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Incidence of adrenal insufficiency after severe traumatic brain injury varies according to definition used: clinical implications[†]

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Background. Adrenal insufficiency impacts on the haemodynamic management of patients in intensive care. Very little is known about the incidence of adrenal insufficiency in the first 10 days after traumatic brain injury.

Methods. We retrospectively reviewed the charts of 113 traumatic brain injury patients within 10 days of their injury. They all had a high-dose corticotropin stimulation test performed because of haemodynamic instability. Blood cortisol concentrations were measured at baseline, 30 and 60 min after the administration of high-dose corticotropin. The incidence of adrenal insufficiency was determined according to various definitions used in the literature.

Results. The baseline cortisol concentration was <414 nmol litre⁻¹ (15 µg dl⁻¹) in 78% of patients and <690 nmol litre⁻¹ (25 µg dl⁻¹) in all patients. The cortisol concentration did not rise above 500 nmol litre⁻¹ (18 µg dl⁻¹) at 30 and 60 min in 49 and 22% of patients, respectively. The cortisol concentration did not rise by 250 nmol litre⁻¹ (9 µg dl⁻¹) at 30 and 60 min in 48 and 25% of patients respectively. Primary adrenal insufficiency defined by an abnormal baseline cortisol concentration and an abnormal response to the high-dose corticotropin stimulation test was present in 13–28% of patients according to the cut-off values used.

Conclusions. The incidence of adrenal insufficiency varies from 25 to 100% in the first 10 days after traumatic brain injury. The range of incidences reported illustrates the need for standardization of the definition of adrenal insufficiency. This has a direct impact on treatment. Sampling at 60 min after the high-dose corticotropin stimulation test seems to correlate better with the maximum secreting capacity of the adrenal glands.

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Adrenal insufficiency has emerged in recent years to be a crucial and prevalent problem in intensive care.¹ Hypopituitarism has recently been reported to occur in 35–80% of patients in rehabilitation following head injury.^{2–5} Adrenal insufficiency accounts for ~30–50% of these cases.

Little is known about adrenal function in the early (<10 days) post-traumatic period when it is most likely to influence critical care management. Two recent papers report an incidence of 13–15% of poor responsiveness to a low-dose stimulation test in traumatic brain injury patients during the first month after injury.^{6,7} It is likely

that traumatic brain injury could produce secondary adrenal insufficiency due to disruption of the hypothalamus or pituitary gland. In these cases, the adrenal glands are expected to mount an appropriate response to the low-dose stimulation test since they are not yet atrophic. Thus one would underestimate the true incidence of adrenal insufficiency and potentially under-treat patients using only the low-dose stimulation test to define adrenal insufficiency.

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Furthermore, uncertainty regarding the true incidence of adrenal insufficiency in this setting is compounded by the lack of agreement on what is considered to be an appropriate response of the hypothalamic–pituitary–adrenal axis in intensive care patients. Several authors think that a random cortisol concentration (414 or 690 nmol litre⁻¹) should define adrenal insufficiency¹⁸ while others use only the response to a stimulation test. Consequently, there is confusion about the definition of an abnormal hypothalamic–pituitary–adrenal axis response in critically ill patients.

The aim of our study is to describe the incidence of adrenal insufficiency early after traumatic brain injury (<10 days), using different suggested definitions. Secondly, since blood sampling for cortisol concentrations has been reported at both 30 and 60 min post high-dose corticotropin stimulation test, we wished to define which of these sampling intervals was more appropriate.

