Hypopituitarism in Pediatric Survivors of Inflicted Traumatic Brain Injury

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Abstract

Endocrine dysfunction is common after accidental traumatic brain injury (TBI). Prevalence of endocrine dysfunction after inflicted traumatic brain injury (iTBI) is not known. The aim of this study was to examine endocrinopathy in children after moderate-to-severe iTBI. Children with previous iTBI ($n=14$) were evaluated for growth/endocrine dysfunction, including anthropometric measurements and hormonal evaluation (nocturnal growth hormone [GH], thyrotropin surge, morning and low-dose adrenocorticotropin stimulated cortisol, insulin-like growth factor 1, IGF-binding protein 3, free thyroxine, prolactin [PRL], and serum/urine osmolality). Analysis used Fisher's exact test and Wilcoxon's rank-sum test, as appropriate. Eighty-six percent of subjects had endocrine dysfunction with at least one abnormality, whereas 50% had two or more abnormalities, significantly increased compared to an estimated 2.5% with endocrine abnormality in the general population ($p<0.001$). Elevated prolactin was common (64%), followed by abnormal thyroid function (33%), short stature (29%), and low GH peak (17%). High prolactin was common in subjects with other endocrine abnormalities. Two were treated with thyroid hormone and 2 may require GH therapy. In conclusion, children with a history of iTBI show high risk for endocrine dysfunction, including elevated PRL and growth abnormalities. This effect of iTBI has not been well described in the literature. Larger, multi-center, prospective studies would provide more data to determine the extent of endocrine dysfunction in iTBI. We recommend that any child with a history of iTBI be followed closely for growth velocity and pubertal changes. If growth velocity is slow, PRL level and a full endocrine evaluation should be performed.

Key words: pituitary; prolactin; shaken baby syndrome; short stature; traumatic brain injury

Introduction

ACCIDENTAL TRAUMATIC BRAIN INJURY (TBI) causes hypothalamic pituitary dysfunction in 25–50% of children and adults.^{1,2} Normal pituitary function is crucial for neurocognitive development, linear growth, and onset of puberty. Inflicted traumatic brain injury (iTBI), or shaken baby syndrome, is the leading cause of death from child abuse and the most common cause of severe TBI in infants. However, prevalence of endocrine dysfunction after iTBI has been described in only one previous study.³

Many case reports have documented pituitary dysfunction after TBI in individual children. However, few studies have systematically evaluated the prevalence of endocrine dysfunction in children after TBI.^{4–8} Among studies in children, there is a 16–61% prevalence of hypopituitarism at 1–5 years after injury.^{4–8} Two studies with prospective data in the pediatric age range have shown an incidence of 10⁴ and 29%⁸ pituitary deficiency at 1 year after injury. Less is known about endocrine function after iTBI. Of course,

the rate of post-traumatic hypopituitarism would likely be higher in those children who died from their iTBI.

Methods

We performed a pilot study of endocrine function in children with history of moderate-to-severe iTBI. The study was approved by the local institutional review board.

Patients were eligible for inclusion if they had been diagnosed with unequivocal iTBI by the child abuse team when they were infants or toddlers (between 2004 and 2009) and were age 2.0–9.0 years of age at date of study (between 2008 and 2011). This diagnosis was based on the child's entire evaluation, including history, physical examination, and other findings, and outside investigation. Informed consent for participation was obtained from a parent or legal guardian, and assent was obtained from patients over 7 years of age. Specific inclusion criteria included history of iTBI occurring before 2 years of age, brain injury requiring hospitalization, and more than 1 year having elapsed since injury, as well as current

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age of 2.0–9.0 years. Children were excluded if they were already being treated for endocrine deficiencies or if there was no history of brain injury.

Families were recruited from a clinic that monitors children after known child abuse and were followed clinically by the investigators (K.M. and T.C.). Approximately 24 children are admitted with iTBI to our institution yearly. A subset of the more severely injured children are followed in this clinic. A research coordinator (T.W.) discussed the study, answered questions, and obtained informed consent from parents or guardians (including consent to obtain previous medical records).

