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Hypopituitarism induced by traumatic brain injury in the transition phase

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ABSTRACT. Traumatic brain injury (TBI) has been associated with hypopituitarism in general and GH deficiency (GHD) in particular; the consequences of this on growth and development are likely to be critical in children and adolescents in the so-called "transition phase". In order to verify the consequences of TBI on pituitary function in the transition phase, we studied a population of adolescents and young adults 3 and 12 months after brain injury [no.=23, 9 females, 14 males; age: 16-25 yr; body mass index (BMI): 21.9±0.6 kg/m^2]. At 3 months, hypopituitarism was present in 34.6%. Total, multiple and isolated deficits were present in 8.6, 4.3 and 21.7%, respectively. Diabetes insipidus (DI) was present in 8.6% patients and mild hyperprolactinemia in 4.3%. At 12 months, hypopituitarism was present in 30.3%. Total, multiple and isolated deficits were present in 8.6, 4.3 and 17.4%, respectively. DI was present in 4.3% of patients and mild hyperprolactinemia in 4.3%. Total hypopituitarism was always confirmed at retesting. Multiple and isolated hypopituitarism were confirmed in 0/1 and 2/5, respectively. Two/23 patients showed isolated hypopituitarism at 12 months only; 1 patient with isolated at 3 months showed multiple hypopituitarism at retesting. GHD and secondary hypogonadism were the most common acquired pituitary deficits. These results show the high risk of TBI-induced hypopituitarism also in the transition age. Thus it is recommended that pediatric endocrinologists follow-up pituitary function of children and adolescents after brain injuries.

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INTRODUCTION

Evidence from several studies demonstrates that brain injuries, such as head trauma [traumatic brain injury (TBI)], are very often the cause of acquired hypopituitarism (1-13); this is relevant considering the very high incidence of TBI (14, 15). This evidence comes from studies in adults where appropriate hormonal replacement would provide an obvious endocrine and metabolic benefit but even more benefit to the post-traumatic syndrome. A TBI-induced hypopituitarism would have even more important clinical endocrine consequences in childhood and adolescence given the obvious implications in growth and development (6, 7, 13, 16). Indeed, in a retrospective study it has been demonstrated that there was reduced final height in patients who had TBI in childhood but were diagnosed and treated with hormonal replacement in adulthood only (16). This fits well with evidence that the most common pituitary deficits after TBI are GH deficiency (GHD) and secondary hypogonadism (8, 9, 11, 13). Again, it has to be considered that children and teenagers are particularly susceptible to TBI (6, 7, 13, 16). The most

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common cause of TBI is car crashes, including pedestrian-car and bicycle-car encounters, while falls, child abuse, violence and sports injuries are other culprits (14, 15). Loss of consciousness is the hallmark symptom of TBI and the areas of the brain most often affected by TBI are the frontal and temporal lobes (14). However, infections and micro-hemorrhages are commonly recorded in the hypothalamus and the pituitary after TBI (17-19). This picture of TBI-induced damages in the central nervous system clearly alert about clinical consequences including neuroendocrine dysfunctions (13).

The "transition phase" refers to a broad set of physical and psychosocial changes, arbitrarily defined as starting in late puberty and ending with full adult maturation. This usually implies a period from mid to late teens until 6-7 yr after achievement of final height (20).

Information about pituitary function in children and adolescents after TBI are scanty. Based on the foregoing, in order to clarify this point we performed a prospective study about hormonal functions in adolescents and young adults who had TBI of various degrees of severity.

SUBJECTS AND METHODS

In collaboration with neurosurgeons, neurologists and neuro-radiologists of various Italian centers, under the auspices of the Italian Society of Endocrinology, we tested pituitary function in a population of brain-injured adolescent patients at 3 and 12 months after the head trauma (Table 1). Specifically, 23 patients were studied [9 females, 14 males; age: 19.9±0.6 yr; body mass index (BMI): 21.9±0.6 kg/m^2]. Ten patients had had mild TBI [Glasgow Coma Scale (GCS): 13-15], 6 moderate TBI (GCS: 12-9) and 7 severe TBI (GCS ≤8)). Ten out of these 23 patients were not included in our reports about TBI-induced hypopituitarism in adults that have been published or are now in publication (11, 12).

