

Primary empty sella and GH deficiency: prevalence and clinical implications

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Summary. Primary empty sella (PES) is a particular anatomical condition characterized by the herniation of liquor within the sella turcica. The pathogenesis of this alteration, frequently observed in general population, is not yet completely understood. Recently reports demonstrated, in these patients, that hormonal pituitary dysfunctions, specially growth hormone (GH)/insulin-like growth factor (IGF-I) axis ones, could be relevant. The aim of this paper is to evaluate GH/IGF-I axis in a group of adult patients affected by PES and to verify its clinical relevance. We studied a population of 28 patients with a diagnosis of PES. In each patient we performed a basal study of thyroid, adrenal and gonadal – pituitary axis and a dynamic evaluation of GH/IGF-I after GH-releasing hormone (GHRH) plus arginine stimulation test. To evaluate the clinical significance of GH/IGF-I axis dysfunction we performed a metabolic and bone status evaluation in every patients. We found the presence of GH deficit in 11 patients (39.2 %). The group that displayed a GH/IGF-I axis dysfunction showed an impairment in metabolic profile and bone densitometry. This study confirms the necessity to screen the pituitary function in patients affected by PES and above all GH/IGF-I axis. Moreover the presence of GH deficiency could be clinically significant.

Key words: primary empty sella syndrome, growth hormone, osteoporosis.

Riassunto (*Sella vuota primaria (PES) e deficit di ormone della crescita (GH): prevalenza e impatto clinico*). La sella vuota primaria (PES) è una particolare condizione anatomica caratterizzata dalla presenza di liquor all'interno della sella turcica. La patogenesi di questa alterazione, osservata frequentemente nella popolazione generale, non è ancora completamente chiarita. Recenti lavori hanno dimostrato che le alterazioni ormonali ipofisarie, soprattutto a carico dell'asse ormone della crescita (GH)/fattori di crescita insulino-simili (IGF-I), potrebbero essere frequenti e clinicamente rilevanti in questi pazienti. Obiettivo di questo studio è stato valutare l'integrità dell'asse GH/IGF-I in un gruppo di pazienti affetti da PES e verificare le implicazioni cliniche di un eventuale deficit secretorio. Abbiamo esaminato un campione di 28 pazienti affetti da PES. Ognuno di questi è stato sottoposto ad uno studio basale della funzionalità tiroidea, surrenalica, gonadica e ipofisaria e ad una valutazione dinamica dell'asse GH/IGF-1 dopo test da stimolo con GH-releasing hormone (GHRH) + arginina. Per verificare l'impatto clinico dell'eventuale deficit di GH abbiamo effettuato un attento esame dei parametri metabolici ed ossei. Il deficit di GH è stato riscontrato in 11 pazienti (39.2 %) i quali mostravano, rispetto ai normosecretori, valori peggiori sia a carico dei parametri metabolici che della densitometria ossea. Questo lavoro conferma, quindi, la necessità di valutare la funzionalità ipofisaria nei pazienti affetti da PES ponendo particolare attenzione allo studio dell'asse GH/IGF-1, la cui alterazione potrebbe avere un significativo impatto clinico.

Parole chiave: sindrome della sella vuota primaria, ormone della crescita, osteoporosi.

INTRODUCTION

The empty sella (ES) is an anatomical condition characterized by the presence of cerebrospinal fluid within the sella with a small pituitary gland compressed above the pituitary floor. This condition is defined primary (PES) when the patient had no history of pathological processes or previous pituitary surgery, radiotherapy or apoplexy. In 1951 Busch