Over a 5-year span, attempts were made to contact all 102 patients sequentially attending the clinic who met eligibility criteria; attempts to contact approximately 50 were unsuccessful. Fifteen families agreed to participate (Fig. 1). In one of these subjects, there was difficulty obtaining intravenous (i.v.) access, and the mother withdrew the child from the study. Reasons for declining participation included lack of permission to participate in any research by the county foster care setting, desire to spare the child additional “trauma or intervention,” and lack of concern by parent or guardian.

Details of previous medical history were reviewed, including preinjury health and function, details of injury, results of magnetic resonance (MRI) or computed tomography (CT) brain imaging, other injuries, intercurrent medicines, and residual neurologic problems.

During the research visit, measurements were obtained and recorded for head circumference, weight, height by stadiometer or length by standard length device, and vital signs. Each measurement was taken twice. If measurements differed >0.3 cm for height or length, a third measurement was taken by the same trained staff person, and the average of two closest measurements was recorded. Resultant weight and height measurements was compared with Centers for Disease Control and Prevention (CDC) standards and expressed in z-score, compared to the mean for age and gender.

Subjects were admitted overnight to an endocrine research nursing unit for timed blood sampling. A review of systems form was completed by parents or legal guardians. Physical examination was performed by a physician (B.A. or S.B., as well as S.R.R.). Subjects were put to bed with lights out by 9 PM, and serum samples were obtained from an indwelling i.v. catheter. Care was taken not to disturb sleep during blood sampling for nocturnal hormone profiles.

Physiologic patterns of hormone concentrations were monitored, plus a low-dose adrenocorticotropin (ACTH) test.¹⁴ Growth hormone (GH) stimulation tests were not performed in this pilot study

in order to facilitate recruitment. Patients who had low GH screening later underwent GH stimulation tests. Children weighing 15 kg or more had the following samples obtained for hormone profile evaluation: serum GH every 20 min from 10:00 PM to 4:00 AM⁹; nocturnal thyrotropin (TSH) surge with serum TSH hourly from 2:00 PM to 6:00 PM and 10:00 PM to 4:00 AM^{10–12}; first-morning and low-dose ACTH-stimulated cortisol^{13,14}; insulin-like growth factor 1 (IGF-1); IGF-binding protein 3 (IGFBP3); free thyroxine (FT4); prolactin (PRL); and 12-h fasting serum and urine osmolality (total blood volume, 39 mL, 2.6 mL/kg or less). IGF-1 was not performed in younger children because the normal range for IGF-1 in children younger than 4 years overlaps with the ranges observed in GH deficiency (GHD).¹⁶

Smaller children weighing 10–14.9 kg had the following samples obtained for hormone profile evaluation: GH hourly from 10:00 PM to 4:00 AM; nocturnal TSH surge with serum TSH at 3:00 PM, 4:00 PM, 10:00 PM, 11:00 PM, 12:00 AM, 1:00 AM, and 2:00 AM; first-morning and low-dose ACTH-stimulated cortisol; and IGFBP3, FT4, PRL, and 12-h fasting serum and urine osmolality (total blood volume, 21 mL, 1.4–2.0 mL/kg). Of note, IGF-1 was not obtained in subjects weighing <15 kg.

Assays were performed as follows: GH (ICN ImmuChem™ Double Antibody Assay; ICN Biomedicals, Irvine, CA); IGF-1 (immunoradiometric assay); IGFBP3 (radioimmunoassay; RIA); cortisol (RIA); TSH (immunoradiometric assay); FT4 (mass spectroscopy); PRL (chemiluminescent immunoassay); and serum and urine osmolality (freezing-point depression).

Subjects were considered to have normal results if height was >10 th percentile for age and gender, mean GH was >1.1 $\mu\text{g/L}$ (>1.1 ng/mL), highest GH concentration was >7 $\mu\text{g/L}$ (>7 ng/mL), IGF-1 and IGFBP3 were above -1 standard deviation (SD) for age, PRL was below the upper limit of the assay normal range (≤ 14.7 ng/mL, <639 pmol/L), TSH surge at night was $>50\%$ above nadir afternoon TSH,^{10,12} TSH was within normal limits for time of day,¹⁵ FT4 was within assay normal limits; 8:00 AM cortisol was >8 $\mu\text{g/dL}$ (>220 nmol/L), cortisol peak after low-dose ACTH was >20 $\mu\text{g/dL}$ (>552 nmol/L),¹⁴ and 12-h fasting morning urine was concentrated to 500 mOsm/kg (500 mmol/kg).

