High frequency of empty sella, with gender differences, in the early neuroradiology evaluation of patients with traumatic brain injury. A prospective study

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ABSTRACT

One-hundred four persons aged ≥18 years (62 males and 42 females) who were admitted for traumatic brain injury (TBI) underwent brain computed tomography (CT) scan and assay of serum cortisol, insulin-like growth factor 1 (IGF-1), thyrotropin (TSH) and free thyroxine (FT4). The main purpose was to assess any gender difference and the rate of empty sella (ES).

Women were more likely to have empty sella (19/42 [45.2%] vs 19/62 [30.6%], P = 0.15, OR = 1.9), which was more frequently total ES or TES (16/19 [84.2%] vs 3/19 [15.8%], P = 0.0025, OR = 11.6). Neuroradiology was normal in the remaining 65 patients. Patients with TES were approximately 20–30 years older than both patients with partial ES (PES) and normal sella, but only the comparison with normal sella was significant (P = 0.001 all patients, P = 0.005 males). Presumed deficiency of IGF-1, cortisol or TSH occurred in 33 persons (31.7%; 20 Males [32.2%], 13 Females [30.9%]), 14 (13.5%; 10 M [16.2%], 4F [9.5%]) or 8 (7.7%; 1 M [1.7%], 7F [16.7%]), with only TSH deficiency having significant intergender difference (P = 0.007). The highest or lowest rates of IGF-1 deficiency occurred in men with PES (41.7%) or men with TES (14.3%), of cortisol deficiency in men with PES (33.3%) or women with PES (zero), and TSH deficiency in women with TES (18.7%) or both men and women with PES (zero) and men with normal sella (zero). Within ES, males with no deficiency were older compared to males with at least one hormone deficiency (75.7 ± 17.4 vs 55.6 ± 18.9, P = 0.022); in turn, the former males were also older compared with normal sella males having no hormone deficiency (54.1 ± 25.2, P = 0.023).

In conclusion, ES is detectable in almost 40% of persons who undergo CT within 24 h from TBI. A number of intergender differences concerning ES and the hormones evaluated are apparent.

Introduction

Several retrospective studies, prospective studies and reviews on traumatic brain injury (TBI)-induced hypopituitarism [1–11] are available in the literature.

The generality of studies on TBI have focused on the endocrine side, especially comparing the evolution over time of hormone changes, with minimal or absent attention to the neuroradiology of the hypothalamic-pituitary region in the early phase of TBI as well as to possible gender differences. Particularly, a few studies focused on post-traumatic empty sella that is the herniation of the subarachnoid space within the sella turcica, resulting in flattening of the pituitary [4,12].

A Czech prospective study evaluated 89 TBI patients (women, n = 23) aged 18–65 years (mean 36 years) with a Glasgow Coma Scale (GCS) score ranging from 3 to 14 (median score 7). Patients underwent hormone evaluation at the time of injury and at 3, 6, and 12 months post-injury. Magnetic resonance imaging (MRI), which was also performed at 12 months post-injury, demonstrated an empty sella

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syndrome more frequently in patients with some hormone deficiency compared with those without endocrine dysfunction [12]. One German study examined the independent association of gender and age with injury severity (measured by the GCS), clinical course, pituitary dysfunction and outcome after TBI as measured by the Glasgow Outcome Scale. Age, but not gender, influenced the GCS. Logistic regression revealed an effect only of age and the initial injury severity on the Glasgow Outcome Scale. Gender affected instead the rate of pituitary insufficiency [13]. A Dutch group studied 630 women (53 with TBI) and 533 men (63 with TBI) [14]. Linear regression analysis (adjusted for age, body mass index, chronic diseases, smoking, alcohol use, and gender) was performed to examine the association between TBI and serum anterior pituitary hormone levels and bone mineral density measured by dual-energy x-ray absorptiometry and quantitative ultrasound. Serum follicle stimulating hormone (FSH) was significantly higher in males who had had head trauma compared with those who had not had it. In a study on 51 patients (mean age 36.1 years; 46 men) who were evaluated at least one year after TBI, pituitary hormone deficits were reported to be particularly common and capable of adversely affecting activities of daily living reducing quality of life. There was no gender difference in the rate of growth hormone (GH) deficiency [15]. In an American study, 18 patients with TBI and 16 subjects with subarachnoid hemorrhage underwent pituitary hormone evaluations 5–12 months following TBI [16]. In this series of subjects, the type of event (traumatic or hemorrhagic) and gender did not influence the prevalence of hypopituitarism. In addition, TSH and GH deficiencies were associated with reduced performance-function [16].

