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TRAUMATIC BRAIN INJURY AND ADRENOCORTICOTROPIC AXIS DYSFUNCTION: PREVALENCE, SEVERITY, TYPOLOGY AND TOPOGRAPHY OF TRAUMA

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Traumatic brain injury and adrenocorticotropic axis dysfunction: prevalence, severity, typology and topography of trauma

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Abstract

Introduction: Traumatic Brain Injury is a major public health problem and a precise knowledge on its impact is necessary to improve the related clinical outcomes. The aim of this study is to evaluate the prevalence of adrenocorticotropic axis impairment in these patients and to relate the cortisol levels with the severity of trauma, the typology and topography of the lesions.

Methods: Data from the digital clinical files of all the TBI patients admitted to Centro Hospitalar e Universitário de Coimbra (CHUC) from 1st January until 30th June 2016 and were retrospectively collected and analysed.

Results: Across the 6 months considered, 164 patients with TBI meeting this study criteria were admitted to CHUC. Severe TBI accounted for 17 patients (10.4%), 42 (25.6%) had a moderate TBI and 105 (64%) had a mild TBI. A total of 41 patients (25%) had abnormal cortisol values from which 33 (20.1%) had hypercortisolism and 8 (4.9%) had hypocortisolism. A statistically significant difference was found, suggesting that severity of TBI is associated with differences in cortisol levels ($p = 0.01$). It became apparent that higher than normal cortisol levels were associated with moderate to severe head trauma, while mild head trauma was more associated with normal or subnormal cortisol levels. No differences were found between cortisol median values of intra or extra-axial lesions, neither across topography or gender groups ($p = 0.43$). Significant differences in cortisol levels were also found between groups submitted to clinical and imagological evaluation versus surgical therapy with the patients submitted to surgical therapy presenting higher cortisol levels than those monitored by imagological evaluation

Conclusions: The prevalence of cortisol abnormalities reported in our study is consistent with the range of values set by most studies in this regard and our findings are in line with results from other groups regarding susceptibility of the hypothalamic-hypophyseal axis to head trauma. We found a statistically significant difference in cortisol median values between mild head trauma group and moderate/severe groups, with mild severity group having lower median cortisol levels, but no relation between hypocortisolism and head trauma severity. Thus, at this time, we cannot propose screening to be restricted to a specific subset of patients. Therefore, the screening for hypocortisolism should not be held exclusively according to severity of trauma, and should encompass a wider number of variables, to reflect the complexity of this disorder.

We feel this study should be continued with further patient recruitment, in order to disclose

which patients are most likely to benefit from screening and subsequent treatment of pituitary insufficiency, allowing an early replacement of the hormonal deficits and therefore improving the clinical outcomes of such patients.

Keywords:
Traumatic; Brain; Injury; Neurosurgery; Hypocortisolism; Hypopituitarism; Endocrine; Dysfunction;

Introduction

Traumatic brain injury (TBI) is a major public health problem with an overall incidence ranging between 91/100,000 and 300/100,000 persons per year (1), and it is the leading cause of death and disability in young adults. (2) Its prevalence and incidence have been widely studied due to the important effects they have in global health.

The hypophysis is an endocranial endocrine gland responsible for the production or secretion of several hormones, many of them major regulators of fundamental body functions.

Similarly to other endocranial structures, the hypophysis can be injured during traumatic brain injury. The physiopathology underlying this findings is not yet conclusive and the mainly accepted hypothesis are vascular causes, oedema, infundibular compression or high endocranial pressure.

Previously, loss of pituitary function caused by traumatic brain injury (TBI) was considered rare, accounting for less than 1% of all new cases of hypopituitarism. (3)

However, systematic review studies have shown that hypopituitarism is a common complication of traumatic brain injury with a prevalence of 27.5% in patients with TBI (4), with several studies supporting that anterior pituitary hormone deficiency is far more frequent than previously assumed. (5) (6)

However, there is still a big discrepancy in the prevalence reported by different centres, ranging from 15% to 68% according to Schneider et al. (4) This discrepancy in the results may be due to different laboratory procedures, alongside with different "normal range values", which ultimately reflects in prevalence differences.

Post-traumatic hypopituitarism is a major complication after severe head trauma (7) and patients with posttraumatic hypopituitarism showed impaired quality of life and an adverse metabolic profile, which might contribute to morbidity and poor recovery after brain injury. (4)

There is a vigorous debate on the clinical importance of post-traumatic hypopituitarism, (6) since hypopituitarism can translate into several endocrinological disturbances. Adrenocorticotropic axis insufficiency is one of these endocrinological disturbances and it was chosen in our study because of its key role in clinical settings. Overlooking the condition or failing to replace the deficits it encompasses could be life-threatening. (3)

Thus, recommendations for assessment of adrenocorticotropic axis impairment and hormone replacement after moderate and severe TBI would have impact on clinical outcomes and should be introduced as a standard of care.

