

Abnormalities of Pituitary Function after Traumatic Brain Injury in Children

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ABSTRACT

Traumatic brain injury (TBI) is a frequent cause of neuroendocrine dysfunction typically in male adults. Head injuries are also common in childhood, but only a few case reports outlined the endocrine consequences. The aim of this study was to reveal anterior pituitary function in children with history of hospitalization due to mild to severe head trauma. Our endocrine follow-up study was performed between October 2003 and February 2004 in the Pediatric Department of Petz Aladár County Teaching Hospital, Győr, Hungary. Twenty-six children (17 boys and nine girls, aged 11.47 ± 0.75 years) at 30.6 ± 8.3 months after head injury and 21 age-matched controls were enrolled. Basal and stimulated anterior pituitary and peripheral hormone concentrations were measured by routine laboratory methods. Pituitary dysfunction was detected in 61% of patients with TBI history. All growth hormone (GH) parameters measured and calculated were significantly ($p < 0.05$) lower in TBI group than in controls after L-DOPA stimulation. Similar difference was detected 60 min after insulin provocation. Forty-two percent of all TBI children showed insufficient growth hormone (GH) response in both stimulation tests, 73% of these cases were boys. Cortisol levels of TBI patients were significantly ($p < 0.05$) lower all through the insulin test than values measured in control group. The degree of pituitary dysfunction was independent from the severity of TBI. Our study confirms the high risk for hypopituitarism in children with TBI despite the lack of obvious clinical symptoms. We suggest screening of pituitary function after any kind of brain trauma requiring hospitalization in childhood.

Key words: children; head injury; pituitary dysfunction

INTRODUCTION

TRAUMATIC BRAIN INJURY (TBI) is known to be associated with pituitary lesions both in adults and children (Cyran, 1918; Escamilla and Lissner, 1942; Edwards and Clark, 1986; Benvenga et al., 2000; Eichler et al., 1988; Lopez-Gusman et al., 1992). Although the rela-

tionship between head trauma and hypopituitarism was originally described by Cyran as early as in 1918, only a very limited number of cases was published prior to the end of the last century (Escamilla and Lissner, 1942; Edwards and Clark, 1986). The first meta-analysis of 314 adult patients about the association of TBI with selective or combined pituitary hormone deficiency (PHD) was

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published in 2000 (Benvenga et al., 2000). More authors have emphasized that head trauma frequently occurs in young adults, with around 100 hospitalizations per 100,000/year, and endocrine consequences may develop in about 30–50% of affected victims (Benvenga et al., 2000; Schneider et al., 2005; Urban, et al., 2005).

Though brain injuries are also common in childhood, there are only a few case reports about the endocrine sequelae (Eichler et al., 1988; Lopez-Gusman et al., 1992). One cause of this contradiction could be that patients with TBI generally need intensive care, and medical attention is not focused on endocrine problems in the acute stage. After recovery, subsequent problems are not always followed accurately, and neuroendocrine evaluation is not included in routine follow-up examinations (Clark et al., 1988). On the other hand, hypothalamic or pituitary injury could occur even after mild traumas that do not require hospitalization or which patients are unable to remember (Aimaretti et al., 2004; Benvenga et al., 2000). Clinical observations suggest that the degree of pituitary dysfunction is independent from the severity of TBI (Aimaretti et al., 2004; Benvenga et al., 2000; Eiholzer et al., 1986), and the diagnosis of TBI-induced PHD is difficult when evident clinical symptoms of hypopituitarism (such as diabetes insipidus, growth retardation) are lacking (Childers et al., 1998).

Production of all pituitary hormones, either alone or in combination, may be affected by TBI. Growth hormone (GH) and gonadotropin levels are altered most frequently (Benvenga et al., 2000; Casanueva et al., 2005; Eichler et al., 1988; Lopez-Gusman et al., 1992; GH Research Society, 2000). Some authors found high prevalence of neuroendocrine dysfunction in adolescent (Agha et al., 2004a) and adult patients (Aimaretti et al., 2004; Agha

et al., 2004a,b,c; Benvenga et al., 2000; Bondanelli et al., 2004; Kelly et al., 2000; Lieberman et al., 2001) with history of moderate or severe TBI (Table 1).

