufficiency (syncope) at follow-up year 3	Hormone investigation for erectile dysfunction at follow-up month 16 (serum total testosterone 552 ng/dL; LH peak after GnRH 13.0 mIU/mL). At 17 months, fT4 was 0.72 ng/dL; clinical resolution with LT4 treatment; intermittent use of LT4 throughout; suspended LT4 (patient's decision) with reappearance of clinical manifestations	Clinical resolution with LT4 treatment; irregular treatment, suspended LT4 (patient's decision) and had reappearance of clinical manifestations while off LT4	Syncope at hospital admission requiring intravenous hydrocortisone; irregular use of glucocorticoid (patient's decision) with reappearance of clinical manifestations; hypotension during labor, requiring intravenous hydrocortisone at follow-up year 9. Manifestation of hypothyroidism at follow-up month 10; clinical resolution with LT4 treatment; irregular treatment (patient's decision), with reappearance of clinical manifestations. One month after the first labor (9 years after TBI), fT4 level was 0.66 ng/dL
Cortisol values (μg/dL) on ITT					
Month 3	20.7	15.7	18.8	21.2	21.4
Month 12	25.3	15.6	25.5	17.9	17.0

(Continued)

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Table 2 Continued.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CRH test	NO	At year 3	NO	NO	At year 3
Cortisol, µg/dL		15.9			17.1
ACTH, pg/mL		15.9			14
Follow-up duration (years)	11.1	10.3	6.4	2.8	12.5

ACTH, adrenocorticotropic hormone; CH, central hypothyroidism; CRH, corticotropic hormone; fT4, free thyroxine; GCS, Glasgow coma scale; GOS, Glasgow outcome scale; ITT, insulin tolerance test; LT4, levothyroxine; NO, not obtained; SDS, standard deviation score; T4, thyroxine; TBI, traumatic brain injury.
*Assessments based on Tanner stage and, in boys, testes were measured using Prader's orchidometer.

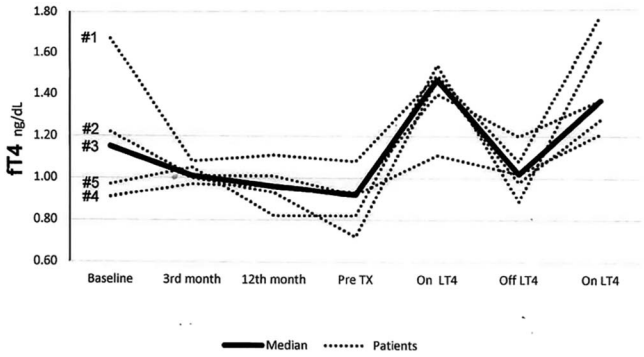

Figure 1

Individual and combined (median) free thyroxine (fT4) levels in five patients with central hypothyroidism secondary to TBI. The sequence of time points shown indicates values measured at hospital admission, at the 3- and 12-month follow-up visits, before levothyroxine (LT4) treatment (pre-Tx), during LT4 treatment (on LT4), LT4 interruption (off LT4) and LT4 reinitiation (on LT4).

Notably, three patients with CH developed CAI: at admission (patient 5) and at follow-up years 3 (patient 2) and 9 (patient 1, after a second TBI). Their main CAI manifestation was syncope. Patient 5 presented severe hypotension during labor at follow-up year 9, which only improved after intravenous hydrocortisone (Table 2).

Patient 1 presented low cortisol values during ITT at follow-up year 9 but did not undergo a CRH test. Patient 2 had low cortisol and ACTH values at baseline, low peak cortisol values during ITTs obtained at follow-up months 3 and 12 and low cortisol and ACTH peak values during the CRH test. Patient 5 had low cortisol and ACTH values at baseline, a low cortisol peak value during the ITT at follow-up month 12 and low peak cortisol and ACTH values during the CRH test (Table 2). The CAI manifestations resolved with the use of glucocorticoid

