Mild traumatic brain injury and immediate hypopituitarism in children

Trauma cranioencefálico leve e hipopituitarismo imediato em crianças

David Gonçalves Nordon[1], Rodrigo Rejtman Guimarães[2], Alcinda Aranha Nigri[3], Sandro Blasi Esposito[4]

[1] Medical Doctor, Pontifícia Universidade Católica de São Paulo.
[2] Medical Doctor and Psychologist, Pontifícia Universidade Católica de São Paulo.
[3] Pediatric Endocrinologist. Professor of Pediatrics. Department of Medicine, Faculdade de Ciências Médicas e da Saúde de Sorocaba, Pontifícia Universidade Católica de São Paulo.
[4] Pediatric Neurologist. Professor of Neurology. Department of Medicine, Faculdade de Ciências Médicas e da Saúde de Sorocaba, Pontifícia Universidade Católica de São Paulo.

Funding source: *Programa Institucional de Bolsas de Iniciação Científica do Conselho de Ensino e Pesquisa da Pontifícia Universidade Católica de São Paulo (PIBIC/CEPE).*

ABSTRACT

Aims: Traumatic brain injury is a common and costly trauma that may lead to hypopituitarism. Its complications may have great impact on public health, especially in children. This study evaluates the prevalence of immediate hypopituitarism in children who suffered mild traumatic brain injury.

Methods: Children who were admitted in the emergency service of *Unidade Regional de Emergência – Conjunto Hospitalar de Sorocaba* due to traumatic brain injury were evaluated for the study. Every patient underwent a head computed tomography at admittance and was classified according to the Glasgow Coma Scale, being traumatic brain injury graded in severe (<9), moderate (9-12) or mild (>12). Those whose parents or guardians agreed to participate and presented mild trauma were included in the study and invited to perform a neuroendocrinological evaluation.

Results: Sixty-eight children were admitted with traumatic brain injury, and 21 agreed to participate. Five patients did not perform the urine and blood exams, two had a moderate TBI, and one had a severe TBI, and therefore were excluded from data analysis. Among the 13 patients whose exams were performed in less than 48 hours from the trauma, five (38.5%) presented hormonal alterations, respectively: single thyroid-stimulant hormone (TSH) elevation, single insuline-like growth factor 1 (IGF-1) elevation, single cortisol elevation, combined folicule-stimulant hormone (FSH) and prolactin elevation, and combined TSH and FSH elevation. None presented symptoms of hypopituitarism. There was no association between head image alterations and hypopituitarism.

Conclusions: The results found in this study lead to probably little significant endocrine dysfunctions, as such hormonal increases may be related to acute trauma response. Considering the literature and the results, it is possible to speculate that the relationship of traumatic brain injury with hypopituitarism in children is different from adults.

KEYWORDS: CRANIOCEREBRAL TRAUMA; BRAIN INJURIES; HEAD INJURIES; THYROID GLAND; HYPOPITUITARISM; CHILD; EMERGENCY MEDICINE.

RESUMO

Objetivos: O trauma cranioencefálico é um trauma comum e dispendioso que pode levar a hipopituitarismo. Suas complicações podem ter grande impacto na saúde pública, especialmente em crianças. Este estudo avalia a prevalência de hipopituitarismo imediato em crianças que sofreram lesão cerebral traumática leve.

Métodos: Foram avaliadas para o estudo crianças admitidas no serviço de emergência da Unidade Regional de Emergência – Conjunto Hospitalar de Sorocaba devido a um trauma cranioencefálico. Cada paciente foi submetido a uma tomografia computadorizada na admissão e classificado pela Escala de Coma de Glasgow, sendo a lesão cerebral classificada em grave (<9), moderada (9-12) ou leve (> 12). Aqueles cujos pais ou responsáveis concordaram em participar e apresentavam a forma leve de trauma cranioencefálico foram incluídos no estudo e convidados a realizar uma avaliação neuroendocrinológica.

Resultados: Sessenta e oito crianças foram internadas com traumatismo cranioencefálico e 21 concordaram em participar. Cinco pacientes não realizaram os exames de sangue e urina, dois tinham a forma moderada e um tinha a forma grave de trauma cranioencefálico, sendo excluídos da análise. Entre as 13 crianças cujos exames foram feitos dentro das primeiras 48 horas após o trauma, cinco (38,5%) apresentaram alterações hormonais, respectivamente: somente elevação de hormônio estimulante da tireoide (TSH); somente elevação de fator de crescimento insulina-símile 1 (IGF-1); somente elevação de cortisol; elevação de hormônio folículo estimulante (FSH) combinada à elevação de prolactina; e elevação de TSH combinada à elevação de FSH. Nenhum dos pacientes apresentou sintomas de hipopituitarismo. Não houve associação entre alterações de neuroimagem e hipopituitarismo.