The hormonal deficit contributes to the chronic disability of TBI patients resulting in cognitive, physical and social sequelae, and reduced quality of life (Clark et al., 1988; Morton and Wehman, 1995; Urban et al., 2005). Hormone replacement therapy, especially GH substitution, was proved to be effective also in cases with acquired growth hormone deficiency (GHD) (Casanueva et al., 2005; Eichler et al., 1988; Ghigo et al., 2005; GH Research Society, 2000; Urban et al., 2005).

Since only a few papers were published on children with pituitary dysfunction after TBI (Eichler et al., 1988; Eiholzer et al., 1986; Lopez-Gusman et al., 1992), in the present study we performed endocrine tests in children 30.6 ± 8.3 months after head injury of different types. Our main goal was to reveal anterior pituitary function in children with a history of hospitalization due to mild to severe head trauma.

METHODS

Our clinical investigations were performed between October 01, 2003 and February 28, 2004 in the Pediatric Department of Petz Aladár County Teaching Hospital, Győr, Hungary. Thirty-eight children previously hospitalized on the same ward because of TBI were screened before the study. Among them, only 26 children, 17 boys and nine girls were enrolled into the endocrine follow-up studies. Out of the other 12 patients, 10 did not attend the second GH stimulation test, whereas two subjects were excluded due to inadequate fall in serum glucose

TABLE 1. TBI-INDUCED PITUITARY DYSFUNCTION ACCORDING TO SOME PREVIOUS PUBLICATIONS

	<i>Age period</i>	<i>No. (M/F)</i>	<i>Affected patients</i>	<i>Proportion of GHD (%)</i>	<i>Proportion of cortisol deficiency (%)</i>
Agha (2004a)	Adolescence and adult	50 (38/12)	80%	18%	16%
Agha (2004b)	Adult	102 (85/17)	28%	11%	13%
Aimaretti (2004)	Adult	100 (69/31)	35%	25%	8%
Benvenga (2000)	Adult	314 (5:1)	80–100%	24%	53%
Bondanelli (2004)	Adult	50 (40/10)	54%	28%	0%
Cohan (2005)	Adult	80	—	—	53%
Kelly (2000)	Adult	22 (18/4)	36%	18%	5%
Lieberman (2001)	Adult	70 (46/24)	50%	15%	46%
Urban (2005)	Adult	—	33–50%	15–21%	—

TBI, traumatic brain injury; M/F, male/female; GHD, growth hormone deficiency.

levels during the insulin-induced hypoglycemia test (ITT). The mean age of our patients was 11.47 ± 0.75 years at the time of endocrine investigations.

The study was approved by the Institutional Review Board of the Petz Aladár County Teaching Hospital. Written information on the purpose and background of the study was provided to patients and their parents. Those who agreed to participate signed written informed consent form before entering the study.

The mean time elapsed between the occurrence of TBI and the diagnostic tests was 30.6 ± 8.3 months. The types of accidents resulted in brain injury were typical of the age of our patients. TBI occurred during playing soccer in two, during skating in one, and during bicycling in two children. Head injury originated in falling from bed in one, from steps in two, and from trees in four cases, whereas two patients were injured by things falling on their heads. The majority of our patients ($n = 12$) were victims of car accidents, which is the most frequent cause of TBI both in Hungary and over the world (Springer and Chollet, 2001).

Different types of injury were distinguished based on the clinical signs, skull x-ray and computed tomography (CT) results (numbers of affected patients are listed): concussion, seven; cerebral edema, two; subdural hemorrhage, two; cranial fracture, seven; and cerebral contusion, eight.

Patients could be also divided into three groups according to the duration of their unconsciousness: it lasted for 1–5 days in four cases, for a few minutes in 15 patients, and no loss of consciousness was found in 7 children.

In the present study, our TBI patients underwent two endocrine evaluations approximately 3 years after their head trauma. During the first examination, medical history, physical conditions, and auxologic parameters were registered and an L-DOPA test was performed. The dose of Dopaflex (Pannonpharma, Hungary) administered orally was adjusted to the patients' weight (150 mg under 15 kg b.w., 250 mg between 15–35 kg b.w., and 500 mg over 35 kg b.w.). Serum samples were obtained at 0 min as well as 30 and 60 min following L-DOPA challenge to evaluate the GH reserve of the pituitary.