Patients and methods

Our local research ethics committee approved the study. We retrospectively reviewed the charts of all patients who had a high-dose corticotropin stimulation test performed because of vasoactive drug requirements (>5 µg kg⁻¹ min⁻¹ of dopamine or >0.02 µg kg⁻¹ min⁻¹ of norepinephrine for at least 24 h) within 10 days of traumatic brain injury. We recorded patient characteristics, Glasgow Coma Score (GCS) on admission, APACHE II and Injury Severity Score on admission, vasoactive drug requirements and duration of use, presence of infection, temperature and use of phenytoin at time of the high-dose corticotropin stimulation test, use of desmopressin, presence of skull fracture, haemodynamic response to the administration of steroids and insulin requirements after steroid administration. The severity of injury was defined according to the GCS on admission (mild, 14–15; moderate, 9–13; and severe, <9). The Glasgow Outcome Scale (GOS) at 6 months post injury was used to evaluate outcome. Patients were classified as Grade 1 (death), 2 (vegetative state), 3 (severe disability), 4 (moderate disability), and 5 (good outcome). The GOS was dichotomized as unfavourable (Grades 1, 2 and 3) or favourable (Grades 4 and 5). Infection was said to be present if two criteria for the systemic inflammatory response syndrome were present with a positive culture or antibiotic usage. The lungs of all patients were mechanically ventilated and vasoactive drugs were being administered. A predefined protocol⁹ was used to manage sedation (with propofol and midazolam) and intracranial pressure (ICP).

The high-dose corticotropin stimulation test was performed by administering 250 µg of tetracosactide (Synacthen®) and measuring plasma cortisol concentrations before the use of tetracosactide (time 0 min) and at time 30 and 60 min. Cortisol concentrations were measured using an automated chemiluminescent assay (Bayer, Advia, Centaur). None of the patients received etomidate.

Definitions of adrenal insufficiency

Multiple definitions of adrenal insufficiency have been used in the literature.^{7,8,10,11} Both baseline cortisol concentrations and response to the low-dose stimulation test or high-dose corticotropin stimulation test are used to define and characterize adrenal insufficiency. Primary adrenal insufficiency is due to adrenal gland failure and thus both baseline and post stimulation concentrations are abnormal. Secondary adrenal insufficiency is due to hypothalamic or pituitary failure and, in the acute setting, the adrenal glands respond well to stimulation while the baseline cortisol concentration is low.

Basal cortisol concentration

A concentration of 414 nmol litre⁻¹ is considered to be the normal minimum value in response to severe stress, particularly hypotension. Hence, it is viewed as the minimal appropriate concentration for intensive care patients.⁸ A concentration below 690 nmol litre⁻¹ has been suggested instead since patients undergoing surgery or sustaining trauma almost invariably have cortisol concentrations above this value.¹² The intensive care literature tends to support this view.^{11,13}

Response to high-dose corticotropin stimulation test

In a study by Annane and colleagues,¹⁰ a rise in plasma cortisol concentration by >250 nmol litre⁻¹ was suggested as the appropriate response of the adrenal glands in intensive care patients with sepsis. This definition is probably the most widely used cut-off to interpret a stimulation test in intensive care. Classically, a rise above 500 or 550 nmol litre⁻¹ is considered normal based on the response of non-critically ill patients to insulin-induced hypoglycaemia.¹²

Statistics

Statistical analysis was undertaken using Statview® (Version 5, 1998, SAS Institute Inc., Cary, NC, USA). All data are expressed and displayed as mean (SD) and as percentages of the total sample, unless otherwise stated. Post high-dose corticotropin stimulation test values of plasma cortisol concentration at 30 and 60 min were compared using simple linear regression. The impact of individual clinical variables (e.g. the presence of sepsis) on baseline and stimulated cortisol concentrations was explored using an unpaired *t*-test or a Mann–Whitney test, as appropriate.

Results

Between January 1998 and August 2004, a high-dose corticotropin stimulation test was performed on 23% (*n*=113/493) of patients admitted in our unit with a diagnosis of traumatic brain injury. The population characteristics are shown in Table 1. The majority of patients had sustained a severe injury. The severity of injury is further demonstrated by the duration of mechanical ventilation and the relatively high incidence of an unfavourable outcome

when compared with our previously published data.¹⁴ Furthermore, 55% of patients reached the maximum phase (phase V: craniectomy or barbiturate coma) of the ICP management protocol and 96% were managed at phase III or more (hypertonic/osmotic solutions, mild hypothermia, mild hyperventilation and vasoactive drugs).

