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The Case of Hypopituitarism in Traumatic Brain Injury

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1. Introduction

Traumatic brain injury (TBI) has until recently been considered a rare cause of loss of pituitary function, accounting for less than one percent of all new cases of hypopituitarism. Newer studies have, however, indicated otherwise, and overlooking the condition in case of the life-threatening adrenal insufficiency after brain trauma may be fatal (Schneider et al., 2007a). Thus, chronic anterior pituitary hormone deficits have been described with a higher frequency than previously anticipated and have caused expert panels to propose recommendations for routine assessment of pituitary function after TBI with appropriate replacement of insufficient axes (Ghigo et al., 2005; Ho, 2007; Tanriverdi et al., 2011).

Most populations have a high incidence of TBI of more than 100 in 100,000 inhabitants. On the one hand it is of clinical importance to identify all patients that would benefit from relevant substitution therapy, but on the other hand it is also of major socio-oeconomic interest to ensure a cost-effective strategy. To perform pituitary testing of all TBI patients would be an impossible task both logistically and financially. It is therefore unfortunate that the area despite numerous studies still lacks identification of valid predictors for development of hypopituitarism, and it has also not yet been clarified, which part of the TBI population that should be tested. Additionally, no larger treatment intervention studies have been performed, and it therefore remains quite unclear whether or not patients would benefit from treatment of hypopituitarism at an early or later stage to facilitate neurorehabilitation and improve survival, morbidity and quality of life.

In this chapter, the published clinical studies of posttraumatic hypopituitarism are scrutinized, and current recommendations are discussed in the lines of currently available evidence, with reference to socio-oeconomic aspects.

2. Pathophysiology of hypopituitarism in TBI

The pituitary gland regulates various endocrine organs including the adrenal cortex, the thyroid gland, and the gonads through integration of central and peripheral feedback signals. Hypopituitarism refers to an insufficient secretion of pituitary hormones.

The pathophysiological mechanism of posttraumatic hypopituitarism remains incompletely understood, but may include primary mechanical injury to the hypothalamic-pituitary region, as well as secondary injury from hypotension, hypoxia, anaemia and brain swelling causing restriction of flow in the hypophyseal portal vessels. Support of this

pathophysiologic concept comes from autopsy studies of patients with fatal head injury in whom up to one-third had anterior pituitary gland necrosis (Ceballos, 1966; Crompton, 1971; Kornblum & Fisher, 1969). However, whether or not data from fatal cases can be generalised to explain long-term hypopituitarism in TBI survivors is not clear. Two MR studies showed results supportive of such hypothesis. Firstly, an observational case-control study included 41 patients with non-lethal head trauma and demonstrated acute changes such as pituitary enlargement, pituitary haemorrhages, infarctions, signal abnormalities and/or partial stalk transsection in about 30% of adult TBI patients (Maiya et al., 2007). Secondly, other observational data suggested that patients with long-term post-TBI hypopituitarism demonstrated more frequently loss of pituitary volume or virtual empty sella, abnormal pituitary gland signal heterogeneity, perfusion deficits and/or lack of posterior pituitary signal as compared to TBI patients with normal pituitary hormonal function (Schneider et al., 2007b). Accordingly, a higher occurrence of midline lesions or damage to deep brain structures were reported in hypopituitary patients with diffuse axonal injury as compared to those with normal pituitary function (Jeong et al., 2010).

One group suggested an aetiologic role of anti-pituitary and anti-hypothalamic antibodies (Tanriverdi et al., 2010), as well as a genetic predisposition for development of TBI-induced hypopituitarism (Tanriverdi et al., 2008a). This has on the other hand not been confirmed in other populations.

In the acute phase post-TBI, the transient effect of stress from critical illness and medication are important mechanisms to consider. The following medications are very likely to be involved in this patient group in the acute phase, and can by themselves cause life-threatening adrenal insufficiency: Adrenal cortisol synthesis can be impaired by the anaesthetic agent etomidate and the antifungal agent ketokonazol, exogenous corticosteroid therapy may suppress the hypothalamo-pituitary-adrenal (HPA) axis and induce adrenal atrophy that may persist months after cessation, and hepatic metabolism of cortisol may be enhanced by drugs such as phenytoin.

3. Diagnosing insufficient pituitary function

The diagnosis of hypopituitarism relies on basal and stimulated anterior pituitary and peripheral target hormone concentrations, and diagnostic test-panels and criteria suggesting hypopituitarism have been defined (, 1998; Lamberts et al., 1998). Both diagnostic criteria and cut-off points are arbitrary, and grey-zones for each pituitary hormone exist. Thus, test results must be interpreted in the light of pre-test probability and clinical features (Feinstein, 1990). Unfortunately, the clinical symptoms in hypopituitarism are most often vague and unspecific, and the diagnostic decision therefore often relies on the pre-test probability of disease. The diagnostic process is therefore highly challenged by vastly different assays for hormone measurements, all having their own reference range, as well as significantly different cut-off levels between normal persons and patients with pituitary deficiency. Establishment of local diagnostic cut-off points are required, but most often lacking. In most centres hypopituitarism is a rare condition, and ensuring own normative data for all the pituitary tests is cumbersome and expensive, why many physicians rely on 'standard' cut-off limits from the literature. Ideally, assessment of TBI patients should be restricted to few highly specialised collaborative centres using stringent diagnostic criteria for hypopituitarism including obligatory confirmation tests in case of an insufficient test outcome. The latter is highly important partly due to intraindividual test variation in normal

people (Bhasin et al., 2010; Vestergaard et al., 1997), partly due to possible transitory changes due to non-pituitary related stress (Fig 1). For logistic reasons such recommendation is often not possible. In the following, assessment of each of the clinically relevant pituitary axes will be scrutinized.