During the second examination, we investigated basal and stimulated GH, and cortisol levels during ITT. 0.1 U/kg b.w. Actrapid (Novo Nordisk, Denmark) was administered i.v. to achieve nadir plasma glucose concentration lower than 2.2 mmol/L. This provocation test was combined with thyrotropin-releasing hormone (TRH; Antepan, JenaPharma, Germany) stimulation (200 μ g, i.v.) to reveal thyroid-stimulating hormone (TSH) and prolactin (PRL) responses of the anterior pituitary. Blood samples were taken for determination of GH, cor-

tisol, TSH, and PRL values before the start of the test and 15, 30, and 60 min thereafter. Baseline serum concentrations of free T4 (fT4) and T3 were also measured. There were at least 3-day intervals between the two investigational set-ups. Twenty-one age-matched short children (aged 10.5 ± 3.2 years) without GH deficiency served as the control group. Their clinical evaluations were performed previously using the same provocation tests and laboratory methods.

Measurement of Hormones

All hormone measurements, except GH, were performed by routine laboratory methods in Győr Children's Hospital, Hungary by the RIA-Mat 280 Fully Automated Analyzer (BYK-Sangtec, Dietzenbach, Germany).

Serum cortisol (nmol/L) was measured by radioimmunoassay (Immunotech Beckman, Prague, Czech Republic). The assay has a calculated sensitivity of 10 nmol/L. The inter-assay coefficients of variation were 9.2%. The intra-assay coefficients of variation were 5.8% for serum samples.

Prolactin in serum (mU/L) was measured by radioimmunoassay (Immunotech Beckman). The assay has a calculated sensitivity of 5 mU/L. The inter-assay coefficients of variation were 8.0%. The intra-assay coefficients of variation were 2.8% for serum samples.

TSH (pmol/L) was measured by immunoradiometric assay (BRAHMS, Hennigsdorf, Germany) in serum samples. The assay has a calculated sensitivity of 1.3 pmol/L. The inter-assay coefficients of variation were 13.5–4.1–2.3% at mean TSH value on 3–48–564 pmol/L, respectively. The intra-assay coefficients of variation were 5.1–2.5–1.5% at mean TSH value on 5.3–49.4–554.5 pmol/L, respectively.

Serum fT4 concentrations (pmol/l) were measured by radioimmunoassay (BRAHMS). The assay has a calculated sensitivity of 1.25 pmol/L. The inter-assay coefficients of variation were 8.7–5.1–3% at mean fT4 level on 8–17.6–51 pmol/L, respectively. The intra-assay coefficients of variation were 5.5–3.5–3.6% at mean fT4 level on 11–20.6–101.5 pmol/L, respectively.

Total T3 level of sera (nmol/L) was measured by radioimmunoassay DiaSorin (Stillwater, MN). The assay has a calculated sensitivity of 0.13 nmol/L. The inter-assay coefficients of variation were 8.3–4.8–4.3% at mean T3 level on 1.3–2.5–7.4 nmol/L, respectively. The intra-assay coefficients of variation were 7.9–3.6–3.1% at mean T3 level on 1.3–2.6–6.9 nmol/L, respectively.

Serum GH (μ U/mL) was measured by chemiluminescence immunoassay (Nichols Advantage System, Nichols Institute Diagnostics, San Clemente, CA). The assay has a calculated sensitivity of 0.06 μ U/mL and a dynamic

TABLE 2. MEAN OF CUMULATIVE AND PEAK GH LEVELS DURING L-DOPA TEST AND ITT (MEAN \pm SEM)

	<i>L-DOPA test</i>				<i>ITT</i>			
	Basal GH (μ U/mL)	Peak GH (μ U/mL)	AUC GH	Mean GH (μ U/mL)	Basal GH (μ U/mL)	Peak GH (μ U/mL)	AUC GH	Mean GH (μ U/mL)
TBI	6.3 \pm 2.1	16.8 \pm 3.12	551 \pm 116	8.9 \pm 1.5	9.9 \pm 2.5	20.5 \pm 3.74	723 \pm 147	11.6 \pm 1.5
Controls	7.5 \pm 2.1	32.0 \pm 3.8	1148 \pm 155	17.0 \pm 2.35	5.8 \pm 2.1	27.1 \pm 3.81	956 \pm 142	15.1 \pm 1.9
<i>p</i>	NS 0.1565	0.0031	0.0028	0.0001	NS 0.5316	NS 0.2253	NS 0.2605	NS 0.0576