The high-dose corticotropin stimulation test was performed on days 2–5 in 65% of patients. It was performed

Table 1 Population characteristics (total *n*=113). Data are mean (SD) [range] or %. ISS, injury severity score; ICU, intensive care unit; MV, mechanical ventilation; RTA, road traffic accident; GOS, Glasgow outcome score; DDAVP, desmopressin

Age (yr)	35 (14) [14–78]
Male (%)	79
APACHE II	16 (6) [6–34]
ISS	23 (10) [4–50]
ICU (days)	17 (13) [3–126]
MV (days)	5 (8) [3–50]
Type of injury	
RTA (%)	63
Fall (%)	24
Other (%)	13
Severity of injury	
Mild (GCS 14–15) (%)	5
Moderate (GCS 9–13) (%)	25
Severe (GCS 3–8) (%)	70
GOS	
Favourable (4–5) (%)	52
Unfavourable (1–2–3) (%)	56
Eosinophil count ($\times 10^6$)	225 (226)
Phenytoin at test	34
Infection at test	49
DDAVP use	49
Skull fracture	41
Mean cortisol baseline (nmol litre ⁻¹)	279 (146) [25–688]
Mean increase in cortisol at 60 min (nmol litre ⁻¹)	375 (249) [193–1257]

on the first day in 10% and after day 5 in 25% of the patients. The incidence of adrenal insufficiency according to various definitions is shown in Figure 1. The mean baseline cortisol concentration was 279 (146) nmol litre⁻¹. Primary adrenal insufficiency defined by an abnormal baseline and abnormal post high-dose corticotropin stimulation test cortisol concentration was present in 13–28% of patients depending on whether a 60 or 30 min sampling time after high-dose corticotropin was used, respectively. Whichever definition was used, the incidence of primary adrenal insufficiency is markedly reduced if the 60 min (rather than the 30 min) cortisol values were used to define adrenal insufficiency. While the

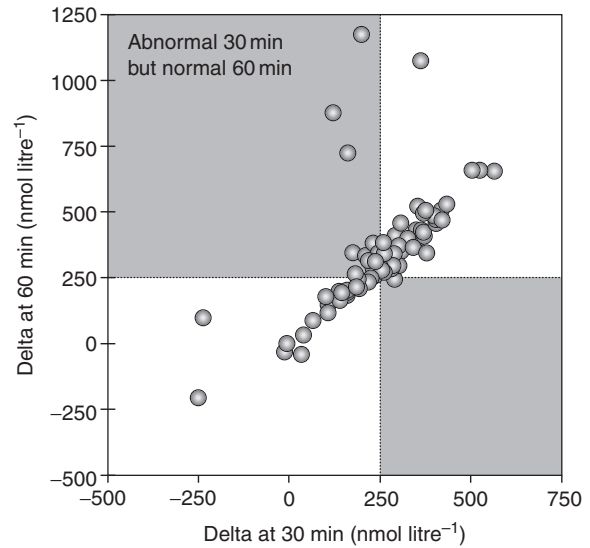


Fig 2 Rise in cortisol concentration after high-dose corticotropin stimulation test at 30 and 60 min. Delta=cortisol after high-dose corticotropin stimulation test – baseline.