However, there are no proven indicators to foresee the arising of endocrine disturbances, as there are no recent studies regarding the prevalence and incidence of TBI's that support the

association between imaging or clinical findings upon clinical onset and the incidence of hypocortisolism in TBI patients.

The aim of this study is to evaluate the prevalence of adrenocorticotropic axis impairment in all TBI patients whose clinical condition motivated admission for 24 hours or more, and to relate the cortisol levels with the severity of trauma (based on Glasgow Coma Scale), the typology and topography of the lesions in order to show the association of these variables with the risk of hypocortisolism.

Multicentre studies would be important in this setting, as they would provide the opportunity to study wider populations and would help to define patient risk groups for systematic screening.

The ability to detect early-stage hypocortisolism might translate into better clinical outcomes, preventing the consequences of late perceived hormonal deficiencies, usually detected after the clinical expression of their consequences.

Materials and Methods

The standard of care of TBI's in CHUC comprises one cranial *CT scan* and the basal cortisol evaluation in the first 72 hours upon admission.

Data were collected retrospectively from the digital clinical files of all the TBI patients referred to Centro Hospitalar e Universitário de Coimbra (CHUC) from 1st January until 30th June 2016, totalling 164 patients. All TBI patients whose clinical condition motivated admission for 24 hours or more were included in this study.

All collected data was anonymized and all individuals with previously known endocrine pathology or under 18 years of age were excluded.

This study was designed and conducted in compliance with the Declaration of Helsinki for medical research. This study was designed retrospectively and only uses anonymized data. The medical doctor in charge is responsible for the compliance of all the ethic responsibilities. Therefore this study is a way to assess the quality of the clinical care and does not need the approval of the ethical commission, since it does not use personal data that could allow the identification of any patient.

Data were collected using a structured Microsoft Excel 2013® study sheet, including information on clinical, radiological, and hormonal parameters as well as sociodemographic values. The collected variables were age, gender, severity of trauma (according to Glasgow Coma Scale), typology and topography of apparent lesions on cranial *CT scan* upon admission, cortisol evaluation in the first 72 hours and the therapeutic measures adopted.

The reference range considered for basal cortisol values was 5 -25 µg/dL. Values not included in this interval were considered alterations to the normal basal cortisol.

The patients were grouped into three categories according to their cortisol levels:

Cortisol dosing < 5 µg/dL = Hypocortisolism

Cortisol dosing > 25 µg/dL = Hypercortisolism

Cortisol dosing = [5-25] µg/dL = No Abnormality in the Corticotropic Axis

Tables and charts were created using Microsoft Office Excel 2013® and Microsoft Office Word 2013®. IBM SPSS 24® was used for statistical analysis. The categorical variables are presented as "number of cases (percentage of total)". Quantitative variables with normal distribution are presented as "mean (standard deviation)". Quantitative variables that do not follow a normal distribution are presented as "median (25th percentile; 75th percentile)".

Association between two categorical variables, such as gender, severity of trauma, typology of lesions, topography of lesions and therapeutic option was evaluated using a Pearson chi-squared test.

Non-parametric tests were used for median comparison across samples, to control for the non-normal data distribution. For every statistical test used, a two sided *P value* < 0.05 was considered statistically significant to reject the null hypothesis.

Results

From the 1st January 2016 until the 30th June 2016, 164 patients with TBI meeting this study criteria were admitted to CHUC, 102 (62.2%) males and 62 (37.8%) females. Patient's age ranged from 19 to 96, with a median of 76 (61; 82). The mean age was 70 years old.

Severity of traumatic brain injury was assessed by initial Glasgow Coma Scale as soon as the patient was admitted. A score of 14–15 was considered mild, 9–13 moderate and 8 or less as severe traumatic brain injury. (8) According to this grouping, 17 (10.4%) had a severe TBI, 42 (25.6%) had a moderate TBI and 105 (64%) had a mild TBI.

All 164 patients underwent a head CT scan upon admission and 97 (59.1%) had a subdural haematoma, 40 (24.4%) had a contusion, 12 (7.1%) had an epidural haematoma, 12 (7.1%) had a sub-arachnoid haemorrhage, 2 (1.2%) had a depressed fracture and 1 (0.6%) had cerebral oedema.