GH, growth hormone; ITT, insulin-induced hypoglycemia test; SEM, standard error of the mean; AUC, area under the curve; TBI, traumatic brain injury.

range of 0–90 μ U/mL. The inter-assay coefficients of variation were 7.5–6.2–8.7% at mean GH values on 0.1–6.2–16.2 μ U/mL, respectively. The intra-assay coefficients of variation were 2.8–3.7–5.4% at mean GH levels on 0.8–5.9–17.1 μ U/mL, respectively.

Statistical Analysis

All data presented are means \pm SEM ($n = 26$ in head trauma group, and $n = 21$ in control group). Statistical analysis in different groups and at various time-points was performed using repeated-measures analysis of variance (ANOVA), followed by Newman-Keuls multiple comparison test, Friedman test followed by Dunn's multiple comparison test, unpaired *t*-test, or Mann-Whitney test, was appropriate. A value of $p < 0.05$ was considered as significant difference; however, a tendency for change was also indicated in some comparisons having the probability value of $0.05 < p < 0.10$. The following statistical software was used for the analysis of data: GraphPad Prism, version 3.02 (GraphPad Software Inc., San Diego, CA).

RESULTS

In this study, head trauma did not result in any neurological sequelae in 23 of 26 patients. Three children suffered from permanent disability: one child had peripheral facial paresis on the left side, whereas two patients had partial hemiparesis. One of these latter patients also had posthemorrhagic hydrocephalus corrected by ventriculoperitoneal shunt operation.

During our provocation tests, there were no serious adverse events related to the drugs used. In the first part of our analysis, we compared basal and stimulated hormone levels between patients with previous head trauma (TBI

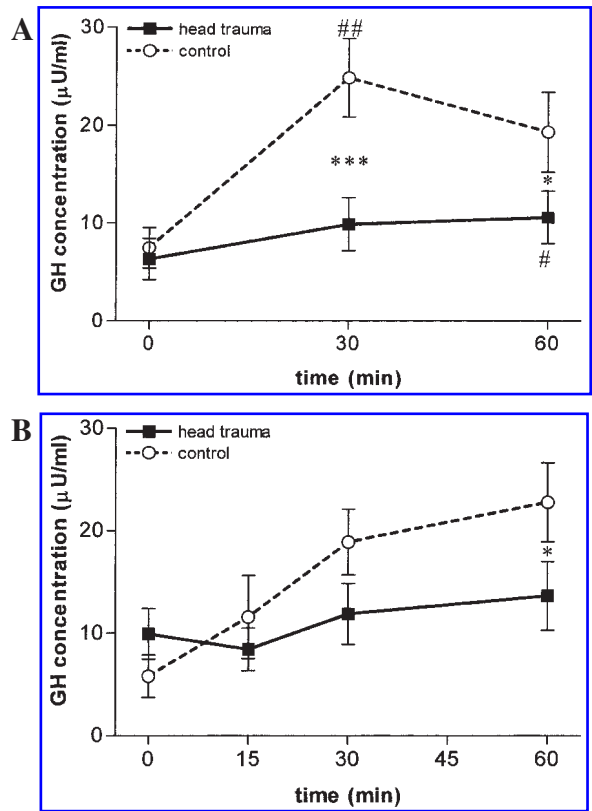


FIG. 1. (A) Friedman analysis of variance (ANOVA), followed by Dunn's multiple comparison test, was performed to compare time-dependent changes of growth hormone (GH) levels during the stimulation tests in the same group. $^{\#}p < 0.05$ and $^{##}p < 0.01$ indicate difference from the value measured at 0 min in the same group. Mann-Whitney test was performed to compare the values between groups at a defined time-point. $^*p < 0.05$, $^{***}p < 0.001$ indicates significant difference from the value measured in the control group. (B) Mann-Whitney test was performed to compare the values between groups at a defined time-point. $^*p = 0.0113$ indicates significant difference from the value measured in the control group at 60 min, whereas a trend for difference ($p = 0.0637$) was detected at 30 min.