Statistical analysis

Statistical analysis was performed using SAS® statistical software (version 9.3; SAS Institute, Cary, NC). Fisher’s exact test was used to compare rates of endocrine abnormality to the general population and also between the elevated PRL group (>14.7 ng/mL, >639 pmol/L) and normal PRL group (≤ 14.7 ng/mL, ≤ 639 pmol/L) for the categorical variables. Wilcoxon’s rank-sum test was used to examine differences between PRL groups for the continuous variables. These statistical methods were chosen as a result of sample size. Data are reported as number and percentage, or median with 25th and 75th percentiles, as appropriate. The z-scores for height and body mass index (BMI) were calculated using SAS® macro (gcalculate-BIV.sas, available on the CDC website).

Results

Children who underwent endocrine evaluation were not clinically different from those who declined participation in age at injury, duration of hospitalization, gender, and current age. At original injury, all of our subjects had evidence of subdural hematoma (with additional ischemia in 6) on CT and/or MRI, 13 of 14 required intensive care, 11 had seizures, and 11 required intubation (Table 1). Thus, severity of TBI in this group was moderate to severe.

Seventy-nine percent of subjects were male, age at injury ranged from 1 to 13 months (median, 5), duration of hospital stay after injury ranged from 5 to 78 days (median, 32; interquartile range [IQR], 19, 52), and age at time of evaluation ranged from 2 to 9

FIG. 1. Recruitment of children after inflicted traumatic brain injury.

TABLE 1. DEMOGRAPHIC AND INJURY CHARACTERISTICS OF THE 14 CHILDREN EVALUATED AFTER INFLICTED TRAUMATIC BRAIN INJURY

Patient	Age at injury (months)	Age at study (years)	Gender	Duration of hosp (days)	Height z-score	ICU	Intubation	Seizures	Subdural hematoma	CNS ischemia	Parent custody
1	1	2.6	f	11	-0.98	+	+	-	+	-	+
2	1	3.0	f	32	-1.26	+	+	+	+	+	-
3	1	3.0	m	24	-3.09	+	+	+	+	+	+
4	2	2.0	m	na	0.84	-	-	-	+	-	+
5	2	3.2	m	19	0.12	+	+	+	+	+	+
6	4	2.0	m	na	0.87	+	+	-	+	-	-
7	5	2.2	m	45	-2.83	+	+	+	+	+	-
8	5	4.2	m	69	-1.02	+	+	+	+	-	+
9	5	5.2	m	78	-0.44	+	+	+	+	-	+
10	7	2.0	m	32	-1.42	+	-	+	+	+	+
11	9	9	m	49	-0.16	+	+	+	+	+	+
12	10	3.6	m	5	-0.70	+	-	+	+	-	-
13	11	3.1	f	52	-1.64	+	+	+	+	-	+
14	13	4.5	m	17	-0.29	+	+	+	+	-	+
Median	5 ^a (2, 10)	3.1 ^a	11/14 (79% male)	32 ^a	-0.8 ^a	13/14	11/14	11/14	14/14	6/14	10/14
(25th,75th %ile) [range]	[1, 13]	(2.3, 4.2)		(19, 52)	(-1.4, -0.2)	(93%)	(79%)	(79%)	(100%)	(43%)	(71%)
		[2.0, 9.0]		[5, 78]	[-3.1, 0.9]						

^aData presented as median (25th and 75th percentile [minimum, maximum]).

Hosp, hospitalization; %ile, percentile; ICU, intensive care unit required; CNS, central nervous system; f, female; m, male; HtSD, number of standard deviations above or below the mean for age; na, not available.

years (median, 3.1; IQR, 2.3, 4.2; Table 1). Height was $\leq 10^{\text{th}}$ percentile in 29% of subjects, with median height z-score of -0.8 (-1.4, -0.2 [-3.1 to +0.9]). Data are presented as median (25th and 75th percentile [range]). BMI showed wide variation, with BMI z-score median of 0.5 (-0.9, 1.3 [-2.3 to +1.9]).