We have realized that, in the context of limitations in the requests for biochemical and instrumental investigations imposed by the Italian Ministry of Health to ensure savings for the national health system, the overwhelming majority of patients admitted to the Emergency Units for head trauma are unwilling to monitor hormone levels over time to detect post-head trauma hypopituitarism (Pht-Hypo). However, when we probed our patients after discharge from the Emergency Unit of University Hospital of Messina and informed them of the risk of Pht-Hypo occurring even many years after head trauma, there was a high rate of willingness to pay out of their pocket for hormone assays, if neuroradiology evaluation in the Emergency Unit showed abnormalities in the hypothalamic-pituitary region. The existence of any such abnormality would have increased the risk of hypopituitarism and made endocrine screening cost-effective.

With this in mind, we started recommending to our neuroradiologists not to miss the study of the sellar region during the brain imaging by CT, brain CT being a routine procedure for patients admitted at our Emergency Unit for head trauma. Based on very pilot initial observations that showed an unsuspected high proportion of empty sella in men, we elected to perform the prospective study reported here.

The aims of this prospective study were (i) to assess the frequency of empty sella in the acute phase of trauma by minimizing enrollment of patients with other causes of empty sella; (ii) to detect possible gender differences in empty sella frequency; (iii) to correlate empty sella with baseline endocrine evaluation.

Materials and methods

Patients

During the 12 months from January 01 to December 31, 2016, we enrolled 104 consecutive patients aged 18 or more years.

Each patient or, when unconscious, one close relative (or the living parents if the son/daughter was not independent yet) had to sign an informed consent.

The following precautions were taken in order to minimize the possibility that radiological alterations of the sellar region pre-existed.

Based on information obtained by the patients and/or their relatives, exclusion criteria were: (i) having been previously admitted to any Emergency Unit for head trauma; (ii) having recollection of head trauma (such as fall, road accident, sports-related) not followed by admission to the hospital; (iii) planning to perform neuroradiology investigation for symptoms such as headache, visual impairment, dizziness; (iv) having endocrine disorders of the hypothalamus-pituitary region (including having undergone either neurosurgery or brain radiotherapy); (v) having other brain disorders (such as cerebrovascular disease, dementia).

Table 1

| Age at trauma and Glasgow Coma Scale of the 104 patients. * |
|------------------------------------------------------------|
| Mean ± SD, range  | Age at trauma | Glasgow Coma Scale |
| [median]         | [median]     | [median]           |
|------------------|--------------|--------------------|
| All (n = 104)    | 61.8 ± 26.9  | 14.6 ± 0.73        |
| [69.5; 18–93]    | [15; 12–15]  |                    |
| Males (n = 62)   | 57.4 ± 22.2  | 14.8 ± 0.46        |
| [62.1; 18–92]    | [15; 12–15]  |                    |
| Females (n = 42) | 68.1 ± 17.6  | 14.3 ± 0.92        |
| [72.5; 22–93]    | [15; 12–15]  |                    |
| Statistics, males vs females | P = 0.012 | P > 0.10          |

Statistically significant values are shown in bold.

* Data are reported as mean ± SD [median; range].

Fig. 1. A) Partial empty sella; B) Total empty sella (Brain CT scan, sagittal plane).
An non-enhanced CT of the brain was performed using SOMATOM® Definition AS 64 (Siemens).