PITUITARY LESION AFTER HEAD TRAUMA IN CHILDREN

TABLE 3. CORTISOL VALUES IN ITT (MEAN \pm SEM)

	Basal cortisol (nmol/L)	Peak cortisol (nmol/L)	AUC cortisol (nmol/L \times min)	Mean cortisol (nmol/L \times min)
TBI	313 \pm 27	511 \pm 36	24,159 \pm 1628	388 \pm 17
Controls	454 \pm 37	712 \pm 50	35,411 \pm 2064	544 \pm 28
<i>p</i>	0.0029	0.0016	<0.0001	<0.0001

ITT, insulin-induced hypoglycemia test; SEM, standard error of the mean; AUC, area under the curve; TBI, traumatic brain injury.

group) and control children (control group). Figures contain time-dependent changes in serum hormone levels, whereas tables contain basal levels and peak concentrations during the provocation tests independently of the actual serum sampling time.

Growth Hormone

Table 2 contains the basal GH concentrations, as well as the following values during GH provocation tests: peak hormone levels, area under the curve (AUC), and mean of cumulative GH concentrations at defined time-points (0–30–60 min) in TBI patients and in controls. According to our results during the L-DOPA test, all GH parameters measured and calculated were significantly ($p < 0.05$) lower in TBI group than in controls. On the other hand, no significant difference could be detected between GH values of TBI and control patients after insulin-induced hypoglycemia test (ITT), although a tendency to decrease ($p = 0.0576$) was seen in mean GH concentrations of children suffered from TBI (Table 2).

During the course of L-DOPA stimulation, basal GH values were similar in both groups, but we have found a significantly ($p < 0.05$) lower GH response in the TBI group at 30 and 60 min (Fig. 1A). The GH response during ITT tended to decrease in TBI patients 15 and 30 min after insulin challenge, and the difference became statistically significant ($p < 0.05$) at 60 min (Fig. 1B).

Cortisol

In Table 3, we summarized basal cortisol levels, as well as the following values during ITT: peak hormone levels, AUC, and means of cumulative cortisol concentrations at defined time-points (0–15–30–60 min) in TBI patients and controls. In TBI patients, all measured and calculated cortisol levels were found to be significantly ($p < 0.05$) lower than those in control group (Table 3).

Cortisol levels of TBI patients were significantly ($p < 0.05$) lower all through the ITT than values measured in the control group (Fig. 2).

TSH and PRL

No statistical difference was found between TBI and control groups in TSH basal concentrations (80.4 ± 8.8 vs. 96.8 ± 15.5 pmol/L, respectively; $p = 0.33$) and in AUC values ($22,100 \pm 2039$ vs. $16,860 \pm 2456$ pmol/L \times min, respectively; $p = 0.13$) during TRH stimulation test. Using the same test, PRL also did not differ significantly between TBI and control group either in its basal concentrations (281 ± 51 vs. 370 ± 43 mU/L, $p = 0.055$) or in AUC values ($45,347 \pm 4049$ vs. $49,995 \pm 4771$ mU/L \times min, $p = 0.47$), respectively.

TRH stimulation resulted in elevation of TSH and PRL at all time points investigated in both groups (Fig. 3A,B); the curves represented a normal response to the stimuli. No significant difference was observed in TSH and PRL values measured in TBI and control groups, even if PRL concentrations showed a tendency to be lower in TBI group (Fig. 3B).

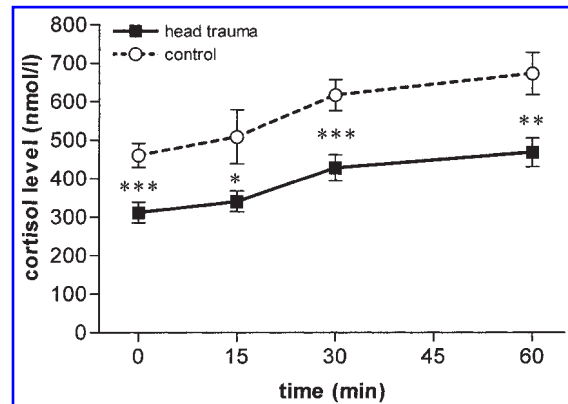


FIG. 2. Unpaired *t*-test was performed to compare the values between groups at a defined time-point. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ indicate significant difference from the value measured in the control group.