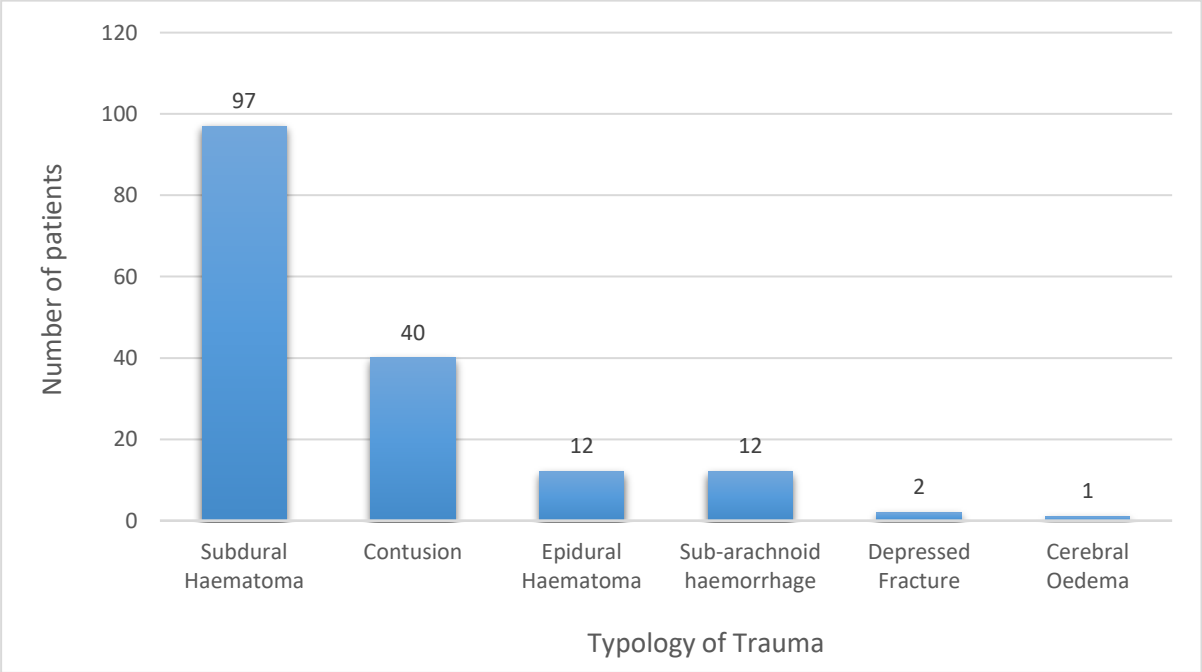

Figure 1 – Number of Traumatic Brain Injury according to Typology

77 (47%) patients underwent a surgical approach and 87 (53%) were monitored with serial imaging and a clinical approach. Therapeutic decision was based upon clinical state, evolution profile and pressure effects including those apparent on *CT scan*.

Adrenocorticotropic Axis Evaluation

All the patients were evaluated for basal cortisol levels within the first 72 hours upon admission, the registered values ranged between 1,40 and 85 mg/dl, with a median of 19 (14; 23) and a

mean value of 19,94 g/dl. 123 (75%) patients had cortisol values within the reference range for CHUC's laboratory test and 41 (25%) had abnormal cortisol values from which 33 (20.1%) had hypercortisolism and 8 (4.9%) had hypocortisolism.

According to the cortisol levels, 3 groups of patients were made (within reference range, hypercortisolism and hypocortisolism). This groups were separately analysed for their frequencies of gender, severity and typology of trauma. The results of this analysis are shown in table 1.

Gender	**Total**	**Normal Cortisol**	**Hypercortisolism**	**Hypocortisolism**
Male	102	77 (75.5%)	21(20.6%)	4 (3.9%)
Female	62	46 (74.2%)	12 (19.3%)	4 (6.5%)
Severity of TBI				
Mild	105	84 (80.0%)	14 (13.3%)	7 (6.7%)
Moderate	42	25 (59.6%)	16 (38.1%)	1 (2.3%)
Severe	17	14 (82.4%)	3 (17.6%)	NP
Typology of TBI				
Subdural Hematoma	97	75 (77.3%)	17 (17.5%)	5 (5.2%)
Contusion	40	31 (77.5%)	7 (17.5%)	2 (5.0%)
Epidural Hematoma	12	9 (75.0%)	2 (16.7%)	1 (8.3%)
Sub Arachnoid Haemorrhage	12	7 (58.3%)	5 (41.7%)	NP
Depressed Fracture	2	1 (50.0%)	1 (50.0%)	NP
Cerebral Oedema	1	NP	1 (100%)	NP
Total	164	123 (75%)	33 (20.1%)	8 (4.9%)

Table 2 – Descriptive statistics regarding cortisol sub-grouping for gender, severity and typology of TBI.
NP = There were no patients included in this category.