3.1 GH deficiency

Measurement of baseline GH concentrations in serum is rarely informative as the secretion of growth hormone (GH) is pulsatile, and stimulation tests estimating the secretory capacity are mandatory. The pulsatile release of GH is physiologically controlled by stimulation by hypothalamic GH releasing hormone (GHRH) and inhibition by the hypothalamic suppressor, somatostatin. GHRH stimulates both GH synthesis and secretion, whereas somatostatin inhibits only GH secretion (Giustina & Veldhuis, 1998). Multiple neurotransmitter pathways and a variety of peripheral feedback signals modulate GH secretion reflected by the large number of accessible stimulation tests, relying on many different mechanisms. The GH secretory response to insulin induced hypoglycaemia during an insulin tolerance test (ITT) seems to be mediated via stimulated GHRH secretion and a concomitant withdrawal of somatostatin inhibition (Giustina & Veldhuis, 1998). ITT is considered the diagnostic gold standard, as it is the most extensively used and validated test, with very high sensitivity and specificity at standard cut-off limits. It has the advantage of allowing evaluation of the integrated hypothalamic-pituitary function concerning both GH- and adrenocorticotropin (ACTH)- secretions. The disadvantage is related to its contraindications including epilepsy and ischaemic heart disease, and the fact that it is both unpleasant for the patients and labour-intensive. Alternative tests such as the GHRH+arginine and the GHRH-GH releasing peptide (GHRP) -6 test have therefore become increasingly popular for assessment of the somatotroph function. Arginine acts via inhibition of hypothalamic somatostatin release, and GHRP-6 probably antagonizes somatostatin activity, thereby increasing the activity of GHRH-neurons (Giustina & Veldhuis, 1998). Because GHRH stimulates the pituitary directly, and thus circumvents the hypothalamus, tests involving GHRH may give false normal results in the early stage of GHD of hypothalamic origin (Darzy et al., 2003). Taking this into account, the GHRHarg test seems to have similar sensitivity and specificity as compared with the ITT in lean subjects (Biller et al., 2002). However, the GHRHarg is known to depend on the body composition and BMI specific cut-offs are needed (Corneli et al., 2005; Makimura et al., 2008). Obesity (Bonert et al., 2004; Rasmussen et al., 1995) and relative central adiposity (Miller et al., 2005) are generally major confounders by being negative determinants for the stimulated GH concentrations. This makes the distinction between organic GHD and obesity difficult, and poses a major problem in diagnosing isolated GHD, in particular. On the other hand, independent of BMI the likelihood of coexistent severe GHD is more than 90% in patients with two or more additional pituitary deficiencies (Toogood et al., 1994).

3.2 ACTH deficiency

As a consequence of diurnal rhythmicity dynamic testing of the HPA axis is most often required. A basal morning cortisol can be used under certain circumstances, since a concentration less or equal to 100 nmol/L is highly indicative of HPA deficiency (Courtney et al., 2000; Watts & Tindall, 1988), whereas a concentration higher than 400 nmol/L is

indicative of HPA sufficiency (Gleeson et al., 2003; Watts & Tindall, 1988). Most commonly basal morning cortisol concentrations are in-between, highly overlapping those of healthy subjects, and dynamic testing is therefore required eventually. At present, the ITT is considered the diagnostic gold standard (Ho, 2007). The test-retest reproducibility is higher than for GH (Vestergaard et al., 1997), but false abnormal results can be seen, in particular, if only borderline attainment of hypoglycaemia is achieved. The 250 μg Synacthen test is often used in clinical practice as it is simple, and without contraindications and unpleasant side effects. It does have limitations, which include a risk of false normal results e.g. in the early phase after hypothalamic or pituitary damage (Klose et al., 2005), as well as in patients with partially degenerated adrenal glands. Irrespective of test preference, there are common problems in interpretation of results and in choice of cut-off level distinguishing normality from HPA deficiency related to the cortisol-assay used (Clark et al., 1998; Klose et al., 2007c), presence of dysproteinaemia and medical treatment with oestrogens (Bonte et al., 1999; Kirschbaum et al., 1999), either as replacement therapy in gonadal insufficiency or as oral contraceptive.

3.3 TSH deficiency

Central hypothyroidism is suspected in patients with low total- (T) or free- (f) T_4 and an inappropriately low TSH. Peripheral thyroid hormone levels have a narrow individual reference range compared with that observed between-individuals (Andersen et al., 2002; Feldt-Rasmussen et al., 1980). The diagnosis therefore depends on the position of the individual's normal set point, which is reflected by TSH in primary hypothyroidism. Whereas measurement of TSH is of major diagnostic importance in primary hypothyroidism, it is of little use in secondary hypothyroidism of hypothalamic or pituitary origin. Most of these patients have a serum TSH within the normal range or even elevated. This apparent contradiction may, to some extent at least, be explained by reduced bioactivity of the circulating TSH (Beck-Peccoz et al., 1985), probably through abnormal glycolysation of the molecule (Oliveira et al., 2001), though the mechanism is not fully understood. The diagnosis of secondary hypothyroidism is thus challenging, as the usual diagnostic criteria based on a normal reference range are not valid. Isolated secondary hypothyroidism is extremely rare and in these patients, samples should be re-analysed by an alternative assay, and low thyroxine binding globulin (TBG) concentrations and non-thyroidal illness have to be excluded before the final diagnosis (Lamberts et al., 1998). Stimulation with thyrotropin releasing hormone (TRH) has given discrepant results (Franklyn, 1997; Hartoft-Nielsen et al., 2004; Lania et al., 2008). The possible confounding by certain antiepileptic drugs is well-described (Cansu et al., 2006; Isojarvi et al., 2001), inducing a biochemical picture mimicking that of secondary hypothyroidism with decreased peripheral thyroid hormone concentrations and a normal TSH.

3.4 LH and FSH deficiency

In postmenopausal women hypogonadotropic hypogonadism is characterised by inappropriately low gonadotropins, and in premenopausal women by amenorrhoea or oligomenorrhoea in addition to low oestradiol and low or normal gonadotropins. Low testosterone and a correspondingly low LH suggest hypogonadotropic hypogonadism in men. Due to the diurnal rhythmicity morning samples are required, and in case of a low or low normal testosterone concentration sampling must be repeated, because 30% of such

men may have a normal testosterone level on repeat measurement (Bhasin et al., 2010; Brambilla et al., 2007). Patients with altered sex hormone binding globulin (SHBG) concentrations are a major diagnostic challenge. According to the The Endocrine Society Clinical Practice Guideline, men in whom total testosterone is near the lower limit of normal or in whom SHBG abnormalities are suspected, evaluation should include measurement of free or bioavailable testosterone levels using validated assays(Bhasin et al., 2010). Conditions associated with high SHBG levels are aging, hepatic cirrhosis and hepatitis, hyperthyroidism, use of anticonvulsants, whereas decreased SHBG levels are seen in obesity, hypothyroidism, nephritic syndrome, diabetes mellitus, and use of glucocorticoids and androgenic steroids.