Conclusões: Os resultados deste estudo apontam para disfunções endócrinas provavelmente pouco importantes, já que algumas das alterações encontradas podem estar relacionadas à resposta ao trauma agudo. Considerando a literatura e os resultados, é possível especular que a relação do trauma cranioencefálico com hipopituitarismo em crianças é diferente dos adultos.

DESCRITORES: TRAUMATISMOS CRANIOCEREBRAIS; TRAUMATISMOS ENCEFÁLICOS; TRAUMA CRANIANO; TIREÓIDE; HIPOPITUITARISMO; CRIANÇA; MEDICINA DE EMERGÊNCIA.

Recebido: novembro de 2011. Aceito: março de 2012.

Endereço para correspondência/Corresponding Author:
David Gonçalves Nordon
Departamento de Medicina, Faculdade de Ciências Médicas e da Saúde, PUC-SP
Rua Marechal Castelo Branco, 91
CEP 18031-300, Sorocaba, SP, Brasil
Telefone: (15) 32346533
E-mail: david@drnordon.com.br

INTRODUCTION

Traumatic brain injury (TBI) is a common and costly trauma that most frequently affects men, adolescents and young adults.[1-3]

The sudden movement of the pituitary stalk may compromise its vascular supply and lead to bleeding and inflammation.[4-6] The most important complication of hypopituitarism in children is the compromising of growth and development.

In adults, hypopituitarism after TBI affects between 24 and 50% of the victims, being isolated hormonal deficit the most common (21.4-36.9%). Growth hormone (GH) deficiency is the most common hormonal deficit (5-25%), followed by hypogonadism (17%), due to the localization of the somatotrophic and gonadotrophic cells in the pituitary. In most studies hormonal deficit shows a considerable improvement 12 months after the incident. The severity of the trauma is generally not related to the development of hypopituitarism.[6-14]

In face of such possible neuroendocrine implications, studying the development of hypopituitarism after a trauma as frequent as TBI may have a great impact on public health, considering prevention and social onus. This study thus aimed to investigate the incidence of immediate hypopituitarism in children who suffered a TBI.

METHODS

The study was approved by the Ethics in Research Committee from *Centro de Ciências Médicas e Biológicas de Sorocaba* in November 2009.

Children younger than 13 years old who were admitted in the emergency service of *Unidade Regional de Emergência – Conjunto Hospitalar de Sorocaba*, Sorocaba, São Paulo state, Brazil, due to TBI were considered for the study. Children received common medical evaluation and treatment according to the Advanced Trauma Life Support (ATLS) guidelines. Every patient underwent a cranial computed tomography (CT) at admittance and was classified according to the Glasgow Coma Scale, according to which TBI was graded in severe (<9), moderate (9-12) or mild (>12). Those who presented mild TBI were invited to the study and performed a neuroendocrinological evaluation. Those whose parents or legal guardians agreed to participate and sign the informed consent form were included, and, when timely, their parents or legal guardians were invited to attend a medical consultation at the next available day in the endocrine triage outpatient clinic.

Every exam was obtained at eight AM in order to standardize hormonal pulsatility; if possible, exams were performed in the emergency unit; if not, they were obtained the following day, before the medical consultation, in which patients were measured and questioned about symptoms related to hypopituitarism. The examinations were: urinalysis for the evaluation of urine density, serum sodium, potassium, urea, and glucose for the calculation of blood osmolarity, all of those for the diagnosis of diabetes insipidus; insuline-like growth factor 1 (IGF-1) for the evaluation of the somatotroph axis; luteinizing hormone (LH), folicule-stimulant hormone (FSH) and estrogen (for girls) or testosterone (for boys) for the gonadotroph axis; cortisol for the corticotroph axis; thyroid-stimulant hormone (TSH) and free thyroxine (T4) for the thyrotroph axis; and prolactin (PRL). Elevated or diminished values were respectively defined as those above or below the age and sex-related reference values from our laboratory which are in accordance to the most commonly used international reference values (Table 1).

Table 1. Normal range values for hormones tested in this study.