None of the subjects were in puberty. One had low morning cortisol, but normal ACTH-stimulated cortisol, and 3 had transient mild TSH elevation not present on follow-up.

Eighty-six percent (12 of the 14 subjects) had at least one endocrine or growth abnormality (Table 2). Of them, 2 had only mild prolactin elevation. If we count only those with one or more abnormalities aside from prolactin elevation, then 57% of subjects (8 of 14) had one or more abnormalities. This is a significantly greater percentage than the estimated 2.5% at most of the general population that might be expected to have any endocrine abnormality ($p < 0.001$). Twenty-nine (4 of 14) percent had two or more abnormalities excluding elevated prolactin, and 50% including elevated prolactin. Elevated prolactin was the most common finding (64%), followed by abnormal thyroid function (33%), short stature (29%), and low GH peak (17%). Five of 9 (56%) of the subjects with elevated prolactin had one or more additional abnormalities, whereas 3 of 5 (60%) with normal prolactin had one or more abnormality (Table 3). None of those with elevated prolactin were receiving psychotropic medication.

Relatively smaller stature (height shorter than 1.28 SDs below the mean for age) is expected in 10% of a population. Relatively smaller stature was noted in 29% of our subjects (95% confidence interval, 8.4%, 58.1%). The 95% confidence limits for expecting height shorter than the 10th percentile in our patient group overlapped that in the general population and was not statistically significant ($p = 0.11$). We observed no correlation between height z-score and GH or thyroid results.

There was no correlation between age at injury and severity of pituitary dysfunction. All who required greater than 30 days of hospitalization had prolactin elevation.

Discussion

Children who have experienced iTBI have previously been studied to evaluate pituitary function in only one previous publication. The current study highlights the importance of close clinical follow-up to evaluate rate of linear growth and development after such an injury occurs. In this pilot study, we found that after moderate-to-severe iTBI, at a median age of 5 months (range, 1–13), at least 86% of the children had at least one endocrine abnormality or relatively shorter height ($\leq 10^{\text{th}}$ percentile), and 50% had two or more abnormalities. There was no correlation between age at injury and severity of pituitary dysfunction. All of those requiring longer hospitalization had prolactin elevation. Diabetes insipidus and cortisol deficiency were not observed in our subjects at the time of this follow-up evaluation, 1 year or more after iTBI. The most common abnormality noted was mildly elevated PRL ($n = 9$), followed by blunted TSH surge ($< 50\%$ nocturnal rise over nadir; $n = 6$), height $< 10^{\text{th}}$ percentile ($n = 4$), and lack of GH peak over $7 \mu\text{g/L}$ ($n = 2$). Two of the children required thyroid hormone replacement and 2 more may require GH therapy. We assume the rate of post-traumatic hypopituitarism would likely be higher in those children who died from their iTBI.

Elevated prolactin level was the most common finding among the subjects studied. PRL elevation is observed after pituitary stalk injury or dysregulation at the level of hypothalamic feedback. By itself, the mild prolactin elevation is of unclear clinical significance, but the presence of PRL elevation suggests the need for further investigation of the hypothalamic-pituitary axis.

Only one previous study has evaluated endocrine function after iTBI. Heather and colleagues described a large number of 64 pediatric patients with inflicted injuries as part of a cross-sectional series of 198 patients and found no cases of permanent hypopituitarism at least 1 year after injury.³ However, our study is different from the previous work in several important ways. Of course, we report far fewer patients than they did. In a detailed comparison of