3.5 ADH deficiency

Central ADH deficiency is suspected in patients with polydipsia and polyuria (urine volume > 3 litres/24 hours). Urine analysis demonstrates dilute urine with low specific gravity and low osmolality. A fluid deprivation test may be necessary in case of intermediary results, or in order to determine the type of diabetes insipidus (central versus nephrogenic or dipsogenic).

4. Prevalence of acute hypopituitarism in TBI

A number of studies have assessed the acute neuroendocrine changes following TBI, in order to investigate their correlation to trauma severity, metabolic derangement and variables that may predict outcome (Cernak et al., 1999; Cohan et al., 2005; Della et al., 1998; Feibel et al., 1983; Hackl et al., 1991). The clinical implications of these findings remain unclear.

Four longitudinal studies have been designed to evaluate the relationship between acute and long-term pituitary hormone status after TBI. Agha et al. (Agha et al., 2005a) found secondary gonadotropin-, GH-, ACTH - and TSH deficiency in 80%, 18%, 16% and 2%, respectively of 56 patients with moderate or severe TBI. At one-year follow-up hormonal abnormalities had recovered in most patients, whereas others had developed de novo deficiencies, and although persistent GH and ACTH deficiency was associated with more severe hyposecretion of GH and cortisol during the acute phase, the authors were unable to identify biochemical predictors of long-term hypopituitarism. Tanriverdi et al. (Tanriverdi et al., 2006) reported pituitary hormone deficiency in 50% of 52 evaluated patients, primarily affecting the gonadothroph axis. However, individual data showed no obvious relationship between early and late pituitary dysfunctions. We (Klose et al., 2007b) described acute hormone alterations in 76% of 46 patients, with patients suffering the most severe TBI exhibiting the highest prevalence of alterations mimicking hypogonadotropic hypogonadism, central hypothyroidism, hyperprolactinaemia, and increased HPA-activity, all in agreement with the alterations seen in non-pituitary critical illness (Fig. 1).

We were unable to identify biochemical predictors of persistent hypopituitarism, and did not find any de novo deficiencies from 3 to 12 months post-TBI, whereas late recovery was observed in 1 of the 7 patients that were hypopituitary at 3 months. Kleindienst et al. (Kleindienst et al., 2009) described hormone alterations in 83% of 71 patients, recovering in most within 2 years follow-up. They reported that initial low GH levels predicted persistent deficiency 2 years post-TBI. The existing data, however, relies on rather small cohorts only

allowing for case description and therefore clear conclusions and recommendations on this issue are still not possible.

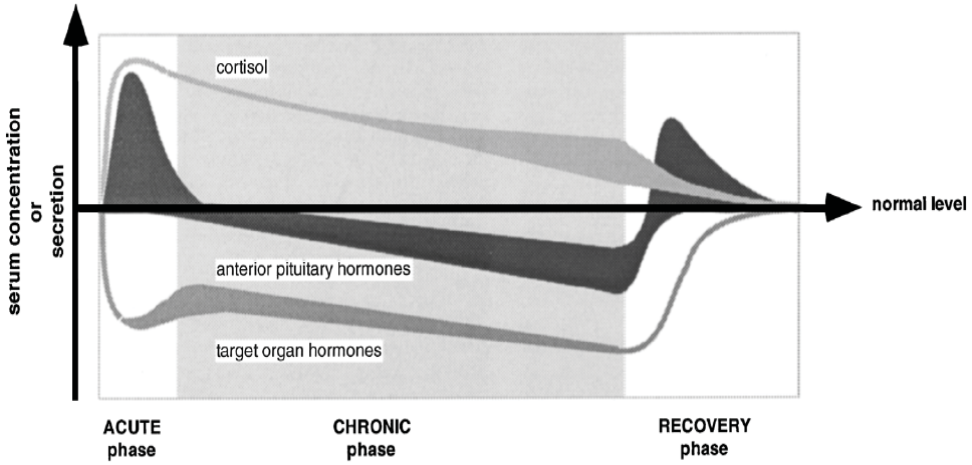


Fig. 1. Simplified concept of the pituitary-dependent changes during the course of critical illness. In the acute phase of illness (first hours to a few days after onset), the secretory activity of the anterior pituitary is essentially maintained or amplified, whereas anabolic target organ hormones are inactivated. Cortisol levels are elevated in concert with ACTH. In the chronic phase of protracted critical illness (intensive care dependent for weeks), the secretory activity of the anterior pituitary appears uniformly suppressed in relation to reduced circulating levels of target organ hormones. Impaired anterior pituitary hormone secretion allows the respective target organ hormones to decrease proportionately over time, with cortisol being a notable exception, the circulating levels of which remain elevated through a peripheral drive, a mechanism that ultimately may also fail. The onset of recovery is characterized by restored sensitivity of the anterior pituitary to reduced feedback control. (Adapted from Van den Berghe, G (1998) Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. *Journal of Clinical Endocrinology and Metabolism*, 83 (6), pp. 1827-1834).

Case reports have provided clinical data to justify an increased attention towards potential occurrence of secondary hypoadrenalism from the acute phase in TBI patients. In order to illustrate the possible pitfall in diagnosing the causes of hyponatraemia in TBI patients, Agha et al. (Agha et al., 2007) reported data from 3 patients with severe TBI, who were initially misdiagnosed as syndrome of inappropriate ADH secretion (SIADH). In two of the cases hypoadrenalism was subsequently suspected due to the combination of hyponatraemia, hypoglycaemia and hypotension, and in the third case because plasma sodium did not correct with fluid restriction. All three patients had extremely low baseline cortisol concentrations of 33 – 110 nmol/L, and undetectable ACTH levels. The condition ameliorated in all upon glucocorticoid replacement. It should be emphasized that patients may present with more subtle signs and symptoms, and still be life-threatened by undiagnosed hypoadrenalism.

5. Prevalence of chronic hypopituitarism in TBI

Anterior pituitary hormone deficiency following TBI has traditionally been considered very rare, and mainly reported as single cases or series of cases. Over the last 10 years, the field has received increased attention and chronic anterior pituitary hormone deficiency has been reported with a prevalence ranging from 1% and up to 83% (Table 1). The results from most studies have suggested that persistent posttraumatic hypopituitarism might be a more common complication in TBI than previously believed, although some studies have failed to show such high occurrence rates (Kokshoorn et al., 2011; van der Eerden et al., 2010).