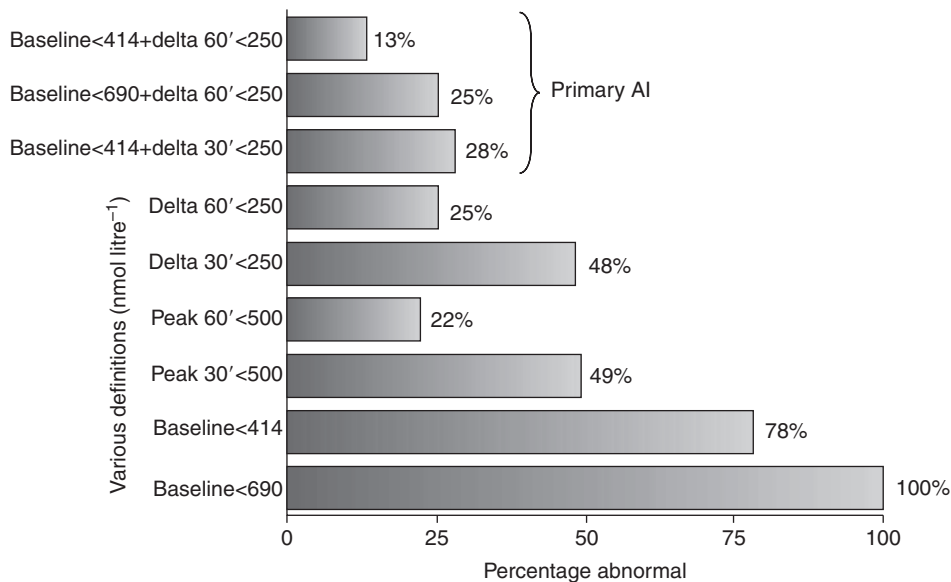


Fig 1 Incidence of adrenal insufficiency according to various definitions Delta=cortisol after high-dose corticotropin stimulation test – baseline. 30', 30 min; 60', 60 min.

two post stimulation values generally correlated well across the study population ($r^2=0.496$; $P<0.0001$), there were many outliers in whom responses were not concordant. Figure 2 shows that several patients (40%) with an abnormal response at 30 min had normalized their response by 60 min; the reverse was not true.

The presence of infection (49% of patients), the phase of the ICP protocol at the time of the test, the temperature, the presence of skull fracture, the use of desmopressin, the severity of injury, the APACHE, ISS and Marshall score and age did not correlate with either baseline cortisol concentration or the response to high-dose corticotropin. Baseline cortisol concentrations did not correlate with the response to the stimulation test. The presence or absence of phenytoin therapy did not significantly affect baseline cortisol concentrations. Eosinophilia is a well-known manifestation of adrenal insufficiency but the maximal level observed in our population was only 1070 and the mean eosinophil count was low $225[226]\times 10^6$.

Discussion

This study showed that the incidence of adrenal insufficiency in severe traumatic brain injury varies enormously depending on the definition used. The incidence of adrenal insufficiency defined by baseline cortisol concentrations may be as high as 100%. Primary adrenal insufficiency accounts for 13–25% of the cases. It also demonstrated that sampling for cortisol at 60 min after a high-dose corticotropin stimulation test is more appropriate than doing so at 30 min. It must be kept in mind that patients included in our study represent a subgroup of all traumatic brain injury patients, namely those most unstable physiologically.

This variation can only generate confusion in scientific discussions, not to mention incapacity to compare population of patients. An agreement must be reached on an appropriate definition of adrenal insufficiency. We agree with other investigators^{18,15} that measurement of baseline cortisol concentrations should form part of the definition. A normal response to a stimulation test does not rule out adrenal insufficiency as it only tests adrenal reserve and not hypothalamic and pituitary function.

The appropriate baseline cortisol concentration must clearly be interpreted according to the degree of stress that the patient is subjected to.¹ Although cut off values of 414 and 690 nmol litre⁻¹ have been proposed to define adrenal insufficiency, no definitive conclusions can be made on this issue since these values were derived from heterogeneous populations of patients. Nonetheless, it is at the moment the only practical option. Given these imperfections in our ability to quantify glucocorticoid activity at the tissue level, any of the currently available laboratory tests may not provide a sufficiently accurate diagnosis of adrenal insufficiency. Consequently, a trial of steroid therapy may be warranted to assess haemodynamic response regardless of

cortisol concentrations and could serve as the best available approach.¹⁶ Our data suggest that 414 nmol litre⁻¹ is probably a more useful cut off in a traumatic brain injury population similar to ours.