Hormone	Values
Thyroid-stimulant hormone (TSH)	1-5 years old: 0.700-6.000 mcUI/ml 6-10 years old: 0.600-5.400 mcUI/ml 11-15 years old: 0.500-4.900 mcUI/ml
Free thyroxine (free T4)	0.70-1.80ng/dl
Luteinizing hormone (LH)	Females pre-puberty: <0.2 mUI/ml Males pre-puberty: < 0.3 mUI/ml
Folicule-stimulant hormone (FSH)	Females pre-puberty: <2.2 mUI/ml Males pre-puberty: <0.9 mUI/ml
Cortisol	8AM sample: 4-22 mcg/dl 4PM sample: 3-17 mcg/dl
Insuline-like growth factor 1 (IGF-1)	1-2 years old: 55-327 ng/ml 2-3 years old: 51-303 ng/ml 3-4 years old: 49-289 ng/ml 4-5 years old: 49-283 ng/ml 5-6 years old: 50-286 ng/ml 6-7 years old: 52-297 ng/ml 7-8 years old: 57-316 ng/ml 8-9 years old: 64-345 ng/ml 9-10 years old: 74-388 ng/ml 10-11 years old: 88-452 ng/ml
Total testosterone	Males pre-puberty: <60 ng/dl
Estradiol	Females pre-puberty: <43 pg/ml
Prolactin	Male: 3.46-19.40 ng/ml Female: 5.18-26.53 ng/ml

RESULTS

During the year of 2010, 68 patients (regardless of trauma severity) were admitted, however only 21 agreed to participate. Of those, 11 (52.3%) were

male; mean age was 6.35 years (±3.08); 18 (86%) had mild TBI, one had moderate, and two had severe TBI. Twelve among the 21 (57%) had no alteration in the head CT; the most common alteration was fracture and hematoma, in five (23.8%). From the 21 patients, five (23%) did not perform the urine and blood exams, two had a moderate TBI, and one had a severe TBI, and were therefore excluded from data analysis.

Among the 13 patients whose exams were performed in less than 48 hours from the trauma, five (38.5%) presented endocrine alterations. Of those, single TSH elevation was present in one, single IGF-1 elevation was present in one, single cortisol elevation was present in one (this patient was the only one who had the blood sample collected at four PM due to technical difficulties; thus, normal value ranged between 3 and 17 mcg/dL), combined FSH and PRL elevation was present in one, and combined FSH and TSH elevation was present in one. None of them presented either signs or symptoms related to their hormonal alterations or anthropometric measures below the third or above the 97th percentiles, what could have suggested previous hormonal alterations. Results are presented in Table 2 and Table 3.

Table 2. Demographic characteristics, Glasgow Coma Scale score, image examination and hormonal changes within 48 hours after mild traumatic brain injury, in 13 children admitted in the emergency service *Unidade Regional de Emergência – Conjunto Hospitalar de Sorocaba,* Sorocaba, São Paulo state, Brazil, in 2010.

Patient number	Sex	Age (years)	Glasgow Coma Scale score	Head computed tomography	Hormonal changes [normal value]
1	M	9	15	Fracture of the frontal and orbital bones	TSH: 7.150 [<6.300]
2	M	5	15	No findings	No findings
3	M	7	14	No findings	No findings
4	F	5	15	Multiple fractures, sub-arachnoid hemorrhage	No findings
5	M	7	15	No findings	No findings
6	F	7	15	Left temporal contusion	IGF-1: 401 [<316]
7	F	1	15	No findings	FSH: 9.7 [<2.90] PRL: 45.30 [<26.53]
8	F	11	15	No findings	No findings
9	M	7	13	No findings	No findings
10	F	8	15	Right temporoparietal hemorrhage, slight medium line deviation and edema	No findings
11	F	3	15	No findings	TSH: 8.262 [<6.300] FSH: 2.7 [<2.2]
12	F	10	15	Bi-frontal penetrating fracture, epidural hematoma	No findings
13	F	5	15	No findings	Cortisol: 17.6 [<17]

Table 3. Hormonal tests results in 13 children between 1 and 11 years of age, within 48 hours after mild traumatic brain injury.