The GCS represents a summary of the TBI patient's level of consciousness as indicated by scores of eye opening, motor responses and verbal responses. Severity of injury is indicated by the total score: 3-8= severe, 9-13= moderate, and 14-15= mild (21).

No patient had known neuroendocrine disease before the pathological event. No patient was under glucocorticoid treatment during the prospective study. Patients who had been treated with glucocorticoids during their stay in the Intensive Care Unit had stopped glucocorticoid administration al least 2 months before hormonal testing at 3 months. No patient had known neuroendocrine disease before the pathological event. In this prospective study, all patients who were diagnosed as hypopituitaric at 3 months were treated (22-24) as follows: a) desmopressin acetate (0.1 mg tablets po) as appropriate for replacement of diabetes insipidus; b) hydrocortisone or cortisone acetate as appropriate (15-20 and 25-37.5 mg, respectively) for replacement in secondary hypoadrenalism; c) L-T_4 as appropriate for replacement in secondary hypothyroidism. Secondary hypogonadism at 3 months was not replaced waiting for reconfirmation at 12 months. GHD was never replaced after demonstration at 3 months. It had been planned to replace severe GHD with recombinant human GH (rhGH) only after appropriate replacement of other pituitary deficits when present and after retesting confirming the defect at 12 months. The hormonal replacement was eventually withdrawn at least 7 days before retesting for desmopressin acetate and hydrocortisone or cortisone acetate and at least 30 days before for L-T_4 replacement.

In each clinical centre the internal standard reference ranges were used to discriminate abnormal from normal results. Specifically: a) diabetes insipidus (DI) was demonstrated by the presence of massive dilute urine volume (>2.5-3 l/24 h) with low urine osmolality (<300 mmol/kg) (23, 24); b) moderate and severe secondary adrenal insufficiency was demonstrated by early-morning (at 09.00 h) cortisol concentrations <80 µg/l. Low 24-h urinary free cortisol (UFC) levels (<30 µg/24 h) were also taken into account, although UFC measurement is not generally considered a reliable

Table 1 - *Hormonal assay methods.*

Hormone	Kit	Sensitivity	Inter- and intra-assay coefficients of variation
GH (µg/l)	HGH-CTK IRMA and INSIK-5 (Sorin, Saluggia, Italy)	0.15 µg/l	4.9-6.5 and 1.5-2.9%
IGF-I (µg/l)	RIA (Nichols Institute)*	0.013 nmol/l	5.2-8.4 and 2.4-3.0%
Free T_4 (ng/l)	RIA (Techno Genetics, Cassina de' Pecchi, Milano, Italy)	0.39 ng/l	6.6-8.7 and 2.6-7.3%
TSH (mU/l)	IRMA (TSH Irma C.T., Biocode, Liege, Belgium)	0.05 mU/l	4.2-7.1 and 4.0-6.2%
Cortisol (µg/l)	RIA (CORT-CTK 125, DIA Sorin, Disorin Diagnostics, Saluggia, Italy)	<0.5 µg/l	6.6-7.5 and 3.8-6.6%.
Free urinary cortisol (µg/24 h)	RIA kits (Biodata Diagnostics, SpA, Guidonia, Montecelio, Roma, Italy)	7.36 µg/day	1.8-9.17 and 3.24-4.62%
PRL (µg/l)	Immunoradiometric assay (PRL-CTK, IRMA, SORIN, Saluggia, Italy)	0.45 µg/l	3.1-5.8% and 0.9-5.8%
Estradiol (pg/ml)	RIA (Diagnostic Products)	1.4 pg/ml	5.2-9.1 and 5.5-10.5%
Testosterone (ng/ml)	RIA (Diasorin, Saluggia, Italy)	0.05 ng/ml	11.3-13.7 and 3.81-8.07%
LH (mIU/ml)	Immunoradiometric assay (LH IRMA CT, Radim, Italy)	0.20 mIU/ml	7.6-13.8 and 4.6-8.6%
FSH (mIU/ml)	Immunoradiometric assay (FSH IRMA CT, Radim, Italy)	0.18 mIU/ml	4-8.8 and 3.56-7.47%