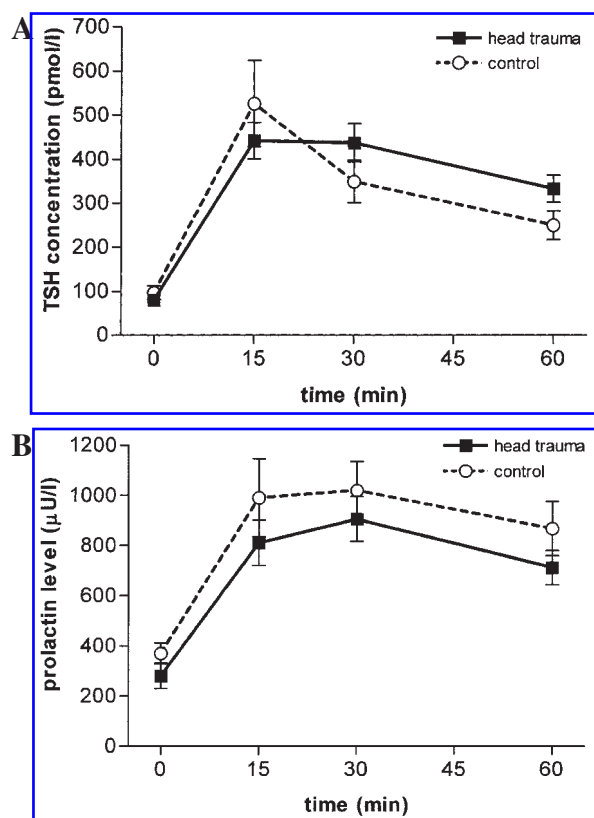


FIG. 3. (A) Unpaired *t*-test was performed to compare the values between groups at a defined time-point. No significant difference ($p < 0.05$) was found. (B) Unpaired *t*-test was performed to compare the values between groups at a defined time-point. No significant difference ($p < 0.05$) was found.

Peripheral Thyroid Hormones

Although fT4 and T3 concentrations were within the normal range in both groups, peripheral thyroid hormone levels were statistically lower in TBI subjects compared to control group. Basal fT4 levels were 12.58 ± 0.30 pmol/L in TBI group and 14.93 ± 0.83 pmol/L in control group ($p = 0.0176$), whereas basal total T3 concentrations were 2.40 ± 0.08 versus 3.00 ± 0.12 nmol/L, respectively ($p < 0.0001$).

Hormonal Changes within the Traumatic Brain Injury Group

In the second part of data analysis, our TBI patients were divided into two groups according to their GH response in L-DOPA and ITT stimulation tests. We found abnormal GH reserve (peak GH < 21 μ U/mL) in both tests in 11 of 26 TBI patients (42% of all). Eight of 11 patients in this GH-deficient subgroup were boys (73%), demonstrating that abnormal GH reserve is more frequent

in boys. In the rest of our patients (GH-sufficient subgroup, $n = 15$), the GH response was normal in both tests ($n = 7$), or it was abnormal only in one provocation test ($n = 8$).

Basal cortisol levels were below normal values altogether in nine TBI patients (34% of all). Low cortisol level was concomitantly seen with abnormal GH reserve in three cases, while it also occurred in six children in the GH sufficient subgroup.

TSH concentrations after TRH stimulation revealed inappropriate response in three TBI patients (12% of all); two of them also had abnormal GH response in both provocation tests.

Interestingly, we found increased PRL level in one TBI child with GH deficiency.

Unexpectedly high GH peak concentrations (30–54 μ U/mL) were observed in five TBI patients (19%) during ITT.

Height of Traumatic Brain Injury Patients

Height Standard Deviation Score (SDS) corrected to chronological age was slightly decreased in TBI patients in GH-deficient subgroup compared to patients in GH-sufficient subgroup (mean and SEM of height SDS was $+0.1 \pm 0.74$ vs. $+0.29 \pm 0.38$, respectively); however, the difference was not statistically significant ($p = 0.59$).

DISCUSSION

The majority of pituitary insufficiency is acquired and deficiency of troph-hormone production may develop in consequence of different external noxa affecting the gland. The pathologic condition of hypophysis-necrosis was first observed after puerperal sepsis (Simonds, 1914). Whereas hypothalamic-pituitary lesions have been commonly described at postmortem examinations, only a limited number of clinical cases with endocrine dysfunction have been reported after traumas (Yuan and Wade, 1991).