Patient	TSH	Free T4	FSH	LH	Prolactin	Cortisol
1	7.150	0.92	0.4	<0.07	15.41	17.1
2	3.936	1.11	0.5	0.1	10.1	9.73
3	2.353	1.29	<0.3	<0.07	3.35	17.5
4	3.487	1.12	0.7	<0.07	13.77	16.7
5	2.540	1.5	<0.3	<0.07	8.87	17.9
6	3.892	1.07	<0.3	<0.07	10.19	18
7	3.302	1.05	9.7	<0.07	45.30	11.6
8	2.263	1.40	1.8	<0.07	11.27	21.3
9	3.895	1.07	<0.3	<0.07	10.32	15
10	2.594	1.56	0.6	<0.07	24.88	15.2
11	8.262	0.94	2.7	<0.07	10.26	15.6
12	2.161	1	0.4	<0.07	5.46	6.1
13	3.429	1.31	1.49	<0.07	17.83	17.6
Mean values	3.789	1.18	1.50	0.07	14.39	15.33
Standard deviations (±)	1.867	0.21	2.98	0.008	10.76	4.03

TSH: thyroid-stimulant hormone; T4: thyroxine; FSH: folicule-stimulant hormone; LH: luteinizing hormone.

No patient with mild TBI needed intensive care treatment, presented post-trauma amnesia or loss of consciousness. Also, none received glucocorticoids during hospitalization or any other drug that could interfere with the endocrine system, or needed any surgical intervention.

DISCUSSION

This sample had an equal distribution of patients according to sex, in spite of the evidence of TBI being more frequent in boys.[3] However, due to the small number of patients included, data on this is insufficient for statistical significance.

The incidence of hypopituitarism in children is not commonly studied. A systematic review of the last 14 years can only provide five studies (either cohort or sectional) that evaluate the neuroendocrine impact of such trauma.[15-19] Most of them performed delayed evaluations that were generally inconclusive in defining the need of an endocrine evaluation or the impact of neuroendocrine dysfunction caused by TBI in the patient's life. The only consistent finding in all of them is growth hormone deficiency; all other hormones deficiencies or excesses were found in occasional patients, and, unlike adults, none of them presented any alteration in the gonadotrophic axis.

There is much discordance among the published studies and their results. Firstly, because they do not adopt the same methodology for diagnosis or pituitary insufficiency definition.[20] Secondly, because the studies performed neuroendocrine exams at different periods of time after the TBI (from immediate to 10.3 years), what may compromise the results not only for several different confounders, but also for the organism capacity of healing itself. Thirdly, because evaluation methods are different. Moon et al.[15] highlights that no stimuli tests were performed, as they may have adverse and possibly severe effects on children; Kadhr et al.,[16] on the other hand, performed stimuli tests for every child.

Using symptoms for diagnosis suspicion, as performed in Poomthavorn's study,[19] may be a confounder itself; pituitary disfunction may be asymptomatic,[15] as observed in the present study: even though almost 40% of the examined children had neuroendocrine dysfunctions, none of them were symptomatic.

The results found in this study lead to probably little significant endocrine dysfunctions; PRL, IGF-1, FSH and cortisol increase may be related to acute trauma response. TSH elevation without free T4 repercussion may be the beginning of a secondary hypothyroidism, though with no impact in the patient's quality of life yet. Only the continuous follow-up can show whether a dysfunction is temporary or not; the presented studies, more specifically Einauldi's,[16] indicate that such dysfunctions tend to resolve themselves with time.

Considering the current theory of pituitary stalk lesion during the trauma, stimulating hormones (such as TSH, ACTH, FSH, LH) and organ-active hormones (such as free T4, cortisol, IGF-1, testosterone, estradiol) deficits, rather than excess, would have been expected. Moreover, in accordance to Einauldi et al.[17] and contrarily to what is observed in adults,[8-13] our study did not identify central hypogonadism or GH deficiency. Therefore, it is possible to speculate that the physiopathology of TBI and hypopituitarism in children is different from adults.

CT alterations had no relation to hypopituitarism, as was expected considering that no relation between Glasgow Coma Scale score and pituitary insufficiency has ever been found.[6-13,18] A study investigated hypopituitarism in patients with either TBI or extra-cranial traumas and showed similar suppression patterns in 10 days of follow-up, what suggests that hypopituitarism may be more related to trauma severity in general than to the specific type of trauma.[21] As opposed to that, another study related hypopituitarism to lesions in the deep and central areas of the brain by magnetic resonance imaging (MRI).[22] Given the difference between CT and MRI it is possible that in the former study such relation existed, despite not observed.

Guidelines[23] suggest investigating pituitary dysfunctions after TBI; data available to date for children, however, do not provide sufficient information for a definite decision on that, as even long-term studies did not find any compromise in quality of life, development or growth in the affected subjects.