One coauthor (SLV) performed the CT scans. Partial empty sella (Fig. 1A) was considered when pituitary thickness was $\geq 3$ mm and $\leq 50\%$ of the sella was filled with cerebrospinal fluid, while total empty sella (Fig. 1B) was considered when pituitary thickness was $< 3$ mm and $> 50\%$ of the sella was filled with cerebrospinal fluid [17].

### Imaging

Endocrine investigations consisted in measurement of the following hormones: morning and afternoon serum cortisol (reference range: 6.7–22.6 µg/dl and $< 10$ µg/dl, respectively), insulin-like growth factor-1 (IGF-1) (age-dependent reference range from 163 to 424 ng/ml.

### Table 2

Neuroradiology of sella turcica and its relationship with age in patients stratified by gender.

|                   | Empty sella |
|-------------------|-------------|
|                   | Normal      | Partial | Total | Partial + Total | Other abnorm. |
| All (n=104)       | 65 (62.5%)  | 15 (14.4%) | 23 (22.1%) | 38 (36.5%) | 1 (1.0%) |
| Males (n=62)      | 42 (67.8%)  | 12 (19.3%) | 7 (11.3%) | 19 (30.6%) | 1 (1.6%) |
| Females (n=42)    | 23 (54.8%)  | 3 (7.1%)   | 16 (38.1%) | 19 (45.2) | 0 |
| Statistics        | 19.3 vs 7.1%| 11.3 vs 38.1% | 3/19 = 15.8% | 16/19 = 84.2% | % |

### Table 3

Distribution of empty sella in age subgroups.

|                   | Males (n=62) | Females (n=42)* |
|-------------------|--------------|-----------------|
|                   | Empty sella  | Empty sella     |
|                   | No (n=42)    | Yes (n=23)      |
|                   | Partial empty sella (n=12) | Partial empty sella (n=3) | Part + Total empty sella (n=19) | Part + Total empty sella (n=19) |
| Age, years        |              |                |
| ≤30               | 11           | 1              | 0               | 0/1 | 1 | 0 | 0 | 0/1 |
| 31–40             | 4            | 4              | 4/8 (50%)       | 1   | 1 | 1 | 1 | 2/3 (66%) |
| 41–50             | 4            | 2              | 2/7 (28.6%)     | 1   | 1 | 1 | 1 | 2/3 (66.7%) |
| 51–60             | 3            | 1              | 1/4 (25%)       | 3   | 2 | 1 | 3 | 3/6 (50%) |
| 61–70             | 0            | 0              | 1/5 (20%)       | 1   | 0 | 3 | 3 | 3/4 (75%) |
| 71–80             | 12           | 3              | 2               | 6   | 0 | 6 | 6 | 6/15 (40%) |
| ≥81               | 4            | 2              | 4               | 6/10 (60%) | 5 | 0 | 5 | 5/10 (50%) |

Statistics of the intergender comparison within patients with empty sella. Partial empty sella, $df = 4$, $\chi^2 = 6.67$, $P = 0.15$; Total empty sella, $df = 4$, $\chi^2 = 1.88$, $P = 0.76$; Partial + Total empty sella, $df = 5$, $\chi^2 = 6.18$, $P = 0.29$. * One man (aged 48 years) had increased volume of sella turcica, with the upper boundary of pituitary being mildly convex.
for 1–20 years through 55–166 ng/ml for >80 years), TSH (reference range: 0.3–4.2 mU/L) and free thyroxine (FT4) (reference range: 0.61–1.12 ng/dl). For diagnosis of GH deficiency were relied only on IGF-1, since basal circulating GH measurement is not helpful to diagnose GH deficiency [7]. In case of low serum TSH, subclinical hyperthyroidism was excluded because of normal or low normal FT4 levels.

