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The frequency and the diagnosis of pituitary dysfunction after traumatic brain injury

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Abstract

Purpose Clinical research studies over the last 15 years have reported a significant burden of hypopituitarism in survivors of traumatic brain injury (TBI). However, debate still exists about the true prevalence of hypopituitarism after head injury.

Methods We have reviewed the literature describing the frequency of post-traumatic hypopituitarism and discuss the factors which may explain the variable frequency of the reported deficits in clinical studies including research methodology and the natural history of the disease.

Results Pituitary hormone perturbations in the acute phase following injury are frequent but are difficult to attribute to traumatic pituitary damage due to physiological hormonal changes in acute illness, the confounding effect of medications, other co-morbidities and lack of appropriate control subjects. Nevertheless, a small number of studies have emphasised the clinical importance of acute, dynamic disturbance of the hypothalamic–pituitary–adrenal axis. There is a much larger evidence base examining the frequency of hypopituitarism in the chronic, recovery phase following head injury. These studies report a very broad prevalence of long-term pituitary hormone dysfunction in survivors of TBI. However, systematic review suggests the prevalence to be between 27 and 31%.

Conclusion Survivors of head injury are at risk of pituitary hormone dysfunction and we suggest an approach to the diagnosis of post-traumatic hypopituitarism in routine clinical practice.

Keywords Hypopituitarism · Traumatic brain injury · Post-traumatic hypopituitarism

Introduction

Traumatic brain injury (TBI) is a global public health problem and the leading cause of death and disability among young people in developed countries. It is estimated that approximately 57 million people worldwide have been hospitalised following TBI [1]. A study from 13 European countries reported the incidence of TBI to be 235/100,000 per year [2]. In the United States (US), TBI accounts for 2.5 million visits to the Emergency Department and contributes to 50,000 deaths annually [3]. Survivors frequently suffer physical and neuropsychiatric sequelae [4]. Men are twice as likely to suffer head injury compared to women [1].

Hypopituitarism following TBI was first recognised a century ago [5]. Evidence from autopsy studies, dating back several decades, confirmed the frequent finding of vascular and traumatic injuries to the hypothalamic-pituitary region in TBI victims [6, 7]. However, it is only in the last 15 years that researchers have attempted to define the true prevalence of post-traumatic hypopituitarism (PTHP) in survivors of head injury.

While PTHP is now recognised as relatively common, there is a considerable variation in the reported prevalence, with a recent systematic review reporting a range of 15–68% [8]. The reason for this is not fully understood but is likely to be multifactorial and influenced by the timing of assessment, different endocrine testing protocols, severity of injury and differences between children and adults. Most clinical research in the field has focused on survivors of moderate to severe TBI who have been hospitalised. However, emerging research suggests that repetitive concussive brain injuries

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can also result in pituitary hormone deficiencies and that even a single typical concussion may result in chronic hypopituitarism [9].

This review will discuss the frequency of PTHP reported in the literature and summarise the research which identifies those at highest risk of hypopituitarism. Also, we will review the appropriate timing and suggest a protocol for pituitary hormone evaluation.

Prevalence of hypopituitarism following TBI

Several retrospective and prospective studies have reported a highly variable prevalence of chronic anterior pituitary dysfunction following head injury in adults ranging from 5 to 76.4%. Some of the variability can be explained by the timing of testing. PTHP is a dynamic illness and a small number of prospective studies, which performed repeat testing on the same subjects during the acute and chronic phase following head injury, have confirmed that hormone deficiencies detected early following injury may recover up to 1 year [10, 11]. While the temporal trend in PTHP appears to be one of improvement, a small number of subjects develop new hormone deficiencies during long-term follow up [12]. However, the wide range in the estimated prevalence of hypopituitarism following TBI cannot be explained solely by a variable time of evaluation. Different cohort characteristics and methodological differences related to the criteria and tests used to diagnose hypopituitarism have an important influence of the reported prevalence of PTHP. Studies that used confirmatory tests have reported lower frequency of hypopituitarism [13–15].