TABLE 2. GROWTH AND ENDOCRINE FINDINGS OF THE 14 CHILDREN EVALUATED AFTER INFLECTED TRAUMATIC BRAIN INJURY

Normal value	Cortisol		Thyroid		Growth hormone			Vasopressin			Prolactin		Height		Summary
	8:00 AM cortisol (>8)	Peak cortisol (>20)	Free T4 (1.0–2.8)	TSH 1600 ≤ 3	TSH surge % >50%	GH mean >1.1	GH peak >7	IGF-1	IGFBP3	Serum osmolality (270–310)	Urine osmolality	Prolactin <14.7	Short height (<-1.28 SD)	No. of abnormal axes	
N	14	13	14	14	14	14	12	4	13	13	13	14	14	14	14
1	17.6	37.8	1.2	0.8	18 ^a	7.4	16.6	na	2260	303	989	22.1 ^a		2	2
2	27.9	32.6	1.6	3.9 ^a	53	23	55.7	na	3520	296	137	53.5 ^a		1	1
3	21.8	55.6	2.1	1.0	230	4	12.2	na	1330	286	1245	14.2	a	1	1
4	23	42	2.1	3.2 ^a	83	11.3	28.4	na	2140	295	555	10.8		0	0
5	12	26.8	2.1	1.9	49 ^a	3.0	3.1 ^a	47.4	1800	295	567	8.6		2	2
6	10.3	30.6	1.4	1.2	44 ^a	6	12.5	na	2990	286	137	22.3 ^a		2	2
7	37.6	52.1	1.9	2.0	4 ^a	5.9	14.1	na	2610	298	181	15.6 ^a	a	3	3
8	29.2	na	1.3	1.1	117	4.7	na	272	3160	na	na	15.9 ^a		(1) ^T	(1) ^T
9	63.7	52.1	1.3	0.6	74	2.2	7.3	354	3600	287	507	17.9 ^a		(1) ^T	(1) ^T
10	18	36	1.9	6.6 ^a	10 ^a	3.2	6.9 ^a	na	1880	292	849	25 ^a	a	4	4
11	3.4 ^a	38.7	1.7	1.8	125	3.1	8.2	162	3760	292	1059	23.8 ^a		(1) ^T	(1) ^T
12	15.4	26.7	1.4	1.0	95	3.4	na	na	2680	286	1049	5.6		0	0
13	8.8	26.2	1.6	2.0	92	8.7	20.8	na	3020	295	876	31.3 ^a	a	2	2
14	15.6	34.9	1.4	2.7	21 ^a	8.4	24.1	na	na	334 ^a	607	3.3		2	2
No. abnormal	1/14	0/13	0/14	3/14	6/14	0/14	2/12	0/4	0/13	1/13	0/13	9/14	3/14		

Patients are shown in the same order as on Table 1 (in order of age at time of inflicted traumatic brain injury. (1)^T refers to mild prolactin elevation only.

^aAbnormal.

T4, thyroxine; TSH, thyrotropin; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP3, IGF binding protein 3; na, not available; SD, standard deviation.

TABLE 3. ENDOCRINE ABNORMALITIES IN THE 14 CHILDREN EVALUATED AFTER INFLICTED TRAUMATIC BRAIN INJURY, OVERALL, AND ACCORDING TO WHETHER THERE WAS PROLACTIN ELEVATION

Variable	Overall (%) (n = 14)	Normal prolactin (%) ≤ 14.7 ng/mL (n = 5)	Elevated prolactin (%) > 14.7 ng/mL (n = 9)
Prolactin high (> 14.7 ng/mL) ^a	9 (64)		
GH peak low (< 7 μg/L) ^a	2/12 (17)	1/4 (25)	1/8 (12)
TSH surge low (≤ 50%) ^a	6 (33)	2 (40)	4 (44)
Short stature (< -1.28 SD) ^a	4 (29)	1 (20)	3 (33)
Serum osmolality high (> 310 mOsm/L) ^a	1/13 (8)	1 (20)	0/8 (0)
Peak cortisol low (< 20 μg/dL)	0 (0)	0 (0)	0 (0)
At least one abnormality	12 (86)	3 (60)	9 (100)
Total with abnormality (not including prolactin elevation)	8 (57)	3 (60)	5 (56)
Number of abnormalities			
0	6 (43)	2 (40)	4 (44)
1	4 (28)	1 (20)	3 (33)
2	3 (21)	2 (40)	1 (11)
3	1 (7)	0 (0)	1 (11)

Data presented as *n* (%). Fisher's exact test was used for comparisons between results in normal prolactin and elevated prolactin groups.

^aIncluded in count of abnormalities.

GH, growth hormone; TSH, thyroid stimulating hormone; SD, standard deviation.

our results to theirs, we identified that our patient population was more severely injured than the cohort in their study using the Abbreviated Injury Scale (AIS).¹⁷ Each of our subjects had evidence of subdural hematoma on CT and/or MRI, thus had moderate-to-severe injuries (AIS 4–5). In contrast, 39% of their patients had an AIS score of only 2–3, consistent with mild injury.