For the purposes of this study, all serum samples were stored at −20°C until assay and a given hormone of all patients was measured in a single run to avoid inter-runs differences. Analytes were measured by these commercial immunoassay kits: Access-cortisol (Beckman Coulter, Inc, Brea, CA, USA), Access-Hypersensitive TSH (Beckman Coulter, Inc), Access-FT4 (Beckman Coulter, Inc), and Immulite 2000 IGF-1 (Siemens Medical Solutions-Diagnostics-USA, Malvern, PA, USA; formerly Diagnostic Products Corporation, Los Angeles, CA). The TSH kit is a third generation assay with a functional sensitivity of 0.01–0.02 mIU/L. Because (i) data are reported in an aggregate modality, and (ii) our study was based on neither dynamic tests nor invasive procedures but merely on a few baseline measurements on blood that had been drawn for routine blood chemistry, no Ethics Committee approval was needed.

Statistics

Data are reported as mean ± SD, median and range. Differences between means were analyzed by the ANOVA test. If data had non-gaussian distribution, the ANOVA test was performed after log10 transformation. Differences between proportions were analyzed by the χ² test or Fisher’s exact test, as appropriate. The P value was set at ≤0.05 to indicate significant difference, and comprised between 0.05 and 0.10 to indicate borderline, trendwise difference.

Table 4
Hormone deficiencies according to neurology.

| Normal (n = 65) | Empty sella (n = 38) | All (n = 104) |
|----------------|----------------------|--------------|
| (42 M, 23 F)   | Partial              | Total        | Partial + Total |
| (12 M, 3 F)    |                       | (7 M, 16 F)  | (19 M, 19 F)    |
|                |                       | (62 M, 42 F) |
| **Cortisol deficiency (< 7 µg/dl)** | | | |
| All            | 7 (10.8%)            | 4 (26.7%)    | 3 (13.0%)      | 7 (18.4%)      |
| Males          | 5 (11.9%)            | 4 (33.3%)    | 1 (14.3%)      | 5 (26.3%)      |
| Females        | 2 (8.7%)             | 0            | 2 (12.5%)      | 2 (10.5%)      |
| **Cortisol deficiency (≥ 11 µg/dl)** | | | |
| All            | 15 (23.1%)           | 6 (40.0%)    | 4 (17.4%)      | 10 (26.3%)     |
| Males          | 10 (23.8%)           | 5 (41.7%)    | 1 (14.3%)      | 6 (31.6%)      |
| Females        | 5 (21.7%)            | 1 (33.3%)    | 3 (18.7%)      | 4 (21.0%)      |
| **TSH deficiency** | | | |
| All            | 4 (6.1%)             | 0            | 4 (10.5%)      | 4 (10.5%)      |
| Males          | 0                    | 0            | 1 (5.3%)       | 1 (5.3%)       |
| Females        | 4 (17.4%)            | 0            | 3 (15.8%)      | 7 (16.7%)      |
| **IGF-I deficiency** | | | |
| All            | 19 (29.2%)           | 6 (40.0%)    | 7 (18.4%)      | 13 (34.2%)     |
| Males          | 13 (30.9%)           | 5 (41.7%)    | 1 (14.3%)      | 6 (31.6%)      |
| Females        | 6 (26.1%)            | 1 (33.3%)    | 6 (37.5%)      | 7 (36.8%)      |

* One man (aged 48 years) had increased volume of sella turcica, with the upper boundary of pituitary being mildly convex.

Table 5
Combinations of hormone deficiencies according to neuroradiology.