The diversity of the reported prevalences of chronic anterior pituitary hormone deficiency is likely to be explained by differences in study populations, study designs, and diagnostic procedures. Trauma severity varied considerably among the studies (Table 1). In general, a lower prevalence of posttraumatic hypopituitarism tended to be recorded in studies recruiting less severely injured patients (Kokshoorn et al., 2011; van der Eerden et al., 2010), and indicators of increased trauma severity was also suggested to be associated with development of hypopituitarism by some (Bavisetty et al., 2008; Bondanelli et al., 2004; Kelly et al., 2000; Klose et al., 2007a; Schneider et al., 2008), while not by others (Agha et al., 2004; Aimaretti et al., 2005; Leal-Cerro et al., 2005). In 22 TBI patients Kelly et al.(Kelly et al., 2000) identified injury severity in terms of an initial Glasgow Coma Scale score (GCS) of less than 10, diffuse brain swelling and hypoxia/hypotension as risk factors of posttraumatic hypopituitarism. Bavisetty et al. (Bavisetty et al., 2008) found that the degree of injury as defined by acute cerebral CT was the strongest predictor for long-term pituitary deficiencies, and in the cohort examined by us (Klose et al., 2007a), a normal CT excluded development of long-term deficiencies. On the other hand, the role of acute CT was recently contradicted by Kleindienst el al (Kleindienst et al., 2009) who found no relationship between acute or late CT findings and development of hypopituitarism. Other surrogate measures of trauma severity have been suggested to predict post-TBI hypopituitarism, including increased intracranial pressure (Klose et al., 2007a), diffuse axonal injury and basal skull fractures (Schneider et al., 2008).

Recently, Kokshoorn et al. (Kokshoorn et al., 2010) questioned the considerable variation of the reported prevalence, and assessed the impact of methodological differences among the present studies. They confirmed that part of the variation indeed seemed to be caused by differences in study design, diagnostic procedures, and other confounding factors such as BMI, prohibiting simple generalization from the original studies. In general, a lower prevalence of posttraumatic hypopituitarism tended to be recorded in studies using the ITT for the evaluation of the GH reserve (Kelly et al., 2000; Klose et al., 2007a; Kokshoorn et al., 2011), and in the studies using confirmatory tests (Agha et al., 2004; Klose et al., 2007a; Leal-Cerro et al., 2005; van der Eerden et al., 2010).

Table 2 a-d illustrates the relationship between diagnostic stringency and reported prevalence of GH, ACTH, LH/FSH and TSH deficiencies. Diagnostic stringency was rated according to information in the publications on pituitary tests, comparison with own and sufficient normative data and performance of confirmatory testing, There was an apparent association between diagnostic stringency and reported prevalence of GH deficiency (Table 2a). The diagnostic cut-offs have varied considerably between studies, and as suspected, the reported prevalence of GH deficiency increased with increasing test related cut-off limits. Furthermore, some studies only reported severe GH deficiency, whereas others reported both severe and partial cases.

			Anterior Pituitary Hormone deficiency (%)					
Authors	*n*	GCS<13	Total	Multiple deficiencies	GH deficiency*	ACTH deficiency	LH/FSH deficiency	TSH deficiency
Kelly et al., 2000	22	NS	36	23	18^	5	23	5
Lieberman et al., 2001	70	NS	69	18	15	46	1	22
Agha et al., 2004	102	100%	29	6	8 (3)	13	12	1
Bondanelli et al., 2004	50	86%	54	12	8 (20)	0	14	10
Popovic et al., 2004	67	100%	34	10	15 (15)	7	9	4
Aimaretti et al., 2005	70	45%	23	10	20 (16)	7	11	6
Leal-Cerro et al., 2005	170[b]	100%	25	9	6	6	17	6
Schneider et al., 2006	70	78%	36	4	10	9	20	3
Tanriverdi et al., 2006	52	40%	51	10	33	19	8	6
Herrmann et al., 2006	76	100%	24	7	8	2	17	2
Klose et al., 2007	104	58%	15	6	11 (5)	5	2	2
Bavisetty et al., 2008	70	NS	21	4	16	0	10	0
Wachter et al., 2009	53	61%	25	2	2	4	15	6
Kleindienst et al., 2009	23	78%	83	30	39	48	0	0
v der Eerden et al., 2010	107	28%	< 1	0	0	< 1	0	0
Krahulik et al., 2010	87	NS	21	-	14	0	6	0
Park et al., 2010	45	100%	31	13	20	13	18	7
Kokshoorn et al., 2011	112	43%	5	1	3	4	1	0

GCS: Glasgow Coma Scale score; NS: nor specified; *Severe (partial) when reported as such; ^GHD+GHI; [b] only 99 patients tested

Table 1. Present publications on the prevalence of chronic posttraumatic anterior pituitary dysfunction.

A	Diagnostic tests and cut-offs used for the diagnosis of GH deficiency				
Authors	**Test**	**Cut-offs**	**Confirmatory test**	**Prevalence of GH deficiency**	**Diagnostic stringency**
van der Eerden et al., 2010	GHRH-arg; if GHRH-arg response low then ITT or GHRH-arg	GHRHarg: peak GH < 3.5ug/l ITT: peak GH < 3,4 ug/l	Yes	0	
Kokshoorn et al., 2011	ITT; if contraindicated then GHRH-arg	ITT: peak GH < 3 ug/l GHRHarg:: BMI<25; peakGH < 11 ug/l BMI25-30: peakGH <8 ug/l BMI>30: peak GH < 4 ug/l	No	3	
Herrmann et al., 2006	GHRH-arg; if GHRH-arg & IGF-1 low, then additional ITT	GHRH-arg: peak GH < 9 ug/l ITT: peak GH < 3 ug/l	Yes	8	
Klose et al., 2007	ITT; if contraindicated then GHRH-arg	ITT: peak GH < 3 ug/l GHRHarg: peak GH < 9 ug/l	Yes	11	
Leal-Cerro et al., 2005	If IGF-1 low or pituitary deficiency other than GHD, then GHRH-GHRP-6 & ITT &. GST	GHRH-GHRP-6: peak GH ≤ 10 ug/l; If peak GH 10-20 ug/l then confirmed by ITT: peak GH < 3 ug/l GST: peak GH < 3 ug/l	Yes	6	
Agha et al., 2004	GST; if sub-normal then ITT: if ITT contra-indicated then GHRH-arg	GST: peak GH <5 ug/l ITT: peak GH < 5 ug/l GHRH-arg: peak GH < 9 ug/l	Yes	8	
Kleindienst et al., 2009	GHRH-arg	peak GH <9 ug/l	No	39	
Schneider et al., 2006	GHRH-arg	peak GH ≤9 ug/l	No	10	
Aimaretti et al., 2005	GHRH-arg	peak GH <9 ug/l	No	20	
Bondanelli et al., 2004	GHRH-arg	peak GH <9 ug/l	No	8	
Lieberman et al., 2001	Glucagon test in a NS subset of patients	peak GH <3 ug/l	No	15	
Popovic et al., 2004	GHRH-GHRP6	peak GH <10 ug/l	No	15	
Tanriverdi et al., 2006	GHRH-GHRP6	peak GH <10 ug/l	No	33	
Kelly et al., 2000	ITT	NS; <5th percentile from 18 HC	No	18	
Bavisetty et al., 2008	GHRH-arg	peak GH < 12 ug/l	No	16	
Park et al., 2010	ITT	peak GH < 10 ug/l	No	20	
Krahulik et al., 2010	Arginine or GHRH	Arginine: < 10th percentile of HC Glucagon: NS	No	14	-
Wachter et al., 2009	GHRH*	NS	No	2	-