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Table 2 - *Changes in pituitary function at 12 vs 3 months testing after traumatic brain injury.*

Case	Sex	Age (yr)	BMI (kg/m^2)	GCS	3 months	12 months
1	F	18	23.4	10	Normal pituitary function	Secondary hypocortisolism
2	F	22	20.9	14	Normal pituitary function	Secondary hypogonadism
3	F	20	22	3	Normal pituitary function	Normal pituitary function
4	M	20	26	6	Normal pituitary function	Normal pituitary function
5	M	18	18.1	7	Normal pituitary function	Normal pituitary function
6	M	24	24.8	10	Normal pituitary function	Normal pituitary function
7	M	25	19.5	12	Normal pituitary function	Normal pituitary function
8	M	17	24.5	13	Normal pituitary function	Normal pituitary function
9	M	16	23.8	13	Normal pituitary function	Normal pituitary function
10	M	21	23	14	Normal pituitary function	Normal pituitary function
11	F	16	17.6	14	Normal pituitary function	Normal pituitary function
12	F	19	25	15	Normal pituitary function	Normal pituitary function
13	M	23	17.3	15	Normal pituitary function	Normal pituitary function
14	M	25	21	13	Normal pituitary function	Normal pituitary function/HyperPRL
15	M	21	24	10	Hypogonadism/secondary hypocortisolism/HyperPRL	Normal pituitary function
16	M	21	19.9	15	Diabetes Insipidus	Normal pituitary function
17	M	20	23.4	9	Severe GHD	Partial GHD
18	F	19	22	9	Partial GHD	Partial GHD
19	F	21	18	7	Severe GHD	Severe GHD
20	M	16	22	13	Severe GHD	Severe GHD
21	F	20	22.1	4	Severe GHD	Severe GHD/secondary hypogonadism
22	F	18	24.5	8	Total hypopituitarism	Total hypopituitarism
23	M	18	20	8	Total hypopituitarism/DI	Total hypopituitarism/diabetes insipidus

BMI: body mass index; F: female; GCS: Glasgow Coma Scale; GHD: GH deficiency; HyperPRL: hyperprolactinemia; M: male; DI: diabetes insipidus.

parameter for the diagnosis of adrenal insufficiency (23, 24); c) secondary hypothyroidism was demonstrated by low free T_4 (FT_4) (<8 ng/l) concentrations with normal or low normal TSH levels (21-23); d) secondary hypogonadism was demonstrated by: i) in pre-menopausal women by menstrual disturbances, low estradiol levels (<20 pg/ml) with normal or low FSH and LH levels; ii) in men by low testosterone levels (<3 µg/l) with low or normal FSH and LH levels (22-24). GHD was demonstrated by peak GH response to GHRH+arginine (ARG) <16.5 µg/l (3rd centile limit of normal GH response). Peak GH response <9.0 µg/l (1st centile limit) indicated severe GHD; the latter cut-off represents the limit below which severe GHD is demonstrated by the GHRH+ARG test that is a provocative test approximately 3 times more potent than the insulin tolerance test (ITT) (25). That the diagnostic accuracy of GHRH+ARG test with a cut-off of 9 µg/l is the same one of ITT with a cut-off of 3 µg/l has been already demonstrated (26). IGF-I levels were considered in comparison to the 25th centile age-related normal limits (27). It is widely accepted that normal IGF-I levels do not rule out severe GHD, although low levels strongly suggest the presence of GHD. As the concordance between GH peak after provocative test and IGF-I levels markedly increases by adopting the 25th centile of normal IGF-I limits (27, 28), in the present study IGF-I levels below this arbitrary cut-off were considered.