| Normal (n = 65) | Empty sella (n = 38) | All (n = 104) |
|----------------|----------------------|--------------|
| (42 M, 23 F)   | Partial              | Total        | Partial + Total |
| (12 M, 3 F)    |                       | (7 M, 16 F)  | (19 M, 19 F)    |
|                |                       | (62 M, 42 F) |
| **Deficiencies (cortisol def. at < 7 µg/dl)** | | | |
| Any one        | 21 (32.3%)           | 10 (76.9%)   | 3 (13.0%)      | 13 (34.2%)     |
| Any two        | 3 (4.6%)             | 0            | 4 (17.4%)      | 4 (10.5%)      |
| All three      | 1 (1.5%)             | 0            | 1 (4.3%)       | 1 (2.6%)       |
| Males, any one | 14 (33.3%)           | 9 (75.0%)    | 0              | 9 (47.4%)      |
| Males, any two| 2 (4.8%)             | 0            | 0              | 0              |
| Males, any three | 0                  | 0            | 1 (14.3%)      | 1 (5.3%)       |
| Females, any one | 7 (30.4%)         | 1 (33.3%)    | 3 (18.7%)      | 4 (21.0%)      |
| Females, any two | 1 (4.3%)            | 0            | 4 (25%)        | 4 (21.0%)      |
| Females, any three | 1 (4.3%)          | 0            | 0              | 0              |
| **Deficiencies (cortisol def. at ≥ 11 µg/dl)** | | | |
| Any one        | 24 (36.9%)           | 12 (80.0%)   | 4 (17.4%)      | 16 (42.1%)     |
| Any two        | 7 (10.8%)            | 1 (6.7%)     | 4 (17.4%)      | 5 (13.2%)      |
| All three      | 1 (1.5%)             | 0            | 1 (4.3%)       | 1 (2.6%)       |
| Males, any one | 18 (42.8%)           | 10 (83.3%)   | 0              | 10 (52.6%)     |
| Males, any two | 3 (7.1%)             | 1 (8.3%)     | 0              | 1 (5.3%)       |
| Males, any three | 0                  | 0            | 1 (14.3%)      | 1 (5.3%)       |
| Females, any one | 6 (26.1%)          | 2 (66.7%)    | 4 (25.0%)      | 6 (31.6%)      |
| Females, any two | 4 (17.4%)            | 0            | 4 (25.0%)      | 8 (19.0%)      |
| Females, any three | 1 (4.3%)            | 0            | 0              | 1 (2.4%)       |

* One man (aged 48 years) had increased volume of sella turcica, with the upper boundary of pituitary being mildly convex.
was statistically significant (P=0.001 all patients, P=0.005 males).

Details of empty sella

In males, total empty sella was more frequent than that of the other two deficiencies, since it was observed in one-third of the total type in females. When patients are subdivided in age subgroups, it is evident that empty sella is always observed after 40 years (Table 3). After 60 years of age, empty sella is always of the total type in males and most frequently of the total type in females.

In females empty sella is observed after 40 years, with partial empty sella being restricted to the age band 41–60 years. In contrast, partial empty sella has no clear age prevalence in males (Table 3).

For females, means ± SD, median and ranges were calculated by omitting case no. 1, who is suspicious for subclinical primary hypothyroidism.

* Abbreviations: ES = empty sella; PES = partial empty sella; TES = total empty sella; Cortis = cortisol. There was neither borderline nor statistical significant difference when comparing cortisol, TSH or IGF-1 in the PES group with the corresponding analyte in the TES group. Cortisol, TSH or IGF-1 are typed bold face when

Results

Age at trauma and neuroradiology of sella turcica

The average age at trauma (which coincides with age at our observation) was in the seventh decade, males being approximately 10 years younger than females (P = 0.012). The mean brain injury was mild, since GCS averaged 15 in either gender (Table 1).

Overall, empty sella was detected in over one-third of the 104 patients, and in females insignificantly more frequently than in males (45.2% vs 30.6%, P = 0.13). Interestingly, total empty sella was 3-fold more frequent in females than in males (38.1% vs 11.3%; P = 0.0012), while the opposite was true for partial empty sella (19.3% vs 7.1%, P = 0.0069) (Table 2). Only one patient (a 48-year-old man) had other sella abnormalities. This consisted of increased volume of sella turcica, with the upper boundary of pituitary being mildly convex (Table 2). Further to trauma, this finding is consistent with pituitary tumor.

Omitting from analysis the women with partial empty sella because of their small number (n = 3), patients with partial empty sella and normal sella had similar age. In contrast, patients with total empty sella were approximately 20–30 years older than both patients with partial empty sella and normal sella, but only the comparison with normal sella was statistically significant (P = 0.001 all patients, P = 0.005 males) (Table 2).