Table 2. a.

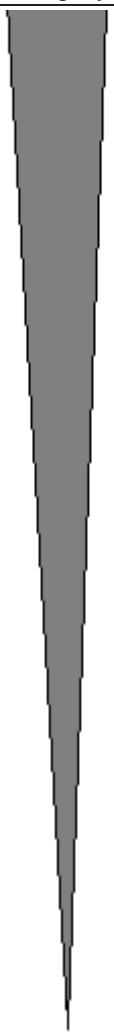
B	Diagnostic tests and cut-offs used for the diagnosis of ACTH deficiency				
Authors	**Test**	**Cut-offs**	**Confirmatory test**	**Prevalence of ACTH deficiency**	**Diagnostic stringency**
Kelly et al., 2000	ITT	peak cort below 283 nmol/l^; pt diagnosed on clinical picture	No	5	
Bavisetty et al., 2008	LDST	peak cort < 331 nmol/l^^	No	0	
Klose et al., 2007	ITT; if contraindicated then SST	peak cort < 500 nmol/l	Yes	5	
Kokshoorn et al., 2011	ITT; if contraindicated then LDST or SST	peak cort < 500 nmol/l	No	4	
Herrmann et al., 2006	Baseline or ITT, selection criteria for ITT NS	baseline cort < 180 nmol/l peak cort < 500 nmol/l	No	2	
Agha et al., 2004	GST; if subnormal then ITT; if ITT contraindicated then SST	GST: peak cort < 450 nmol/l ITT: peak cort < 500 nmol/l SST: peak cort < 500 nmol/l	Yes	13	
Leal-Cerro et al., 2005	Basal cortisol; if low then ITT	Basal cort: < 200 nmol/l ITT: peak cort < 550 nmol/l + peak ACTH < 6.6 pmol/l	Yes	6	
van der Eerden et al., 2010	Basal cortisol; if low then ITT	basal cort < 200 nmol/l peak cort < 550 nmol/l	Yes	< 1	
Schneider et al., 2006	SST	peak cort < 500 nmol/l	No	9	
Tanriverdi et al., 2006	Basal cortisol; if low then LDST	basal cort: < 193 nmol/l LDST: peak cort < 550 nmol/l	No	19	
Park et al., 2010	ITT	peak cort: < 550 nmol/l	No	13	
Kleindienst et al., 2009	SST	peak cort: < 550 nmol/l	No	48	
Aimaretti et al., 2005	Basal morning cortisol and UFC	9.00 h cort: < 220 nmol/l (evt. low 24-h UFC)	No	7	
Bondanelli et al., 2004	Basal morning cortisol	basal cort: < 220 nmol/l	No	0	
Lieberman et al., 2001	Basal cortisol	basal cort: < 193 nmol/l	No	46*	
Krahulik et al., 2010	If basal cortisol < 500 nmol/l, then ACTH test	peak cort: < 5th percentile of HC, NS	No	0	
Wachter et al., 2009	CRH	NS	No	4	-
Popovic et al., 2004	Basal morning cortisol	NS	No	7	-

Table 2. b.

C	Diagnostic tests and cut-offs used for the diagnosis of LH/FSH deficiency				
Authors	**Test**	**Cut-offs**	**Confirmatory test**	**Prevalence of LH/FSH deficiency**	**Diagnostic stringency**
Kleindienst et al., 2009	Baseline	[**M**: T < 3,1 nmol/dl **preF**: E < 60 pg/dl **postF**: E < 10 pg/dl] + inapp low LH&FSH	No	0	
Tanriverdi et al., 2006	Baseline	**M:** T < 4,6 nmol/l + low/norm LH/FSH **preF**: E < 40 pmol/l+inapp low LH/FSH **post F**: LH&FSH in premenopausal range	No	8	
Klose et al., 2007	Baseline	**M**: T < 10 nmol/l & inapp low LH **preF**: a-/oligomenorrhea + low E & inapp low LH&FSH **postF**: LH&FSH in premenopausal range	Yes	2	
van der Eerden et al., 2010	Baseline	**M**: T < 11 nmol/l & low fT & low/norm LH&FSH **preF**: amenorrhea, low E & low/norm LH&FSH **postF**: low gonadotropins	Yes	0	
Leal-Cerro et al., 2005	Baseline; if low then GnRH test	**M**: fT below age dependant ref & low /norm LH&FSH **F**: menstrual distb.+ low E+low/norm LH&FSH **GnRH:** peak LH<10 fold increment above base-line & peak LH > 10 U/l	Yes	17	
Herrmann et al., 2006	Baseline	**M**: T < 9,5 nmol/l + low/normal LH/FSH **preF**: amenorrhea + low E **postF**: LH&FSH in premenopausal range	No	17	
Agha et al., 2004	Baseline	**M**: T < 10.3 nmol/l + low/normal LH&FSH **preF**: amenorrhea + low E **postF**: LH/FSH in premenopausal range	No	12	
Aimaretti et al., 2005	Baseline	**M**: T < 10 nmol/l + low/normal LH/FSH **preF**: menstrual disturb. + E < 20pg/ml	No	11	
Bondanelli et al., 2004	Baseline	**M**: T < 10 nmol/l + low/normal LH/FSH **F**: NS	No	14	
Bavisetty et al., 2008	Baseline	**M:** T < 10 nmol/l ^ **F**: E < 27.6 pg/ml + menstrual disturb.	No	10	
Schneider et al., 2006	Baseline	**M**: T < 12 nmol/l + low/norm LH&FSH **preF**: amenorea after TBI **postF:** inapp low LH&FSH	No	20	
Kelly et al., 2000	M. GnRH F: Baseline	NS	No	23	
Lieberman et al., 2001	Baseline; if low then GnRH	M: low T (NOS) F: menstrual history	No	1	
Popovic et al., 2004	Baseline	**M**: NS **F**: menstrual history	No	9	
Wachter et al., 2009	Baseline / TRH	NS	No	15	
Krahulik et al., 2010	Baseline	M: T<5th perc form HC F: menstrual history; low E	No	6	
Park et al., 2010	Baseline	(M: low T; Pre F: low E with inapp low gonadotropins. Post F: LH/FSH in premenopausal range	No	18	