The results are expressed as mean±SEM and as percentage of abnormal response compared to normative cut-off levels. The statistical analysis was carried out using SPSS Inc. (Cary, NC) package. The correlation between variables was sought calculating the Pearson coefficient. The risk of developing hypopituitarism was calculated by logistic regression analysis. The percentages were compared using chi square test, with Fisher correction when appropriate. A two-tailed *p* value less than 0.05 was taken as showing statistical significance.

Ethics

The study was performed as part of the standard neuroendocrine evaluation for patients who experienced TBI. However a written informed consent on the purpose and background of the study was provided by patients and their parents (for patients <18 yr).

RESULTS (Table 2)

At 3 months, hypopituitarism was shown in 34.6%. Total, multiple and isolated deficits were present in 8.6, 4.3 and 21.7%, respectively. DI was present in

8.6% patients and mild hyperprolactinemia in 4.3% patients. Secondary adrenal, thyroid and gonadal deficits were present in 13.0, 8.6 and 13.0%, respectively. Specifically, 13% patients had secondary adrenal insufficiency, 8.6% patients had secondary hypothyroidism and 13% patients had secondary hypogonadism (1 woman and 2 men; always associated with other pituitary deficits). Severe GHD (peak GH <1st centile i.e. < 9 µg/l) was recorded in 26% patients (isolated in 4 and associated with other deficits in 2). Another 4.3% had GH peak in between the 1st and the 3rd centile limit; this subnormal GH response to a provocative test as potent as GHRH+ARG could be assumed as partial GHD (pGHD). IGF-I levels <25th centile of the age-related normal limits were present in 21.7% of patients always associated with severe GHD.

The 12-month retesting showed hypopituitarism in 30.3% of the patients. Total, multiple and isolated deficits were present in 8.6, 4.3 and 17.4%, respectively. DI was present in 4.3% patients and mild hyperprolactinemia in 4.3%. Secondary adrenal, thyroid and gonadal deficit was present in 13.0, 8.6 and 13.0%, respectively. Specifically, 13% of patients had secondary adrenal insufficiency, 8.6% of patients had secondary hypothyroidism and 17.3% of patients had secondary hypogonadism (3 women and 1 man), in 3/4 associated with other pituitary deficits. Severe GHD was recorded in 21.7% of patients (isolated in 2 and associated with other deficits in 3). Another 8.6% of patients had GH peak in between the 1st and the 3rd centile limit (pGHD). IGF-I levels <25th centile of the age-related normal limits were present in 17.3% of patients, always associated with severe GHD.

Total hypopituitarism at 3 months was confirmed at 12 months retesting. Multiple and isolated hypopituitarism evaluated at 3 months were confirmed in 0/1 and 2/5 patients, respectively. On the other hand, 2/23 patients whose pituitary function was normal at 3 months showed isolated hypopituitarism (for secondary adrenal and gonadal insufficiency) at 12 months, while 1 patient with isolated hypopituitarism developed multiple hypopituitarism at 12-month retesting (Fig. 1).

The occurrence of hypopituitarism and the GH response to the provocative test were not correlated with the GCS both at 3 and 12-month follow-up.