[1] first described this condition in a series of 788 autopsies of consecutive patients without known pituitary diseases. In the past ES is currently reported in the 6-20% of radiological and autoptical examination. The incidental finding of this condition has always been seen as simple anatomical variant without great functional significance, especially in adults [2]. The frequency of this disease was most

commonly seen in multiparous women with obesity and hypertension [2, 3]. Sometimes it could be seen mild hyperprolactinemia, specially in women. The etiology of PES is not fully understood and is frequently correlated, in the previous reports, with vascular, autoimmune or genetic processes [3-7]. The recent widespread use of computed tomography (CT) and magnetic resonance imaging (MRI) technique has made the finding of this condition a very frequent event. Furthermore, the recent evidence, in a few reports on these kind of patients, of a significant impairment of pituitary functions [8, 9], specially GH/IGF-I axis [10,11], allows us the reason to verify this condition. In fact, the great importance of GH/IGF-I axis on cardiovascular, bone and general well-being status enforce us to study this aspect in these kind of patients [12-14]. Our aim was to investigate the prevalence of GH deficiency in this condition and ascertain the impact on some parameters of a great clinical significance. To verify these aspects we studied if the patients, eventually affected by the hormonal dysfunction, showed a worse metabolic and bone profile, like in GH deficient patients of any other etiology.

MATERIALS AND METHODS

We studied a population of 28 patients with PES (24 females, 4 males). In 5 out of 28 patients (18%) a previous diagnosis of hypothyroidism was established and these patients were on stable replacement therapy with levo-tiroxina (mean dose 100 mcg/die). Moreover, two patients, affected by hypocortisolism, received a replacement therapy with cortisone acetate since the diagnosis was established. The other patients didn't take any drugs.

In every patients we performed a fully anamnestic and physical examination to emphasize signs and symptoms susceptible of hypopituitarism. In every patients, following a 10-h overnight fast, blood samples were obtained for serum IGF-I, fT3, fT4, TSH, LH, FSH, testosterone (estradiol in fertile females during follicular phase), PRL, ACTH and cortisol. All subjects underwent intravenous GHRH and arginine stimulation test in the morning between 08.30 and 9.00 to assess the status of GH/IGF-I axis. An indwelling catheter was inserted into a cubital vein and blood was sampled at the time of catheter insertion (0 min). GHRH (Geref diagnostic, Serono) 1 µg/kg was administered by IV bolus along with a 30-min IV infusion of arginine hydrochloride (0.5 g/kg, maximum dose 30 g). Blood samples for GH level were collected at 0, 30, 45, 60 and 90 min after GHRH administration.

The metabolic evaluations were performed with blood samples for glycaemia, total and fractioned cholesterol and triglycerides. To assess the bone status we conducted a mineralometric evaluation by DEXA at femoral and lumbar sites.

A control group of ten patients (5 males, 5 females), matched for general characteristics, that dis-

played an euthyroid nodular disease and referred to our unit, acted as control.

Written informed consent was obtained from all subjects.

Biochemical assays and instrumental examinations

GH serum concentrations were measured by a two-site chemiluminescent immunoassay (Immunolite 2000; DPC, Diagnostic Products Corporation, Los Angeles, CA). The limit of detection was 0.01 µg/L, with intra and interassay variation coefficients of 3.5% and 6.5%, respectively. Severe GH deficiency was defined, in accordance with literature data [9], as a GH peak lower than 11.0 ng/ml for BMI < 25 kg/m², and lower than 8.0 ng/ml for BMI > 25 kg/m². IGF-I serum concentrations were determined by a two-site chemiluminescent immunoassay (DPC, Diagnostic Products Corporation, Los Angeles, CA) after acid-ethanol extraction. The sensitivity of the method was 20 µg/L. The intra and interassay coefficients of variation assay were 3.9% and 7.7%, respectively, in the concentration range of 65- 825 µg/L. IGF-I value was considered reduced if it results below the lower value of the 95% confidence interval for age and sex. The other hormonal determinations were performed by commercially available automated chemiluminescence immunoassay systems. The intra and interassay coefficients of variation for all methods were less than 5.8% and less than 7.8%, respectively.

The normal ranges for the other assays were: ACTH, 1.5-11.5 pmol/L; TSH, 0.4-4.2 mIU/L; free T4, 0.71-1.85 ng/dL; free T3, 1.45- 3.48 pg/mL; Estradiol, 20-245 pg/mL; Testosterone, 2.8-8.0 ng/dL; LH, 1.0-18.0 mIU/mL; FSH, 4.0-13.0 mIU/mL; PRL, 1.6-18.8 ng/mL in males and 1.4-24.2 ng/mL in women; Cortisol, 138-690 nmol/L.