Traumatic brain injury was recognized as a cause of neuroendocrine dysfunction almost 90 years ago (Cyran, 1918). Mainly in the last decades several papers were published about the endocrine consequences of TBI in adults (Benvenga et al., 2000; Cyran, 1918; Edwards and Clark, 1986; Eichler et al., 1988; Escamilla and Lisser, 1942; Yuan and Wade, 1991); however, few articles were written about trauma-induced pituitary damages in children (Eichler et al., 1988; Eiholzer et al., 1986; Lopez-Gusman et al., 1992).

Hypothalamic-pituitary damage is considered to be the consequence of different pathologic events (Ceballos, 1966; Crompton, 1971; Lopez-Gusman et al., 1992; Yuan

and Wade, 1991), e.g. direct trauma with rapid dislocation of the gland resulting in partial or complete transection of the stalk; vascular insults including intracranial bleeding, vasospasm (Oertel et al., 2005), hypotension, thrombosis, infarction concomitant cerebral hypoxia with brain edema and pituitary swelling (Kelly et al., 2000). Patterns of endocrine abnormalities following brain trauma vary depending on the site of the injury: hypothalamus, the anterior/posterior pituitary, or the pituitary stalk. Severe damage to the lower part of the stalk or anterior lobe may result in low basal levels of all anterior pituitary hormones and in deficient responses to their releasing factors (Yuan and Wade, 1991).

Mild or moderate head trauma may result in temporary lesion of the pituitary function right after the injury, but these endocrine symptoms could be spontaneously resolved after the acute phase (Aimaretti et al., 2004; Bondanelli et al., 2004; Clark et al., 1988). If the brain trauma causes permanent pituitary lesion most of the cases are diagnosed shortly after TBI (Benvenega et al., 2000; Childers et al., 1998), although some endocrine abnormalities could also appear much later (Aimaretti et al., 2004; Benvenega et al., 2000; Liberman et al., 2001).

Publications propose the evaluation of pituitary function in all patients with TBI (Bondanelli et al., 2004; Childers et al., 1998; Kelly et al., 2000; Urban et al., 2005; Yuan and Wang, 1991). The most common pituitary dysfunctions caused by TBI in adults are GHD and gonadotropin deficiency (Agha et al., 2004b; Benvenega et al., 2000; Bondanelli et al., 2004; Clark et al., 1998). The function of the gonadotroph-gonadal axis was not investigated in this study since normal hormone ranges are hard to define in prepubertal or pubertal age (Childers et al., 1998; Morton and Wehman, 1995).

In our present study more than 60% of children showed some kind of endocrine dysfunction in pituitary level following brain trauma. Diminished GH pool during provocation tests was the most frequent finding, and its 42 % prevalence in all TBI cases is higher than that was reported in adults (11–28%; see Table 1). The laboratory methods used in our study is comparable to those used in previous adult studies, therefore it is probably not responsible for the higher percentage of patients with poor GH response. The explanation for this difference may include the following factors:

- (i) We have performed L-DOPA and ITT tests to reveal pituitary GH reserve in our patients. These tests are recommended by guidelines of endocrine societies for diagnosis of inherited and acquired GHD in childhood (GH Research Society, 2000; Juul et al., 2002). However, the diagnostic value of these provocation tests has been strictly criticized in a recent publication

since repeated tests in the same children resulted in discordant measures (Gandrud and Wilson, 2004). Deep hypoglycemia caused by ITT is considered to be an efficient provocative test of GH and cortisol response in adults (Agha et al., 2004b), but its reproducibility was found to be limited in larger cohort of pediatric patients (Gandrud and Wilson, 2004).

- (ii) The cut-off levels defined in both assays (i.e., 21 $\mu\text{U/mL}$ corresponding to 7 ng/dL) were higher than those accepted in adult studies, since we have followed the suggestions of International Guidelines of APA/LWPES and ESPE (GH Research Society, 2000; Juul et al., 2002) and Hungarian consensus for diagnosis of GHD.

Although 42% of our TBI patients had abnormal GH levels 3 years after their head trauma, there was no significant height reduction in this subgroup compared to height of patients with sufficient GH response. However, we have no correct auxological data on height at the time of TBI, and our 3-years observational period seems to be short to detect significant height reduction.