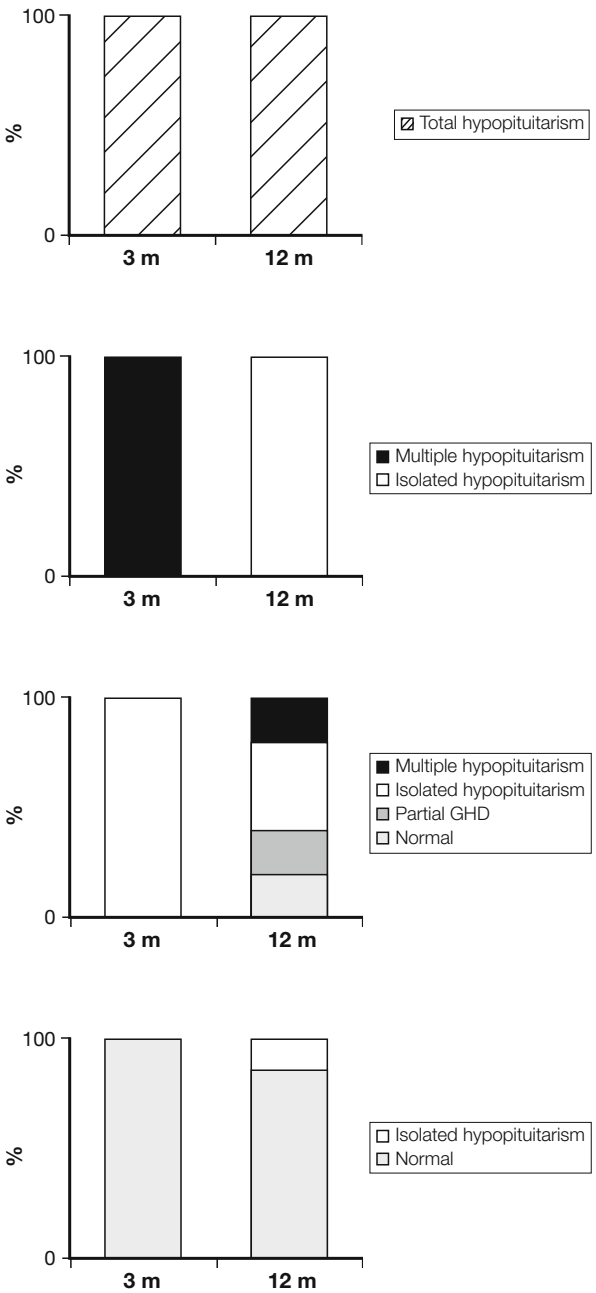

Fig. 1 - *Changes in pituitary function at 12 vs 3-month-testing after traumatic brain injury in the transition phase. BMI: body mass index; GHD: GH deficiency.*

DISCUSSION

This prospective study demonstrates that the high risk for TBI-induced hypopituitarism is also present in the transition age, i.e. adolescence. As previously demonstrated in adult populations (12), the early diagnosis of total hypopituitarism is always confirmed in the long-term after the brain injury, representing about 8.6% of patients. On the other hand, it is also shown that pituitary function after TBI may improve or worsen over time but collectively multiple or isolated pituitary deficits are recorded in a further

21.7% of patients at 12 months after the TBI. GHD and secondary hypogonadism are the most frequent pituitary deficits.

That brain injuries in general, and head trauma (TBI) in particular, are very often the cause of hypopituitarism has been well established (1-13). In the above mentioned papers, the percentage of patients with acquired hypopituitarism after TBI varied between 20 and 60%. Given the high incidence of TBI (14, 15), this evidence therefore indicates a relevant problem in clinical endocrinology. Moreover, the peak of TBI incidence is in the younger ages (15-30 yr) (15). The demonstration of frequent post-traumatic hypothalamus-pituitary lesions well explain the high incidence of hypopituitarism and also the possibility that neuroendocrine abnormalities after brain injury would further progress or, alternatively, would be transient allowing recovery of pituitary function over time (12).

In agreement with our previous study in adults (11, 12), the present results in the transition age show that no more than 60% of subjects display fully normal pituitary function 1 yr after TBI. In another 8-10%, it is likely to be normal although there is slight impairment of somatotroph function (partial GHD) due to significant reduction of the GH response to the GHRH+ARG test.

On the other hand, after TBI, 15% of patients in the transition age show total and multiple hypopituitarism. Moreover, in a further 17% different isolated deficits have been recorded. In all, 30-34% of patients have some degree of pituitary impairment.