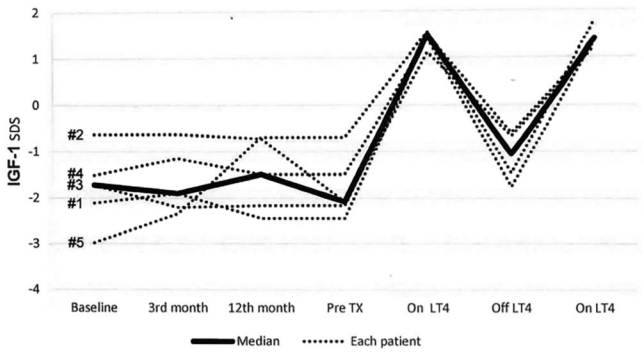

Figure 2

Individual and combined (median) IGF-1 values in five patients with central hypothyroidism secondary to TBI. The sequence of time points shown indicates values measured at hospital admission, at the 3- and 12-month follow-up visits, before levothyroxine (LT4) treatment (Pre-Tx), during LT4 treatment (on LT4), LT4 interruption (off LT4) and LT4 reinitiation (on LT4).

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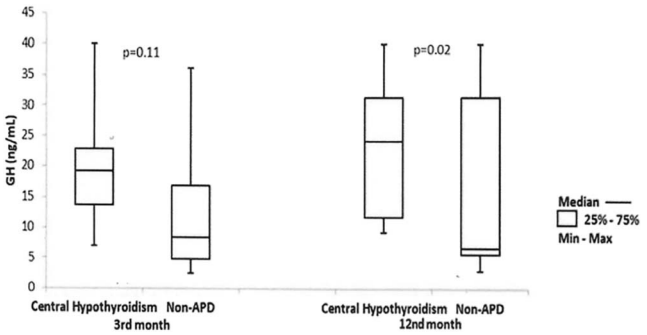

Figure 3

Peak GH values (median, minimum and maximum values) during the insulin tolerance test (ITT) combined with the TRH stimulation test in patients with central hypothyroidism secondary to TBI (n = 5) versus those without anterior pituitary dysfunction (n = 18) at the 3-month and 12-month follow-up visits. Nonparametric Mann–Whitney test (*P = 0.02).

in all these patients and reappeared when this treatment was discontinued.

Comparisons between the CH group versus the non-APD group

As shown in Table 1, the median fT4 values 3 months (P = 0.01) and 12 months (P = 0.01) after the TBI event were lower in patients in the CH group than in those in the non-APD group. Both groups had comparable median TSH values measured before and after TRH stimulation (Table 1). At 12 months, the median peak GH value after the ITT/TRH stimulation test was higher in patients in the CH group (P = 0.02) than in those in the non-APD group (Table 1 and Fig. 3). In addition, the median IGF-1 SDS values were significantly lower in the CH group than in the non-APD group at baseline and at the 3- and 12-month follow-up visits (Table 1).

No cases of diabetes insipidus, hypogonadism or precocious puberty were observed in the study cohort.

Discussion

This long-term, prospective, longitudinal study followed a cohort of children and adolescents who experienced a TBI event and identified the incidence and types of anterior pituitary abnormalities developing after this type of event in this age group. The present analysis focused primarily on patients who developed CH, and the close, standardized follow-up approach adopted allowed the identification of the moment when the clinical manifestations started to develop in these patients and their response to levothyroxine administration. Due to the clinical presentation and laboratory findings of these patients, their benefits derived from levothyroxine treatment and the potentially severe repercussions of untreated hypothyroidism among children and adolescents, we opted to analyze this group separately and compare it with another group that also experienced a TBI event but had no APD.

The incidence of CH over a median follow-up of 6.5 years among all patients who experienced a TBI event in our study was 16%. If we had followed our patients for only 1 year, the incidence of CH would have been 10%. Both these rates are greater than those reported in most studies on this topic, which range from 0 to 14.2% (Supplementary Table 2). These large discrepancies in incidence rates may be explained by variations in the laboratory criteria used to diagnose CH across the studies and the time points of follow-up after the TBI event and, possibly, by the fact that the clinical manifestations of CH often mimic neurological sequelae. In addition, a therapeutic trial with levothyroxine was infrequent in previous studies. The results of our study would have been different had we adopted other specific laboratory criteria: low fT4 level (observed in two patients and only after 17 months of follow-up), fT4 decrease >20% (three patients), TSH delta <7 μIU/mL (two patients) and TSH peak <9 μIU/mL (one patient).