Glycaemia, total and fractionated cholesterol and triglycerides levels were determined by standard methods.

All the patients were analyzed with MRI to confirm the diagnosis of ES. The bone mineral density was assessed by Dual-energy X-ray absorptiometry (DEXA) using a Hologic QDR 2000 Plus densitometer (Hologic Inc., Walthorn, MA). In every patients we measured both lumbar (L1-L4) and proximal femur BMD. BMD values are presented as T-score, which express the comparison of a patient's BMD to adult reference values, representing, the number of SD, a BMD measurement is above or below the mean bone mass of a young normal population matched for sex and age.

Statistical analysis

The results are presented as mean ± standard deviation (SD) unless otherwise specified.

The statistical analysis was performed utilizing the GraphPad Software (San Diego, USA). The differences between the groups of sample examined, were evaluated using unpaired t test, confirmed by Mann-Whitney test. The correlation of the degree of asso-

Table 1 | Clinical and biochemical characteristics of the study population and mean hormonal values

	Entire group	Reference range
Total number	28	—
Age	55 ± 11	—
Male / female	4 ± 24	—
BMI	27.7 ± 4.9	19.5-24.5 kg/m ²
Glycemia	93 ± 18.5	70-110 mg/dL
Total cholesterol	200 ± 42	120-220 mg/dL
LDL cholesterol	129 ± 37	< 160 mg/dL
HDL cholesterol	51 ± 15	35-80 mg/dL
Triglycerides	124 ± 43	50-180 mg/dL
ft3	2.49 ± 0.65	2.5-3.9 pg/mL
ft4	1.1 ± 0.78	0.6-1.15 ng/mL
TSH	2.03 ± 1.54	0.34-5.6 µIU/mL
Cortisol	250 ± 160	138-690 nmol/L
ACTH	17.8 ± 9.71	0-46 pg/mL
PRL	18.7 ± 18.9	M < 18 ng/mL; F < 24 ng/ml
GH (basal)	0.75 ± 1.08	0.06-5 ng/mL
GH (peak)	14.1 ± 13.91	> 16 ng/mL
IGF-I	140.8 ± 89.47	Specific age-gender limits

ciation for the other two parameters was determined using the Pearson's r correlation test, validated by the Spearman's rank and Kendal tau correlation tests. Values of p less than 0.05 were considered significant.

RESULTS

The clinical and biochemical characteristics of the entire population are illustrated in *Table 1*. The mean age of the entire population was 55 ± 11 years. Mean body mass index (BMI) of the studied population was 27.7 ± 4.9 Kg/m². None of patients was evaluated, previously, for GHD. The reason for radiological evaluation was: headache (30%), oligomenorrhea (27%), fatigue and mood depression (18%), ophthalmological symptoms like worse of visual acuity and diplopia (15%) and previous traumatic brain injury (10%). All the MRI scans showed a radiological finding of total PES (more than 50% of the sella filled with CSF; pituitary height ≤ 2 mm).

Table 2 | Mean GH peak value, during the test, in GHD vs no GHD

	GHD	no GHD	P value
GH basal	0.2 ± 0.2	1.05 ± 1.3	n.s.
Gh peak	3.6 ± 3.3	21 ± 14	0.0034
IGF-I	107.3 ± 85.7	162.2 ± 20.7	0.1213

Baseline endocrine evaluations proved normal values in all patients except in 4 (14.2%) where a slight hyperprolactinemia was observed (*Table 1*).

The dynamic evaluation, performed by GHRH plus Arginine stimulation test, revealed an impairment of GH response in 11 (8 females and 3 males) out of 28 (39.28%) (*Table 2*).