A chi-squared test of independence was calculated comparing the frequency of cortisol disturbances in the mild, moderate and severe trauma groups. A statistically significant difference was found, suggesting that severity of TBI is associated with differences in cortisol levels ($p = 0.01$). After sub-groupings were made, it became apparent that higher than normal

cortisol levels were associated with moderate to severe head trauma, while mild head trauma was more associated with normal or subnormal cortisol levels (Pearson chi-square $p < 0.01$).

A chi-squared test of independence was calculated comparing the frequency of cortisol disturbances with each of the following parameters: gender, typology, topography and therapeutic measures applied. No statistically significant difference was found between these pairs of variables.

No differences were found between cortisol median values of the following groups: intra or extra-axial lesion topography ($p = 0.25$, Mann-Whitney U test), laterality (right vs left-sided lesions) Kruskal-Wallis test ($p = 0.36$) and brain lobe lesion predominance (KW test, $p = 0.83$).

There was a trend towards higher cortisol levels in patients with Contusions and/or SAH versus patients admitted with subdural or epidural hematomas (KW, $p = 0.07$).

No differences were found across topography groups ($p = 0.58$), or across gender groups ($p = 0.43$).

We found a statistically significant difference in cortisol median values between mild head trauma groups (GCS 14-15) and moderate/severe groups (Independent Samples Mann-Whitney U, $p < 0.01$), with mild severity groups having lower median cortisol levels.

Significant differences in cortisol levels were also found between groups submitted to clinical and imagological evaluation versus surgical therapy with the patients submitted to surgical therapy presenting higher cortisol levels than those monitored by imagological evaluation, which is consistent with the hypothesis of cortisol response to surgical injury, similar to the response shown in acute phase after TBI. (9)

Logistic regression analysis was unable to disclose independent variables with predictive value for abnormal cortisol levels post-trauma; injury severity was the closest variable to become an independent predictor; such effect could eventually be disclosed with a larger patient sample.

Discussion and Conclusions

Overlooking adrenocorticotropic axis impairment could be life-threatening and therefore our choice was to assess this axis for its clinical importance.

There is a wide variation of the frequencies of hormone deficits reported. (4) This may be due to the different methodological tools used to assess pituitary function, which may influence the reliability and comparability between samples. The assessment of the adrenocorticotropic axis may require dynamic stimulation tests to distinguish normal from deficient responses rather than simple basal cortisol values. Therefore, it is not possible to effectively compare studies which obtained basal cortisol values and studies whose cortisol values were obtained through dynamic tests.

In spite of that, the prevalence of cortisol abnormalities reported in our study is consistent with the range of values set by most studies in this regard and our findings are in line with results from other groups regarding susceptibility of the hypothalamic-hypophyseal axis to head trauma.

In our study, there was a small number of patients with hypocortisolism, so it is recommended that the sample size is widened to cover a larger sample and to have a stronger representativeness of the problem in study.

One of the possible study limitations is that we screened the patients for basal cortisol abnormalities on a single sample, which may have led to underestimation of the prevalence of hypocortisolism because of the irregular evolution it carries through time. (6)
A standardized setting of multiple measures should be collected to avoid underestimating the problem and to screen patients beyond the acute stress phase, which is proven to increase measured cortisol levels.

We found a statistically significant difference in cortisol median values between mild head trauma groups (GCS 14-15) and moderate/severe groups (Independent Samples Mann-Whitney U, $p < 0.01$), with mild severity groups having lower median cortisol levels. These findings corroborate the hypothesis that higher cortisol levels are associated with acute stress, and further support the need to use a wider screening, with more cortisol measurements in order to avoid overlooking hypocortisolism in patients who are in acute phase during the first measurement. Furthermore, the responsiveness of each patient to the acute stress is not even, and different patients might have different periods of hormonal response to acute phase stress, which may explain the presence of hypocortisolism in patients of every trauma severity group.

We found no relation between hypocortisolism and head trauma severity (lower mean levels of cortisol were actually found in mild trauma cases); thus, at this time, we cannot propose

screening to be restricted to a specific subset of patients.

Therefore, the screening for hypocortisolism should not be held according to severity of trauma alone. Instead, the screening for hypocortisolism should encompass a wider number of variables, to reflect the complexity of this disorder.

Even though the logistic regression analysis showed that injury severity was the closest variable to become an independent predictor of hypocortisolism, this regression was unable to disclose independent variables with predictive value for abnormal cortisol levels post-trauma. Such effect could eventually be disclosed with a larger patient sample.

Patients with hypopituitarism require replacement of the deficient hormone as part of their clinical standard of care. Adequate hormone replacement can, in general, reverse the symptoms of hypopituitarism and normalize the risks associated with it. (10)

We feel this study should be continued with further patient recruitment, in order to disclose which patients are most likely to benefit from screening and subsequent treatment of pituitary insufficiency, allowing an early replacement of the hormonal deficits and therefore improving the clinical outcomes of such patients.

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