Unlike the previous study in the adult population (12), the follow-up at 12 months after TBI demonstrated a substantial stability of the pituitary alterations or normal pituitary function in the transition age. Total and multiple hypopituitarism were always confirmed at retesting while some trend toward decrease was recorded with regard to isolated hypopituitarism (from 21.7 to 17.4%). It seems therefore that multiple pituitary deficits achieved after TBI remain quite stable over time, probably reflecting some irreversible damage of the hypothalamus-pituitary unit (17-19). This finding has, however, to be confirmed by more prolonged follow-up studies. These findings support the need for neuroendocrine evaluations both in the first months after the TBI (i.e. 3-6 months) and a retesting of the pituitary function later on (i.e. 12 months after). As a matter of fact, a single pituitary function-testing only 1 yr after TBI could save money and time, but it could misdiagnose patients with severe forms of hypopituitarism (i.e. patients with multiple or total acquired hypopituitarism).

In the transition age like in adulthood (11, 12), it is herein confirmed that severe GHD is the most common brain injury-induced pituitary deficit either isolated or associated with other pituitary deficits at 12 as well as at 3 months after TBI. It is well known that GH has multiple beneficial effects in addition to its promotion of linear growth and in particular in the transition phase. These include maintenance of normal body composition, structure function and metabolism through adult life. Therefore, the onset of a TBI-induced GHD in this particular phase of life could be of particular importance for the adult health consequences. The second most frequent pituitary deficit following brain injury is secondary hypogonadism, though considerable percentages of patients with secondary hypoadrenalism and hypothyroidism are present (8, 9, 11, 12, 20). Regarding the diagnosis of secondary adrenal insufficiency, the evaluation of the adrenal reserve by dynamic test would increase its reliability. Dimopoulos et al. (29, 30) have already showed that secondary adrenal insufficiency after TBI is more appropriately diagnosed by ACTH test.

This picture clearly represents a warning for pediatric endocrinologists to pay attention to this clinical problem planning continuous follow-up of pituitary function in brain injured patients.

Moreover, it should also be taken into account that a definite picture of pituitary function just after TBI is not available yet. How many and to what extent pituitary functions can be impaired in the acute phase following a brain injury like TBI and how much of a role this impairment has in the probabilities of survival and recovery are questions awaiting answers. This clearly applies also to childhood and adolescence.

In conclusion, the results of this study show the high risk of TBI-induced acquired hypopituitarism in the transition age as well as in adulthood. Thus it is recommended that pediatric endocrinologists follow up pituitary function of children and adolescents after brain injuries.

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REFERENCES

1. 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 (Oxf) 2005, 62: 525-32.
2. Dimopoulou I, Tsagarakis S, Theodorakopoulou M, et al. Endocrine abnormalities in critical care patients with moderate-to-severe head trauma: incidence, pattern

and predisposing factors. Intensive Care Med 2004, 30: 1051-6.