These patients compared with normo responsive group, showed non significant lower basal GH levels (0.285 ± 0.204 vs. 1.05 ± 1.3) while GH peak after stimulus was significant different (3.6 ± 3.3 vs 21 ± 14, p = 0.0034).

This subgroup of patients also showed lower levels of IGF-I (107.3 ± 85.7 vs 162.2 ± 20.7) but without significant statistical difference (p = 0.12).

Regarding the metabolic parameters we found a worse profile in GHD vs no GHD, specially for total cholesterol and triglycerides, where the differences were statistical significant (*Table 3*). Lastly the evaluation of bone mineral density, performed by DEXA, showed a worse mineral content in patients in which GH impairment was established vs the normo responsive ones, especially in the femoral site (T score lumbar site: - 0.8 ± 1.1 vs - 0.4 ± 0.8 p = 0.32; T score femoral site: - 1.4 ± 0.6 vs - 0.2 ± 0.8 p = 0.001).

Every patient belonging to the control group (ten patients at all, 5 females and 5 males) showed normal baseline endocrine evaluation and a normal GH peak during the stimulation test. The metabolic parameters and the mineral content were within the reference range for normal population.

DISCUSSION

In our study we found that the presence of GH deficiency is not a rare event in adult patients affected by primary empty sella. This condition is always seen, in the past, as a simple anatomical variant with poor clinical significance. In the older reports only hyperprolactinemia was underlined and hypopituitarism was seldom reported in symptomatic patients. The etiology of this condition is not fully understood. Some authors have focalized their attention on autoimmune diseases like lymphocytic hypophysitis [4-6] while the largest series reported in literature [11] failed to find a clear association with autoimmune disorders. Because of the clear association with sex female, some authors try to correlate

Table 3 | Metabolic and bone parameters GHD vs no GHD

	GHD	no GHD	P value
Glycemia	93 ± 24	92.7 ± 14	n.s.
Total cholesterol	216.5 ± 24	189 ± 38	p = 0.03
LDL cholesterol	142.6 ± 36.15	119 ± 34	n.s.
Triglycerides	152.3 ± 48	104 ± 31	p = 0.0021
Lumbar site T score	- 0.8 ± 1.1	- 0.4 ± 0.8	n.s.
Femoral site T score	- 1.4 ± 0.6	- 0.2 ± 0.8	p = 0.0013

pregnancy, during which pituitary volume could double, with the onset of the disease, especially in case of multiple pregnancies. Obesity is frequently present and it is believed responsible to induce hypercapnia that can be the cause of chronic CSF pressure elevation. This one may lead, in subjects with predisposing anatomical factors like a hypoplastic diaphragm sellae, to the intrasellar herniation of the suprasellar subarachnoid space [9]. All these features and some recent reports, that show how hypopituitarism could be present and serious, allow us to verify this aspect. Some reports, indeed, underline that the development of hypopituitarism often goes unrecognized and that the diagnosis could be delayed. In a series of patients analyzed few years ago, the authors showed how the 20% of patients with severe normovolemic hyponatremia displayed an unrecognized hypopituitarism, mostly due to empty sella [15]. Other few reports, more recently, found relevant pituitary function impairment in patients with a diagnosis of PES [8, 16, 17]. GHD seems to be the most frequent deficiency related to PES, showing a prevalence from 30 to 60%. About 6% of the patients is affected by hypogonadism whereas ACTH or THS deficiency are uncommon (1%) [8]. Moreover the importance of the unrecognized presence of an empty sella, with the onset of hypocortisolism related to ACTH deficiency, is showed in another recent case report in which, the presence of this condition has caused a profound cardiovascular distress in a patient underwent surgery for cardiovascular disease [18] and in another review that showed how a shade off complex symptomatology, complaints of weakness, fatigue, weight loss, nausea and vomiting, was related to a ACTH deficiency due to the presence of a PES [19, 31]. More recently some authors confirmed the clinical importance of a undiscovered PES [20]. Besides these, our attention is focalized on the relevant presence, in this kind of patients, of some clinical aspects that are typical of metabolic syndrome. We know, from some years ago, how the GH deficiency syndrome itself could be seen as a particular metabolic syndrome and the Endocrine Society states a precise and defined space for GH deficiency's diagnosis and treatment [21, 22]. It is clearly defined, indeed, how patients suffering by these pituitary dysfunction showed a worse metabolic and cardiovascular profile [23-25] and that these alterations are strictly related to the severity of the dysfunction [26]. Furthermore the bone quality is also related to the GH/IGF-I pattern [27]. In fact these two molecules are critical in achievement and maintenances of bone mass. GH may act either directly on skeletal cells or through IGF-I, that could be synthesized by liver or by peripheral tissues. Osteoblast cell differentiation is greatly modulated by GH. Also IGF-I increases bone remodelling and regulates the function of the osteoblast. All these aspects become particularly significant if we keep in mind how our population is older than the past and how important is the im-