Table 2. c.

D	Diagnostic tests and cut-offs used for the diagnosis of TSH deficiency				
Authors	**Test**	**Cut-offs**	**Confirmatory test**	**Prevalence of TSH deficiency**	**Diagnostic stringency**
van der Eerden et al., 2010	Baseline	fT4 < 8 pmol/l & norm/low TSH	Yes	0	
Leal-Cerro et al., 2005l.	Baseline; if low then TRH	fT4 < 7,7 pmol/l & norm/low TSH TRH: TSH peak < 7 mU/ml	Yes	6	
Agha et al., 2004l.	Baseline	fT4 < 8 pmol/l & norm/low TSH	No	1	
Bondanelli et al., 2004.	Baseline	fT4 < 10,3 pmol/l & norm/low TSH	No	10	
Aimaretti et al., 2005.	Baseline	fT4 < 10,3 pmol/l & norm/low TSH	No	6	
Tanriverdi et al., 2006.	Baseline	fT4 < 10,3 pmol/l & norm/low TSH	No	6	
Kleindienst et al., 2009.	Baseline	fT4 < 10 pmol/l or TT3 < 0,8 ng/dl & TSH < 0,45 U/L	No	0	
Herrmann et al., 2006.	Baseline	fT4 < 10 pmol/l & norm/low TSH	No	2	
Bavisetty et al., 2008.	Baseline	Low TT4 (NS) and fT4 < 10 pmol/l^	No	0	
Klose et al., 2007.	Baseline	fT4 < 12 pmol/l & norm/low TSH	Yes	2	
Schneider et al., 2006	Baseline	fT4 < 12 pmol/l & norm/low TSH	No	3	
Lieberman et al., 2001	Baseline; TRH in some (NS)	Low fT4 and normal/low TSH; or normal fT4 and low TSH TRH: TSH < 5mU/l	No	22	
Wachter et al., 2009	Baseline TRH	NS	No	6	
Popovic et al., 2004	Baseline	NS	No	4	
Kelly et al., 2000.	TRH	NS^^	No	5	
Krahulik et al., 2010.	Baseline	FT4 and TSH (NOS)	No	0	
Park et al., 2010l.	Baseline	Low FT4 & norm/low TSH; NOS	No	7	
Kokshoorn et al., 2011.	Baseline	NS	No	0	

BMI: body mass index; cort: cortisol level; disturb: disturbances; E: estradiol; F: females; fT_4: free thyroxine; ftest: free testosterone; GHD: GH deficiency; GHRHarg: GHRH-arginine test; GHRH-GHRP-6: GHRH-GHRP-6 test; GnRH: GnRH-test; GST: glucagon stimulation test; HC: healthy control; inapp: inappropriately; ITT: insulin tolerance test; LDST: low-dose synacthen test; M: males; norm: normal i.e. within the normal range; NOS: not otherwise specified; NS: not specified; preF: premenopausal women; postF: postmenopausal women; pt: patient; SST: short synacthen test; test: total testosterone level; TBG: thyroid binding globulin; TRH: TRH-test; tT_4: total thyroxine; UFC: urine free cortisol; ^5th percentile from 18 HC; ^^5th percentile from 39 HC; * 7,1 % of the total cohort had a peak cortisol < 500 nmol/l in response to the SST.

Table 2. a-d. Overview of diagnostic procedures and reported prevalence in previous studies on chronic posttraumatic hypopituitarism. Studies are ranged according to diagnostic stringency based on stimulation tests, cut-off criteria, as well as performance of confirmatory tests or not.

GH deficiency, being the most frequently observed deficiency in the studies, was often found to be positively associated with BMI, which was not surprising as obesity (Bonert et al., 2004; Rasmussen et al., 1995) and relative central adiposity (Miller et al., 2005) are major confounders, and negative determinants for the stimulated GH concentrations in persons without hypothalamo–pituitary disturbances. This makes the distinction between organic GH deficiency and obesity difficult or even impossible, and poses a major diagnostic problem in isolated GH deficiency, in particular. The earliest TBI studies using the GHRH+arg test used a fixed cut-off independent on BMI of the subjects, and only later studies adjusted for the known confounding from BMI, by application of BMI related cut-offs that were then available. Many of the studies should in fact reanalyse their data with this information in hand in order to clarify the 'true' number of individuals with GHD, or at least less emphasis should be paid on these study results in meta-analyses, reviews and recommendations.

The association between diagnostic stringency and reported prevalence is not as clear when it comes to secondary hypoadrenalism. However, the two studies reporting the lowest prevalence also applied the most stringent criteria. Kelly et al. defined their cut-off limit for the ITT as the 5th percentile of peak GH derived from 18 healthy control subjects. It was not further specified, but was somewhat below 283 nmol/l, which is striking. Establishment of local diagnostic cut-off points are generally recommended, due to assays dependency. However, cut-offs limits, based on 5th percentiles from normative data from such small populations, may be heavily influenced by outliers, which may explain the low cut-off limit used in this study. This hypothesis seems reinforced by the fact that although passing the biochemical definition having peak cortisol of 286 nmol/l, one patient was diagnosed with secondary hypoadrenalism on clinical manifestations (Kelly et al., 2000). In the other end of the spectrum, Libermann et al. reported a total prevalence of anterior pituitary hormone deficiency of 69%, including 46% with secondary hypoadrenalism. The occurrence of secondary hypoadrenalism would, however, be reduced to 7%, if data had relied on the results from dynamic testing.