3. Benvenga S, Campenni A, Ruggeri RM, Trimarchi F. Hypopituitarism secondary to head trauma. J Clin Endocrinol Metab 2000, 85: 1353-61.
4. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C. Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 2000, 93: 743-52.
5. Lieberman SA, Oberoi AL, Gilkison CR, Masel BE, Urban RJ. Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J Clin Endocrinol Metab 2001, 86: 2752-6
6. Casanueva FF, Ghigo E, Popovic V. Hypopituitarism following traumatic brain injury (TBI): a guideline decalogue. Athens TBI and Hypopituitarism Study Group. J Endocrinol Invest 2004, 27: 793-5.
7. Popovic V, Aimaretti G, Casanueva FF, Ghigo E. Hypopituitarism following traumatic brain injury. Growth Horm IGF Res 2005, 15: 177-84.
8. Agha A, Rogers B, Mylotte D, et al. Neuroendocrine dysfunction in the acute phase of traumatic brain injury. Clin Endocrinol (Oxf) 2004, 60: 584-91.
9. Agha A, Rogers B, Sherlock M, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 2004, 89: 4929-36.
10. Bondanelli M, De Marinis L, Ambrosio MR, et al. Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 2004, 21: 685-96.
11. 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.
12. Aimaretti G, Ambrosio MR, Di Somma C, et al. Prospective study about brain injury-induced hypopituitarism over 12 month follow-up. J Clin Endocrinol Metab 2005, provisionally accepted.
13. Ghigo E, Masel B, Aimaretti G, et al. Consensus guidelines on screening for hypopituitarism following traumatic brain injury. on behalf of participants in the hypopituitarism following traumatic brain injury consensus workshop. Brain Inj 2005, 19: 711-24.
14. Agency for Health Care Policy and Research. Rehabilitation for traumatic brain injury, Summary, Evidence Report/ technology Assessment. AHRQ Publications, Silver Spring, MD, 1998.
15. Servadei F, Verlicchi A, Soldano F, Zanotti B, Piffer S. Descriptive epidemiology of head injury in Romagna and Trentino. Comparison between two geographically different Italian regions. Neuroepidemiology 2002, 21: 297-304.
16. Casanueva FF, Leal A, Koltowska-Haggstrom M, Jonsson P, Goth MI. Traumatic brain injury as a relevant cause of growth hormone deficiency in adults: A KIMS-based study. Arch Phys Med Rehabil 2005, 86: 463-8.
17. Daniel PM, Prichard MML, Triep CS. Traumatic infarction of the anterior lobe of the pituitary gland. Lancet 1959, 2: 927-30.
18. Kornblum RN, Fisher RS. Pituitary lesions in craniocerebral injuries. Arch Pathol 1969, 88: 242-8.
19. Crompton MR. Hypothalamic lesions following closed head injury. Brain 1971, 94: 165-72.
20. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M; European Society of Paediatric Endocrinology. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol 2005, 152: 165-70
21. Goetz C, Pappert E. In: Goetz C, Pappert E eds. Textbook of Clinical neurology. Orlando: Saunders. 1999.
22. Thorner MO, Vance ML, Laws Jr ER, Horvath E, Kovacs K. The Anterior pituitary. In: Wilson JD, Foster DW, Kronenberg HM, Reed Larsen P eds. Williams Textbook of Endocrinology. 9th ed. Philadelphia: WB Saunders Company. 1998, 165-211.
23. Faglia G. Clinical aspects of the pituitary gland. In: Pinchera A ed. Endocrinology and Metabolism. London: McGraw-Hill International. 2001, 73-89.
24. Lamberts SW, de Herder WW, van der Lely AJ. Pituitary insufficiency. Lancet 1998, 11, 352: 127-34.
25. Ghigo E, Aimaretti G, Arvat E, Camanni F. Growth hormone-releasing hormone combined with arginine or growth hormone secretagogues for the diagnosis of growth hormone deficiency in adults. Endocrine 2001, 15: 29-38.
26. Aimaretti G, Corneli G, Razzore P, et al. Comparison between insulin-induced hypoglycemia and growth hormone (GH)-releasing hormone + arginine as provocative tests for the diagnosis of GH deficiency in adults. J Clin Endocrinol Metab 1998, 83: 1615-8.
27. Aimaretti G, Corneli G, Baldelli R, et al. Diagnostic reliability of a single IGF-I measurement in 237 adults with total anterior hypopituitarism and severe GH deficiency. Clin Endocrinol (Oxf) 2003, 59: 56-61.
28. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? J Clin Endocrinol Metab 2002, 87: 477-85.
29. Dimopoulou I, Tsagarakis S, Douka E, et al. The low-dose corticotropin stimulation test in acute traumatic and non-traumatic brain injury: incidence of hypo-responsiveness and relationship to outcome. Intensive Care Med 2004, 30: 1216-9.
30. Dimopoulou I, Tsagarakis S, Theodorakopoulou M,et al. Endocrine abnormalities in critical care patients with moderate-to-severe head trauma: incidence, pattern and predisposing factors. Intensive Care Med 2004, 30:1051-7.