When patients are subdivided in age subgroups, it is evident that empty sella is always observed after 30 years (Table 3). After 60 years of age, empty sella is always of the total type in males and most frequently of the total type in females.

In females empty sella is observed after 40 years, with partial empty sella being restricted to the age band 41–60 years. In contrast, partial empty sella has no clear age prevalence in males (Table 3).

Hormone levels and correlation with neuroradiology

Hormone deficiency of at least one hormone (as defined under Materials and Methods) and its relationship with sellar neuroradiology are summarized in Tables 4 and 5, while Table 6 gives details for hormone status in patients with empty sella.

The only patient, a 48-year-old man, with increased volume of sella turcica had a single deficiency (IGF-1, 24 ng/ml [data not shown]; reference range for age 46–50: 94–252 ng/ml). IGF-1 deficiency prevailed over the other two deficiencies, since it was observed in one-third of patients regardless of gender (Table 4). This frequency was similar in patients with partial empty sella and patients with normal sella. However, within empty sella, IGF-1 deficiency prevailed in patients with partial empty sella compared to those with total empty sella (40% vs 18%, P = 0.044), the difference being accounted for by males (41.7% PES vs 14.3% TES, P = 0.33) (Table 4). TSH deficiency was the rarest deficiency (P = 0.86 Normal vs PES vs 14.3% TES, P = 0.33) (Table 4).

For females, means ± SD, median and ranges were calculated by omitting case no. 1, who is suspicious for subclinical primary hypothyroidism.

* Abbreviations: ES = empty sella; PES = partial empty sella; TES = total empty sella; Cortis = cortisol. There was neither borderline nor statistical significant difference when comparing cortisol, TSH or IGF-1 in the PES group with the corresponding analyte in the TES group. Cortisol, TSH or IGF-1 are typed bold face when

Table 6

Hormonal levels according to neuroradiology and gender. *

| no. yrs ES | Cortis (µg/dl) | TSH (mU/L) | IGF-1 (ng/ml) | no. yrs ES | Cortis (µg/dl) | TSH (mU/L) | IGF-1 (ng/ml) |
|------------|---------------|------------|---------------|------------|---------------|------------|---------------|
| 1 9 33 PES | 12.9          | 1.64       | 84            | 101 50 PES | 27.2          | 11.6       | 81            |
| 2 78 34 PES| 18.8          | 1.38       | 205           | 43 56 PES  | 21.1          | 1.04       | 128           |
| 3 42 35 PES| 8.2           | 1.62       | 75            | 72 56 PES  | 9.6           | 2.71       | 99            |
| 4 82 40 PES| 18.1          | 0.47       | 90            | 79 41 TES  | 25.7          | 0.02       | 72            |
| 5 75 42 PES| 5.8           | 1.64       | 130           | 99 58 TES  | 5.9           | 1.13       | 89            |
| 6 31 45 PES| 20.8          | 1.0        | 71.3          | 59 62 TES  | 25.5          | 0.71       | 154           |
| 7 104 60 PES| 6.4           | 1.39       | 125           | 29 65 TES  | 22.3          | 0.06       | 29            |
| 8 74 71 PES| 15.3          | 0.41       | 52            | 12 68 TES  | 15.2          | 0.64       | 93            |
| 9 95 71 PES| 13.4          | 1.62       | 138           | 80 71 TES  | 12.7          | 1.37       | 110           |
| 10 97 79 PES| 1.9          | 0.48       | 150           | 93 72 TES  | 4.8           | 0.02       | 87            |
| 11 81 81 PES| 21.9          | 1.0        | 103           | 62 73 TES  | 17.3          | 0.54       | 206           |
| 12 34 84 PES| 5.3           | 0.62       | 78            | 89 73 TES  | 9.2           | 0.73       | 122           |
| 13 28 67 TES| 6.3           | 0.29       | 55            | 38 75 TES  | 21.3          | 1.37       | 61            |
| 14 36 71 TES| 21.5          | 1.52       | 91            | 55 79 TES  | 22.6          | 1.0        | 24            |
| 15 13 73 TES| 13.9          | 0.8        | 158           | 98 81 TES  | 24.5          | 0.64       | 114           |
| 16 5 86 TES| 13.5          | 0.41       | 60            | 10 85 TES  | 47.0          | 1.13       | 67            |
| 17 91 86 TES| 28.9          | 1.52       | 99            | 54 88 TES  | 31.9          | 2.25       | 105           |
| 18 23 88 TES| 13.6          | 0.47       | 76            | 41 89 TES  | 23.3          | 0.66       | 50            |
| 19 103 91 TES| 18.0         | 2.72       | 73            | 69 90 TES  | 20.1          | 0.73       | 72            |