The definition of gonadotropin deficiency mostly differed as concern the chosen cut-off of testosterone in men (Table 1c). Not unanticipated, those studies applying the lowest cut-offs tended to report lower prevalences of gonadotropin deficiency. Furthermore, studies following the general recommendation of repeated sampling in case of a low or low normal testosterone concentration, reported lower prevalences of gonadotropin deficiency (Klose et al., 2007a; van der Eerden et al., 2010), which is probably due to the low test-retest reproducibility (Bhasin et al., 2010; Brambilla et al., 2007) of testosterone measurements.

Although the diagnosis of secondary hypothyroidism is challenging, the studies used very similar definitions, with cut-offs mostly differing according to the local reference ranges applied (Table 1d). Only one study differed significantly, reporting a prevalence of 22%, explained by a much wider definition (Lieberman et al., 2001). Applying the general definition (low fT4 and low/normal TSH) to this study, the prevalence would have been lowered to 12%.

Certain antiepileptic drugs may have various side effects on the endocrine function. Given the relatively high incidence of posttraumatic epilepsy in TBI survivors, biochemical alterations induced by epilepsy in itself or the antiepileptic drugs may have confounded the estimated prevalence in the present TBI studies. There are, however, insufficient data to enable a proper evaluation of the impact of such confounder.

Thus, diagnostic uncertainties are likely to have affected the published prevalences, and although plentiful in general, it is of special interest in post-TBI hypopituitarism, given that

the large majority of these patients were reported with isolated GHD or with only one additional deficit. This is in contrast to patients with objective evidence of hypothalamic-pituitary damage, and thus a high pre-test probability of hypopituitarism, where isolated GHD is less frequent.

6. Outcome studies on hypopituitarism in TBI

Concerns have been raised whether undiagnosed and thus untreated hypopituitarism may contribute to the mortality and severe morbidity seen in TBI. The magnitude of such contribution has still not been defined, and again data are conflicting.

Increased disability, decreased QoL and a greater likelihood of depression has been described in patients with posttraumatic GH deficiency (Bavisetty et al., 2008; Kelly et al., 2006), although others have suggested that neuropsychological and QoL deficits are more closely associated to presence of haemorrhagic lesions on CT, than to hypopituitarism per se (Wachter et al., 2009). Although not taking presence of cerebral lesions into account, we described that when adjusted for confounders such as trauma severity, posttraumatic hypopituitarism remained an independent predictor of the classical phoenotypic features of hypopituitarism, including an unfavourable lipid and body-composition profile, as well as worsened QoL (Klose et al., 2007d), which could point to an association. Bondanelli et al. (Bondanelli et al., 2007) found that peak GH was an independent predictor of poorer outcome as measured by rehabilitation scales evaluating cognition, disability and functional dependency. Such association between cognitive function impairment and GH axis integrity was recently questioned by Pavlovic et al. (Pavlovic et al., 2010) who applied a very extensive neuropsychological battery, selected for high sensitivity for subtle brain dysfunction. No differences were found comparing patients with GH deficiency and those with normal GH function, and no correlation was found between neuropsychological variables and stimulated peak GH or insulinlike growth factor-I (IGF-I) levels.

A recent study focused on another outcome measure, and found reduced aerobic- and endurance capacity in patients with posttraumatic isolated GHD as compared to those with normal pituitary function (Mossberg et al., 2008).

Discrepancies in the reported outcome data, are likely to be explained by lack of power, variable diagnostic validity questioning the grouping of patients, and problems to correct for the enormous heterogeneity of co-morbidities in TBI patients. Furthermore, use of different patient reported outcome questionnaires complicates direct comparison.

7. Treatment of pituitary insufficiency

7.1 Acute phase

Although pituitary hormone alterations are a very common phenomenon in the acute phase after TBI, the diagnosis entails plenty of problems, and currently there are no reliable diagnostic cut-offs for anterior pituitary hormone deficiency in critically ill patients. Furthermore, there is no evidence to support a clinical benefit from hormonal replacement therapy with GH, thyroid hormone, nor reproductive hormones in the critically ill. Treatment with pharmacological doses of GH has been shown to increase morbidity and mortality (Takala et al., 1999), whether or not administration of thyroid hormone is beneficial or harmful remains controversial (De Groot, 2006; Stathatos et al., 2001), and no conclusive clinical benefit has been demonstrated for androgen treatment in prolonged

critical illness (Angele et al., 1998). The diagnosis of adrenal failure and management of this disorder also remains controversial, with poor agreement among the experts. The threshold that best describes the patients at need for acute or chronic glucocorticoid replacement is still to be defined and is likely to depend on the underlying illness. The evidence of a clinical benefit from glucocorticoid replacement therapy in the acute phase of TBI relies on case reports (Agha et al., 2005b; Webster & Bell, 1997). At present time, recommendations are pragmatic and mainly rely on the clinical evaluation of the patient, where a combination of hyponatraemia, hypoglycaemia, and hypotension is highly suggestive (Agha et al., 2005b; Cooper & Stewart, 2003), but not prerequisite, of secondary hypoadrenalism, and should elicit an immediate therapeutic trial of glucocorticoid replacement. The subsequent treatment response should guide the decision of further treatment and follow-up.

7.2 Chronic phase

The negative effects of chronic glucocorticoid-, thyroid- and gonadal hormone deficiencies are well recognised, as is the beneficial effect from appropriate replacement therapy. Yet randomised clinical trials have never been performed in such classical endocrine deficiencies, and neither are randomised studies available to document such effect in TBI patients. These deficiencies and their treatment, however, have more distinct clinical features, than e.g. GH deficiency, which is the most frequently reported deficiency in TBI patients. It is associated with impaired linear growth and attainment of normal body composition in children, but in adults the features are less specific with reduced lean body mass, decreased exercise capacity, reduced bone mineral density, unfavourable changes in the lipid profile and decreased QoL.