Limitations of this study include the fact of being a sectional study, what does not allow a long-term evaluation of pituitary insufficiency in children after TBI and its impact in the patient's life. No stimulus test was performed, as the researchers concurred it would lead to possible unnecessary complications and discomfort to the patients. Even though sample size was small it is in accordance with what is found in the literature and period of evaluation, considering that most studies gathered their sample in an average 10-year period. Given the scarce data on the subject this study may contribute specifically for the analysis of immediate pituitary dysfunctions in children, what has only been adequately studied in 30 children so far. More studies are necessary in order to adequately define whether children who suffered TBI should undergo neuroendocrine surveillance or not.

REFERENCES

1. Cassidy JD, Carrol LJ, Peloso PM, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;36:28-60.
2. Schneler AJ, Shields BJ, Hosteler SG, et al. Incidence of pediatric traumatic brain injury and associated hospital resource utilizations in the United States. Pediatrics. 2006;118:483-92.
3. Koizumi MS, Lebrão ML, Mello-Jorge MHP, et al. Mortalidade por traumatismo crânio-encefálico no município de São Paulo, 1997. Arq Neuropsiquiatr. 2000;58:81-9.
4. Urban RJ. Hypopituitarism after acute brain injury. Growth Horm IGF Res. 2006;16(suppl.A):s25-9.
5. Poomthavorn P, Zacharin M. Traumatic brain injury-mediated hypopituitarism: report of four cases. Eur J Pediatr. 2007;166:1163-8.
6. Agha A, Thompson CJ. High risk of hypogonadism after traumatic brain injury: clinical implications. Pituitary. 2005;8:245-9.
7. Tsagarakis S, Tzanela M, Dimopolou I. Diabetes insipidus, secondary hypoadrenalism and hypothyroidism after traumatic brain injury: clinical implications. Pituitary. 2005;8:251-4.
8. Leal-Cerro A, Flores JM, Rincon M, et al. Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. Clin Endocrinol. 2005;62:525-32.
9. Popovic V. Gh deficiency as the most common pituitary defect after TBI: clinical implications. Pituitary. 2005;8: 239-43.
10. Tanriverdi F, Senyurek H, Unluhizarei K, et al. High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. J Clin Endocrinol Metab. 2006;91:2105-11.
11. Aimaretti G, Ambrosio MR, Di Somma C, et al. Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study. J Clin Endocrinol Metab. 2005;90:6085-92.
12. Aimaretti G, Ambrosio MR, Di Somma C, et al. Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clin Endocrinol (Oxf). 2004;61: 320-6.
13. Bavisetty S, Bavisetty S, McArthur DL, et al. Chronic hypopituitarism after traumatic brain injury: risk assessment and relationship to outcome. Neurosurgery. 2008;62:1080-91.
14. Nordon DG, Guimarães RR, Nigri AA. Traumatic brain injury and hypopituitarism. Rev Fac Ciênc Méd Sorocaba. 2011;13:1-3.
15. Moon RJ, Sulton T, Wilson PM, et al. Pituitary function at long-term follow-up of childhood traumatic brain injury. J Neurotrauma, 2010;27:1827-35.
16. Khadr SN, Crofton PM, Jones PA. Evaluation of pituitary function after traumatic brain injury in childhood. Clin Endoncrinol. 2010;73:673-44.
17. Einaudi S, Matarazzo P, Peretta P, et al. Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study. J Pediatr Endocrinol Metab. 2006;19: 691-703.
18. Niederland T, Makovi H, Gal V, et al. Abnormalities of pituitary function after traumatic brain injury in children. J Neurotrauma. 2007;24:119-27.
19. Poomthavorn P, Maixner W, Zacharin M. Pituitary function in paediatric survivors of severe traumatic brain injury. Arch Dis Child. 2008;93:133-7.
20. Kokshoorn NE, Wasenaar MJE, Biermasz NR, et al. Hypopituitarism following traumatic brain injury: prevalence is affected by the use of different dynamic tests and different normal values. Eur J Endocrinol. 2010;162:11-8.
21. Wagner J, Dusick JR, McArthur DL, et al. Acute gonadotroph and somatotroph hormonal suppression after traumatic brain injury. J Neurotrauma. 2010;27:1007-19.
22. Jeong JH, Kim YZ, Cho YW, Kim JS. Negative effect of hypopituitarism following brain trauma in patients with diffuse axonal injury. J Neurosurg. 2010;113:532-8.
23. Ghigo E, Masel B, Aimaretti G. Consensus guidelines on screening for hypopituitarism following traumatic brain injury. Brain Inj. 2005;19:711-24.