For females, means ± SD, median and ranges were calculated by omitting case no. 1, who is suspicious for subclinical primary hypothyroidism.

* Abbreviations: ES = empty sella; PES = partial empty sella; TES = total empty sella; Cortis = cortisol. There was neither borderline nor statistical significant difference when comparing cortisol, TSH or IGF-1 in the PES group with the corresponding analyte in the TES group. Cortisol, TSH or IGF-1 are typed bold face when

** In the intergender comparison, significant was only one difference in the normal group and regarded cortisol (14.5 ± 5.5 vs 18.8 ± 8.6 µg/dl, P = 0.017 by ANOVA).
(7.7% of the 104 patients), particularly in males compared to females (1.6% vs 16.7%, P = 0.007; OR = 0.02 [0.01–0.7]); this sex-dimorphism was observed both in the normal group and empty sella group (Table 4). Of note, there was no instance of TSH deficiency in the partial empty sella group. Depending on threshold used, cortisol deficiency occurred in approximately one-fourth or one-eighth of the 104 patients. Using the more stringent threshold of serum cortisol <7.0 µg/dl, cortisol deficiency was slightly more frequent in males than in females, particularly in the empty sella group (26.3% vs 10.5%). The highest frequency was observed in males with partial empty sella (33.3%, but 41.7% using the threshold of serum cortisol ≤11.0 µg/dl) (Table 4).

Consistently, occurrence of any one deficiency was the most frequent pattern, while occurrence of all three deficiencies was the rarest (Table 5). Within the empty sella group, two or all three deficiencies were observed in the total empty sella group solely, using the threshold of serum cortisol at <7.0 µg/dl, cortisol deficiency was slightly more frequent in males than in females, particularly in the empty sella group (26.3% vs 10.5%). The highest frequency was observed in males with partial empty sella (33.3%, but 41.7% using the threshold of serum cortisol ≤11.0 µg/dl) (Table 4).

Table 7

| Neuroradiology of sella turcica                           | Normal (cortisol normal at ≥ 7.1 µg/dl) | Empty (cortisol def. at ≤ 7.1 µg/dl) |
|-----------------------------------------------------------|-----------------------------------------|--------------------------------------|
| **Males**                                                 | 54.1 ± 25.2 [64], n = 26                | 75.7 ± 17.4 [81], n = 9               |
| **Females**                                               | 66.7 ± 19.6 [72.5], n = 14              | 73.0 ± 12.0 [73], n = 11              |
| Statistics, M vs F                                        | P = 0.14                                | P = 0.56                             |
| **Normal (cortisol normal at ≥ 11.1 µg/dl)**              |                                        |                                      |
| **Males**                                                 | 54.8 ± 25.8 [64], n = 22                | 75.7 ± 17.4 [81], n = 9               |
| **Females**                                               | 70.1 ± 15.3 [73], n = 13                | 74.9 ± 11.9 [73], n = 9               |
| Statistics, M vs F                                        | P = 0.11                                | P = 0.56                             |
| **At least one deficiency (cortisol def. at < 7 µg/dl)**   |                                        |                                      |
| **Males**                                                 | 54.3 ± 21.7 [52.5], n = 16              | 55.6 ± 18.9 [52.5], n = 10            |
| **Females**                                               | 66.1 ± 22.6 [73], n = 9                 | 66.1 ± 15.9 [68.5], n = 8             |
| Statistics, M vs F                                        | P = 0.22                                | P = 0.25                             |
| , vs Normal (M)                                           | P = 0.86                                | P = 0.022                            |
| , vs Normal (F)                                           | P = 0.93                                | P = 0.41                             |
| **At least one deficiency (cortisol def. at ≤ 11 µg/dl)**  |                                        |                                      |
| **Males**                                                 | 53.5 ± 21.7 [52.5], n = 20              | 55.6 ± 18.9 [52.5], n = 10            |
| **Females**                                               | 61.7 ± 21.5 [64], n = 19                | 65.8 ± 14.6 [68.5], n = 10            |
| Statistics, M vs F                                        | P = 0.36                                | P = 0.23                             |
| , vs Normal (M)                                           | P = 0.98                                | P = 0.022                            |
| , vs Normal (F)                                           | P = 0.81                                | P = 0.23                             |