There are limited data on treatment effect in this specific subpopulation of patients with anterior pituitary hormone deficiency. Two studies have compared clinical and other outcome variables measured at baseline and after one year of hGH replacement in TBI patients and in patients with non-functioning pituitary adenoma (NFPA) from Pfizer International Metabolic (KIMS) database(Casanueva et al., 2005; Kreitschmann-Andermahr et al., 2008). At one-year follow-up, IGF-I SDS levels had increased to the normal range, and improved QoL was observed, in TBI as in NFPA patients, suggesting that TBI patients with GH deficiency benefit from hGH replacement in terms of improved QoL in a similar fashion as do NFPA patients. Worth mentioning, however, is the fact that this registry study was biased in having included only patients diagnosed with GHD, and this cohort is therefore not representative for a general cohort of TBI patients. Recently, data was published from a study including 23 patients with posttraumatic GH deficiency/insufficiency randomised to either a year of placebo or GH replacement therapy (High, Jr. et al., 2010). Data suggested that some of the cognitive impairments observed in these patients might be partially reversible with appropriate replacement therapy. Similar observations were recorded by Maric et al. (Maric et al., 2010). Reimunde et al. (Reimunde et al., 2011) compared the effect of daily neurocognitive rehabilitation plus GH replacement, with neurocognitive rehabilitation alone and reported larger scale improvements in the GH deficient TBI patients on combined treatment schedule. Although encouraging, there is still inadequate evidence to demonstrate that pituitary replacement therapy improves the metabolic profile, neuro-cognitive symptoms, psychosocial problems, and work-related activities in TBI patients, and larger randomised placebo-controlled studies are much awaited, and crucial for proper evidence based clinical decisions.

8. When should testing and treatment be considered in patients with TBI?

Currently no evidence exists to suggest introduction of anterior pituitary hormone screening in the acute phase, due to both the aforementioned diagnostic difficulties and lack of evidence of the beneficial effects from hormonal substitution. Adrenal insufficiency should be treated upon clinical suspicion.

The temporal relationship between TBI and hypopituitarism is poorly understood. Longitudinal studies examining TBI patients at variable time points from the acute phase to years after the trauma, have reported transient, permanent, and de novo deficiencies all through the time span (Agha et al., 2005a; Kleindienst et al., 2009; Klose et al., 2007b; Tanriverdi et al., 2006). Part of this variation may be ascribed to diagnostic difficulties, including those caused by the stress of severe illness, but may also in some cases be related to medication effects, and lack of test re-test reproducibility. It is therefore often recommended that neuroendocrine evaluation should be performed no earlier than one year post trauma unless the clinical picture indicates otherwise (Ghigo et al., 2005; Ho, 2007; Tanriverdi et al., 2011).

Another important issue is which patients that should be considered for neuroendocrine evaluation. This is particularly important considering the high incidence of TBI (> 100 in 100,000 inhabitants). On the one hand it is of clinical importance to identify all patients that would benefit from relevant substitution therapy, but on the other hand it is of major socio-oeconomic interest to ensure a cost-effective strategy. To perform pituitary testing in all TBI patients would be an impossible task both logistically and financially. Unfortunately, the area lacks valid clinical, biochemical or other predictors and it has not yet been clarified, which part of the TBI population that should be tested (Klose & Feldt-Rasmussen, 2008). Symptoms of hypopituitarism are usually very unspecific and highly overlap those of TBI patients in general, and can thus rarely be used for patient selection. Different markers of increased trauma severity, and injury location have been proposed as predictive (Bavisetty et al., 2008; Kelly et al., 2000; Klose et al., 2007a; Schneider et al., 2007b; Schneider et al., 2008), but unfortunately data are very inconsistent.

Finally, data are still awaited to document the effect of hormone replacement therapy in this patient category, and until such data are available, one should be cautious to introduce uncritical routine anterior pituitary testing and replacement therapy. Certain categories of patients with TBI may be at a greater risk, including those with increased ICP (Klose et al., 2007a), CT abnormalities (Bavisetty et al., 2008), diffuse axonal injury, and those with basal skull fractures (Schneider et al., 2008), and should probably be regarded with a higher priority for pituitary assessment.

9. Conclusion

Anterior pituitary hormone alterations are frequently encountered in the acute phase after TBI. The relevance and therapeutic implications of such endocrine changes are still debated. Acute phase assessment of the growth hormone, thyroid, and gonadal axis is not recommended, as there is no evidence of a clinical benefit from replacement therapy at this stage. Untreated adrenal insufficiency can be life threatening. As biochemical assessment is difficult in the acute phase, the diagnosis should mainly be based on the clinical picture, and immediate treatment instituted on suspicion.

Chronic anterior pituitary hormone deficits are reported with a much higher frequency than previously thought, and this has caused expert panels to propose recommendations for

hormone assessment of pituitary insufficiency and consequent appropriate replacement after TBI. Which subgroups of patients that should be considered for assessment, and at what time-point is, however, still debated.

Introduction of a routine screening program at this stage would be tempting, but remains problematic. The annual incidence rate of TBI leading to hospitalisation is roughly 100 in 100,000 inhabitants (Engberg & Teasdale, 2001), and it is thus of major socio-oeconomic interest to ensure a cost-effective screening strategy, as pituitary testing in all TBI patients would be an impossible task both logistically and economically. Much larger cohorts are needed for further evaluation and confirmation of reliable screening markers. Future studies should be designed to ensure a high diagnostic robustness for proper identification of reliable predictors, and to ensure that data can be generalised to an every-day TBI population, as the results may be highly dependent on selection criteria, confirmation of abnormal test results or not, and use of different diagnostic tests and criteria. Coexisting morbidities such as obesity and epilepsy, may also confound the results of neuroendocrine testing, and thus render the diagnostic process as well as the decision-making regarding replacement therapy difficult. Had the patients with high BMI had additional hormone deficiencies to GHD, and all patients diagnosed with isolated GHD been lean many of the reported results would have been more convincing. Finally, properly designed randomised intervention studies are awaited to document an effect of hormone replacement therapy in this patient category, and until such data are available, one should be cautious to introduce uncritical routine anterior pituitary testing and replacement therapy in TBI patients.

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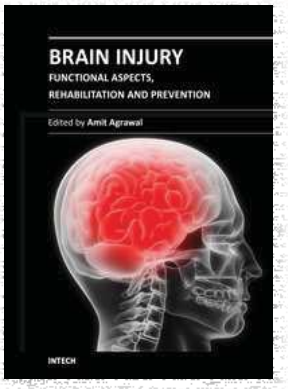

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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