Involvement of other pituitary hormones and axes were also observed in our TBI group. However, no clear correlation could be demonstrated among the damages of different pituitary axes.

The basal cortisol concentrations and its levels during ITT provocation were significantly reduced in our TBI patients (Fig. 2, Table 3). However, the lower basal cortisol levels have not correlated with clinical signs, no symptoms of acute or chronic hypoadrenia could be observed. Published results of TBI induced corticotrophic insufficiency in adult TBI patients are also inconsistent (Table 1) from low basal cortisol levels (Agha et al., 2004b; Benvenega et al., 2000; Dimopoulou et al., 2004; Yuan and Wang, 1991), to normal corticotrophic function (Bondanelli et al., 2004). In the most recent prospective study adrenal insufficiency was found in 53% of 80 patients in younger ages with moderate or severe TBI (Cohan et al., 2005). This difference could demonstrate an age-dependent vulnerability of the hypothalamic-pituitary-adrenal axis, although this assumption has to be confirmed in further studies.

Hypothyroxinemia with preserved TSH response to TRH was described in adults (Fleischer et al., 1978; Gunn et al., 1991; Rudman et al., 1977; Yuan and Wade, 1991). In a recent study, free T4, TSH, or both were low in 21.7% of adult patients, whereas 87% had both TSH and free T4 below the mid-normal level (Lieberman et al., 2001). We also observed decrease in concentrations of peripheral thyroid hormones in our pediatric cohort, but the values were in age-related normal ranges. TSH response to TRH was also blunted in 12% of our TBI children.

Only one of our TBI patients had elevated PRL level, whereas TRH induced PRL concentrations showed a slight decrease in TBI group. Although an association between TBI and hyperprolactinemia has been published (Eiholzer et al., 1986; Yuan and Wade, 1991), hyperprolactinemia seems to be a rare and probably transitory sequela of TBI in childhood.

Permanent or transient central diabetes insipidus (CDI) developed in 0–35% of adult patients after head injury according to previous publications (Agha et al., 2004a,c; Benvenega et al., 2000; Yuan and Wade, 1991). In our patients no clinical sign of CDI could be found either in the medical records of the acute phase or 3 years after the head trauma.

According to the majority of previous publications, the severity of post-TBI GHD is unrelated to the age of the patient, Glasgow Coma Scale (GCS) score, CT results, or involvement of other pituitary axes (Aimaretti et al., 2004; Benvenega et al., 2000; Cyran, 1918; Ghigo et al., 2005). In contrast to these observations, a correlation between severity of TBI (GCS score) and occurrence of pituitary dysfunction was demonstrated by Bondanelli et al. (2004). Our data suggest no clear correlation between the type of head injury and post-traumatic GH response (data not shown), although the number of patients in different trauma groups is low for statistical analysis. Similarly, no significant connection was found between the duration of unconsciousness and GH response during stimulation tests.

Patients could present non-specific clinical symptoms (such as fatigue) as alarming signs of pituitary dysfunction after TBI (Cyran, 1918). If it is undiagnosed, it could lead to life-threatening endocrine crisis (Schneider et al., 2005). Despite the very poor clinical signs of PHD, some of our cases should require hormone replacement therapy according to their actual hormone levels.

Present study provides data only at one time-point after head injury, but further studies may reveal time-dependent post-traumatic changes in functions (deterioration or improvement) of different pituitary axes injured.

CONCLUSION

Our study confirms the high risk for pituitary dysfunction in children with TBI, even if obvious clinical symptoms are lacking.

Our results indicate that (i) head trauma occurs mainly in young men; (ii) car accidents are the most common cause of TBI; (iii) the severity of PHD does not correlate with the intensity of TBI; and (iv) a higher proportion of GH and cortisol deficiency in childhood seems to be characteristic for this age group of TBI patients.

Our suggestion is to screen and follow up pituitary function after any kind of brain trauma requiring hospitalization in childhood. Pediatricians and endocrinologists should keep in mind the possibility of TBI as cause of pituitary dysfunction. These recommendations are in full concordance with the consensus guidelines on screening for hypopituitarism following TBI in adults (Ghigo et al., 2005; Urban et al., 2005).

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