**Statistics, Empty vs Normal**

P = 0.023
P = 0.036
P = 0.022
P = 0.077
P = 0.85
P = 0.019
P = 0.17
P = 0.017
P = 0.04
P = 0.007
P = 0.022
P = 0.017
P = 0.007
P = 0.023
P = 0.007
P = 0.023

Statistically significant values are shown in bold.

Discussion

Secondary empty sella may be caused by pituitary adenomas undergrowing spontaneous necrosis (ischemia or hemorrhage), by infective, autoimmune, and traumatic causes, or by radiotherapy, drugs, and surgery [17]. Studies with evaluation performed in the early phase of TBI are detailed in Table 8 [12,18–24]. The frequency of empty sella depends on the setting. For instance, in the general population, it has been reported to range from 8 to 38% using MRI [17,25]. Rates of GH/IGF-I deficiency, ACTH/cortisol deficiency or FT4 deficiency were 12.5%, 62.5% or 50% in 16 patients with empty sella on MRI. Concerning gonadotropin/testosterone deficiency, which we did not evaluate, its rate was 18.7% [26].

In patients with total and partial primary empty sella, these hormone abnormalities have been reported: 59% and 8% (GH/IGF-I deficiency), 47% and 4% (TSH/FT4 deficiency), 15% and 4% (ACTH/cortisol deficiency), 55.9% and 10.6% (gonadotropin/testosterone or estrogen deficiency) [20].

The somatotrophic cells are supplied by the long portal vessels, located in the wings of the pituitary gland, and are exquisitely sensitive to damage. GH deficiency is thought to be the most common endocrine
Abbreviations: ES = empty sella; GCS = Glasgow Coma Scale; TBI = traumatic brain injury; PES = partial empty sella; TES = total empty sella; SHBG = sex hormones-binding globulin; PRL = prolactin; GH = growth hormone; IGF-1 = insulin-like growth factor 1; TSH = thyrotropin; FT3 = free triiodothyronine; FT4 = free thyroxine; FSH = follicle stimulating hormone; LH = luteinizing hormone; ACTH = adrenocorticotropic hormone; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate. Only data on hypothalamic-pituitary-adrenal/thyroid axis and GH-IGF-1 axis are reported.
disturbance occurring after three months from TBI and is the one most likely to recover spontaneously [27].

There are limitations in our study. These include the relatively small cohort of patients evaluated and the lack of a comprehensive endocrine evaluation consisting of both baseline and dynamic tests. Exclusion criteria contributed to the relatively small size of our cohort, but, importantly, they minimized the possibility that empty sella antedated the occurrence of TBI. However, the aim of the study was not to perform an exhaustive endocrine evaluation of all axes.

Data presented in this study form an argument to identify patients discharged from the Emergency Unit who are worthy of being followed up because of post-traumatic empty sella, and therefore prone to develop hypopituitarism. Larger studies with a long follow-up are needed to confirm the gender differences we have described.

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