The European Thyroid Association recommends considering the diagnosis of a mild form of CH in any patient with a >20% decrease in fT4 level from previous values and initiating a therapeutic trial with levothyroxine (32). We applied a similar strategy in the present study, but we used as a major criterion for the diagnosis of CH the presence of clinical manifestations consistent with hypothyroidism associated with a fT4 decrease >20% and/or fT4 values within or below the lowest quartile. By adopting this strategy, we found an incidence of post-TBI CH greater than that reported in the literature. The most important parameter indicating that this was the right approach was the resolution of clinical manifestations of hypothyroidism with levothyroxine. Notably, the fT4 reference values adopted when the study started followed those recommended at that time (33), which applied uniformly to patients aged 1–20 years, rather than the currently recommended age-specific ranges. Therefore, new studies adopting current age-specific values for fT4 are necessary to confirm the results of the present study.

The finding of abnormal GH and IGF-1 levels in the CH group was surprising. Even though hypothyroidism is accompanied by blunted GH response in stimulation tests (34), the median GH peak at 12 months was higher in the CH group than in the non-APD group (P = 0.02) (Table 1). Peak values >30 ng/mL were observed in three out of the five patients in the CH group and in only two of those in the non-APD group. A similar finding was reported by Niederland and coworkers in five out of 26 children during ITT after a TBI event (8). The abnormal GH response in three of our patients in the CH group could be explained by decreased IGF-1 negative feedback or neurosecretory dysfunction (35). Studies have shown increased GH response in patients with primary hypothyroidism during the TRH test conducted

alone (36, 37, 38) or combined with GHRH (39), which has not been observed in normal controls. This finding could be an additional clue to identify patients with post-TBI CH. In addition, the median IGF-1 levels were significantly lower in the CH group compared with the non-APD group during the first year of follow-up (Table 1). Of note, the concomitant increase in fT4 and IGF-1 levels during the levothyroxine therapeutic trial (Figs 1 and 2) corroborated the diagnosis of CH. Similar findings have been previously reported during treatment of hypothyroidism due to other etiologies (40, 41, 42). The temporary levothyroxine suspension resulted in a decrease in both fT4 and IGF-1 levels, which increased again when this treatment was resumed (Figs 1 and 2). Although the levothyroxine suspension helped establish the diagnosis of CH in our patients, we would not recommend the rechallenge test for diagnosing post-TBI CH.

Several studies have shown a positive association between the degree of brain damage and the prevalence of APD in adults (43, 44, 45). In contrast, the same association has not been consistently shown in children (8, 9, 11, 12). In the present study, the clinical, imaging and neurological findings were comparable between the CH and non-APD groups. However, the number of patients with severe neurological disability (GCS ≤ 8) was too small to allow for a proper comparison.

The therapeutic trial with levothyroxine in our patients with clinical suspicion of CH, even in those with fT4 levels within the normal reference range, was critical in establishing the diagnosis of this endocrine deficiency. A striking finding was the asynchrony between GH and IGF-1 levels and the synchrony between IGF-1 and fT4 levels during levothyroxine use. Taken together, these data indicate the occurrence of a hidden, nonclassical form of post-TBI CH in children and adolescents. The diagnosis of this form of hypothyroidism is important since part of the sequelae attributed to neurological lesions after TBI can, in fact, be manifestations of CH.

A characteristic that makes the present study unique among other similar studies is the fact that all patients were prospectively followed for a long time by a single endocrinologist. Potential limitations of the study include the small sample size, absence of brain magnetic resonance imaging, lack of concomitant measurement of fT3 and fT4 and absence of TSH measurements at 90 and 120 min during the TRH test.

Conclusions

The longer observation period, careful valorization of clinical manifestations, use of a nontraditional laboratory approach and the therapeutic trial with levothyroxine in the present study revealed a higher rate of post-TBI CH in children and adolescents than that reported in the literature. The identification and treatment of this nonclassical form of CH were beneficial for the patients.

Patients with a history of TBI should be offered a therapeutic trial with levothyroxine if presenting clinical manifestations consistent with hypothyroidism along with fT4 levels within or below the lowest quartile or fT4 decrease >20% from baseline and IGF-1 level ≤−1 SDS from the normal reference range.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-24-0184.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work.

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Author contribution statement

GMG and LL conceived the study, GMG carried out the clinical endocrine evaluations, and GMG and LL interpreted the laboratory data and wrote the article. LA performed the neurological and neurosurgical evaluations, analyzed the brain CT results during the patients' hospitalizations and contributed to writing the article.

Data Availability

The datasets generated during the current study are not publicly available but can be obtained from the corresponding author upon reasonable request.

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