The incidence we report may seem surprisingly high and may be attributable to several factors. First, hypothalamic–pituitary–adrenal axis function is known to improve over time as acute critical illness resolves,^{7,17} and our earlier evaluation of patients might account for this rather high incidence. The incidence of adrenal insufficiency (defined as a baseline cortisol concentration <414 nmol litre⁻¹) has been reported in 62–66% of patients in the subacute period after traumatic brain injury (10–30 days).^{5,18} In septic patients, the incidence may be as high as 80% early in the illness.¹¹ These latter figures are broadly comparable to the incidence we report.

Secondly, the severity of injury was high in our population, as demonstrated by the duration of mechanical ventilation and ICU stay, intensity of treatment required to manage ICP and the GOS of the patients. It has been suggested that brain stem function must be intact in order to mount an appropriate response to stress.¹⁹ Brain-dead patients also demonstrate a poor hypothalamic–pituitary–adrenal axis function²⁰ and anatomical abnormalities of the hypothalamus and pituitary gland have been observed in up to 86% of patients in pathological studies.²¹ Altogether, these findings support the concept that the hypothalamic–pituitary–adrenal axis might not respond as expected from the severity of injury in traumatic brain injury patients. In fact, it suggests that severely affected patients are more likely to have adrenal insufficiency.

Thirdly, since the implementation of the Brain Trauma Foundation guidelines for the management of traumatic brain injury, control of abnormal systemic physiology and intracranial hypertension are probably achieved more rapidly and efficiently. Since hypotension, pain and (probably) intracranial hypertension activate the hypothalamic–pituitary–adrenal axis, controlling these factors might limit its activation.²² Blunting of the afferent limb of the peripheral nervous system might reduce stimulus to the hypothalamus.²³ Indeed, hypothalamic–pituitary–adrenal response to stress is delayed until reversal of anaesthesia in surgical patients²⁴ and propofol has been associated with decreased cortisol concentrations but not because of inhibition of steroid secretion by the adrenals.^{25,26}

Whether or not patients with such cortisol concentrations need to be treated remains undetermined. Traumatic brain injury patients may have a poorer outcome if they have adrenal insufficiency⁶ and patients with septic shock seem to benefit from treatment.¹⁰ Like sepsis, trauma can initiate cytokine liberation and influence adrenocorticotropin and cortisol release and action.¹⁵ This could explain the significant incidence of primary adrenal insufficiency in our population. Hypotension is a clear risk factor for poor outcome in traumatic brain injury, and the judicious use of physiological doses of steroids for normalizing

haemodynamics may have clear benefits. Furthermore, glucocorticoids have been shown to have an important role in the production of protective neurotrophin after traumatic brain injury.²⁷ There is a clear need therefore to find ways to identify patient subgroups that are most likely to benefit from steroid supplementation in head injury.

The discordance between post stimulation cortisol concentrations at 30 and 60 min may be an indicator of impaired adrenal responsiveness to ACTH, but we have no evidence to support this suggestion. Until such evidence is available, we would suggest that if the 250 µg dose is used, blood should be sampled at 60 min post stimulation to avoid over-diagnosis of adrenal insufficiency. This issue should also be addressed for the low-dose stimulation test.

It is important that we acknowledge that this study suffers from the limitations inherent in any retrospective study. It would have been helpful to assess the response of our patients to a low-dose stimulation test in order to assess the relative resistance to ACTH. However, a low-dose stimulation test would be more sensitive and thus increase the incidence of primary adrenal insufficiency. Infection was present in 49% of patients at the time of the test. This could clearly influence the incidence of adrenal insufficiency. Careful chart review suggests that infection was not a likely cause of hypotension in the majority of our patients. Furthermore, the incidence of adrenal insufficiency was the same amongst infected and non-infected patients.

Conclusions

After severe traumatic brain injury, adrenal insufficiency is prevalent, regardless of the thresholds used for definition. Haemodynamically unstable patients should be screened to assess their hypothalamic–pituitary–adrenal axis integrity. Both baseline and post stimulation cortisol concentrations must be used to characterize the type of adrenal insufficiency but physicians must be aware of the lack of consensus regarding cortisol cut-off values and their limitations. Further studies are needed to define these cut-off values in traumatic brain injury patients in order to determine who is likely to benefit from treatment.

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