Our study population was shorter than the subjects studied by Heather and colleagues (mean height z-score in our subjects -0.9 ± 1.2 vs. mean $\pm$ SD height z-score $+0.5 \pm 1.3$ in Heather and colleagues).³ Ages at time of injury were similar in the two studies, although our subjects were younger at the time of endocrine study (3.5 ± 1.6 years in our patients vs. 8.3 ± 3.2 in Heather and colleagues). Methodology for diagnosing hormone deficiency in the two studies differed: Their study used a conservative GH peak of $< 5 \mu\text{g/L}$ to identify GHD, whereas our study used spontaneous, overnight GH peak $> 7 \mu\text{g/L}$ to define normality. Heather and colleagues did not indicate the severity of injury in their one case of precocious puberty. We characterized thyroid function by both basal levels (TSH and free T4) while also performing dynamic circadian TSH sampling, whereas Heather and colleagues examined only basal thyroid function tests.³ Thus, it is possible that Heather and colleagues missed identification of central hypothyroidism. PRL elevation was the most common finding in our study subjects (64%), whereas unexplained PRL elevation (17–35 ng/mL) was found in 3% of patients in the other study. Heather and colleagues did not perform a subset analysis either on the inflicted injury patients or on their more severely affected patients. A subset analysis would have been helpful to know whether the PRL elevation occurred in their iTBI patients or in their most severely injured patients.

Our results are consistent with previous retrospective and prospective studies in children after accidental TBI.^{4–8} Previous prospective studies have often found resolution of some endocrine abnormalities by 1 year after TBI. For this reason, we elected to only study children who were at least 1 year after injury. Occurrence of endocrine deficiency may differ according to testing modality and according to whether the study is retrospective or prospective. In the current study, we found an even higher proportion of abnormal growth or endocrine dysfunction after iTBI than we previously found

after accidental TBI.⁸ We believe that the higher occurrence of endocrine abnormalities in the current study (compared to Heather and colleagues) may be related not only to this study being retrospective, but also to differing testing methodology and inclusion of more severely injured subjects in our study.

Limitations to this study included difficult patient recruitment. Many social services agencies would not allow research participation by children in foster care. This may have introduced some degree of selection bias, because our subjects may have different follow-up characteristics from those in alternative custody. In addition, difficult i.v. access and small blood volume (related to age and body size) limited the extent of endocrine testing performed. Selection of endocrine testing to be performed was limited by this being a research study: GH stimulation tests were not performed. Instead, the endogenous spontaneous GH levels were measured at intervals to identify whether there was a peak produced above a value of $7 \mu\text{g/L}$. Normative data exist for nocturnal GH sampling every 20 min for the 6-h period used in this study (10:00 PM to 4:00 AM).⁹ Likewise, the nocturnal TSH surge has been well documented to be deficient in central hypothyroidism and excellent normative data exist for this test.^{10–12,15} Finally, the low-dose ACTH test also has good normative data and has been validated in metaanalysis.^{13,14}

In our study, growth velocity data were not available. It is possible that growth rate was slow in some of our children with hormone deficiencies who were not yet short. Although stature did not correlate with hormone results in our study, it is important to note that growth is affected by multiple factors that were not analyzed in the current study. These could include neurologic impairment, psychosocial adjustment, and nutritional status.

These findings suggest that endocrine dysfunction is more common in children after moderate-to-severe iTBI than previously recognized. Further studies are needed on a larger population to determine more details of endocrine function in this vulnerable patient population. An ideal study would involve multiple medical centers to obtain evaluations in a larger number of children.

The results of our study highlight the need for long-term follow-up of children who have a history of iTBI, particularly in those with injury severity requiring intensive care. Until our study was initiated, the growth pattern of these children was not being monitored,

similar to the common practice at many centers.¹⁸ We recommend that after iTBI, growth should be followed closely with height or length measurements at least every 6 months, along with monitoring of growth trajectories. We recommend that after iTBI, each child should undergo a full endocrine evaluation (including a prolactin level) if they have evidence for growth failure or disturbance in pubertal timing.

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Author Disclosure Statement

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