port of cardiovascular diseases and bone fractures on social cost and on health policy. Our work underlines, once again, how GH/IGF-I axis impairment is frequent in these kind of subjects. We investigated the GH/IGF-I axis by GHRH plus Arginin test. In fact, although the gold standard procedure to diagnose a state of GHD is represented by insulin tolerance test (ITT), it's burdened by some technical and clinical aspects (greater numbers of blood samples, necessity of a continue monitoring of glycaemia and vital functions of the patient both during and after the test, high risk of severe hypoglycaemic crisis). Considering these aspects, we preferred GHRH plus Arginin test that is nowadays recognised as an adequate alternative tool due to the better profile of safety and tolerability. Moreover for this test clear BMI-related cut off limits has been established [22].

It is worthy of note how our population does not showed a significant clinical symptomatology, but only unspecific signs. The reasons that lead us to the discovery of PES were, in the mostly of cases, headache and menstrual disturbances. Mean BMI of the entire population was 27.7 ± 4.9 kg/m², like previous report [11] and not very far from the one in average population in western country. Furthermore, we would clearly underline the clinical implications of our work. In fact, not only we reported a significant impairment of GH/IGF-I axis but also its strongly clinical impact. The correlation of GH deficit with serum markers, like cholesterol and triglycerides, showed once again that patients with GH impairment could be more susceptible to suffer from cardiovascular accidents. To our knowledge this is the first work, in literature, that states these aspects in PES. The association of GHD to a more presence of overweight, in our population, do not alter the significance of the data. We keep in consideration, in the analysis of the dynamic evaluation, the recommended BMI-related cut off limits [22]. Regarding the study of bone status we show how the presence of GH deficiency is related to a worse densitometric data, at femoral site specially. The bone status evaluation, in patients affected by PES and its correlation with GH/IGF-I axis, described by our work, is the first present in literature, too.

Lastly many patients referred, as initial tool for investigation, depression and fatigue. These are other aspects that are present in GH deficiency syndrome [28, 29] and that could be improved by replacement therapy [30]. We think that our work is very important for two reasons: the first is that we confirm, like others recently reported, the presence of GHD in these kind of patients; the second one is that we prove, for the first time in patients with a diagnosis of PES, how this functional impairment has a great clinical impact, both on bone and on metabolic parameters.

Obviously more reports are needed with a more numerous population to confirm these data. Further randomized clinical trials are needed to evaluate the impact of replacement therapy on bone and metabolic diseases, in this particularly kind of patients.

CONCLUSIONS

Keeping in mind how important is the prevalence of this anatomical condition (PES) in general population and how relevant is its impact on cardiovascular and bone diseases, in term of mortality, morbidity and health social costs, it is mandatory to give a strong message to all the medical subspecialties that could be run with this condition. We think, particularly, to neurologists, internal medicine specialists, general practioners and radiologists too. Anyone of them has to alert the patient, in case of incidental findings, on the necessity of a careful endocrine

evaluation. This consultation will be strongly recommended, particularly, in those patients suffering from or with a history of metabolic features, bone diseases or impaired sense of well being.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 22 August 2011.

Accepted on 4 January 2012.

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