Acute hypopituitarism

Anterior pituitary dysfunction

Some alterations in hypothalamic pituitary function in the days following head injury may be physiological responses to critical illness or to drugs (e.g. sedation, opiates) used during this time. For example, low serum sex steroid concentration is present in over 80% of patients after moderate to severe TBI but recovers spontaneously in the majority [10]. Even true deficiency of growth hormone (GH), gonadotrophins and thyrotrophin would not merit replacement during the acute recovery phase. Acute ACTH deficiency, on the other hand, can be life threatening. A small number of studies have assessed ACTH/cortisol reserve in the first 2 weeks following head injury and they have reported a broad prevalence of ACTH deficiency ranging from 4 to 78% [11, 16–23]. This very wide range emphasises the challenges of defining true ACTH deficiency in acute critical illness.

Most studies during the acute phase have been uncontrolled and some relied on a single measurement to define the function of the hypothalamic–pituitary–adrenal axis. A recent study by Bensalah et al. demonstrated the impact of the serum cortisol cut off for the definition of acute ACTH deficiency [23]. The investigators measured a single early morning cortisol on over 200 patients in the first week following TBI and set three thresholds for defining potential ACTH deficiency − 3, 10 and 15 µg/dL. Acute deficiency was reported in 2.8%, 21% and 37% respectively using the three cortisol cut-offs. US researchers performed a controlled study, comparing subjects with moderate to severe head injury and those with extra-cranial trauma (ECT) only [19]. Serum cortisol was measured twice daily for up to 9 days post injury and 53% of subjects were deemed by the authors to have ACTH deficiency/insufficiency (serum cortisol < 25 percentile of values in ECT cohort [15 µg/dL] on two occasions). This study also highlighted the strong relationship between hypocortisolemia and use of anaesthetic agents including etomidate, phenobarbital and propofol.

In another prospective trial, Hannon et al. measured early morning serum cortisol on five separate occasions during the first 10 days after moderate to severe head injury [18]. They reported that 78% of subjects had evidence of ACTH deficiency (defined as serum total cortisol < 11 µg/dL) at some stage during the acute phase. This study also emphasises the highly dynamic nature of ACTH/cortisol in the early days following head injury. Using a different methodology—a glucagon stimulation test—at a median of 12 days post injury, the author and colleagues identified acute ACTH deficiency among 16% of a cohort of patients (n = 50) following moderate to severe TBI [17].

Methodological factors in study design clearly have a major impact on the reported prevalence of acute ACTH deficiency. Also, the fluctuating levels of cortisol in the serum of patients following head injury and the confounding effect of medications further complicate the diagnosis of true ACTH deficiency. Some authors have questioned the value of serum cortisol measurement during the acute phase following head injury in the absence of clinical features of cortisol deficiency. However, acute hypocortisolemia after TBI has been associated with higher vasopressor requirements and higher mortality [18, 19], although a causal relationship cannot be established. Currently available research has not isolated robust clinical risk factors for the development of acute ACTH deficiency after head injury. In particular, severity of injury and abnormalities on cross sectional brain imaging do not predict the likelihood of acute hypocortisolemia. Future studies should focus on harmonising research protocols as well as identifying better biomarkers of cortisol deficiency which might separate subjects with true ACTH deficiency from those displaying adaptive changes in the hypothalamic pituitary adrenal axis.

Chronic hypopituitarism

Natural history

Prospective, longitudinal studies have confirmed that PTHP is a highly dynamic process. Broadly, the temporal trend is towards recovery of pituitary function in most patients; however, research also suggests that new hormone deficiencies can become manifest during long term follow up. Two prospective studies from Ireland, among adults with moderate to severe TBI, have demonstrated that acute neuroendocrine dysfunction following TBI may recover with time. A study of 50 patients described recovery of anterior pituitary function when subjects underwent repeat endocrine evaluation at 6 and 12 months following injury (Fig. 1) [10]. Gonadotroph function was most likely to normalise with time. Recovery of growth hormone and ACTH reserve was observed in 66% and 50% of patients respectively. A subsequent study, found that 78% of adults with moderate/severe TBI had evidence of acute hypocortsiolemia but only 18% had persistent evidence of ACTH deficiency when retested after 6 months [18].

These results mirror those of Klose et al. who showed that early neuroendocrine disturbance was common (76% of subjects) but only 11% had biochemical evidence of hypopituitarism at 1 year post injury [11]. Prospective studies

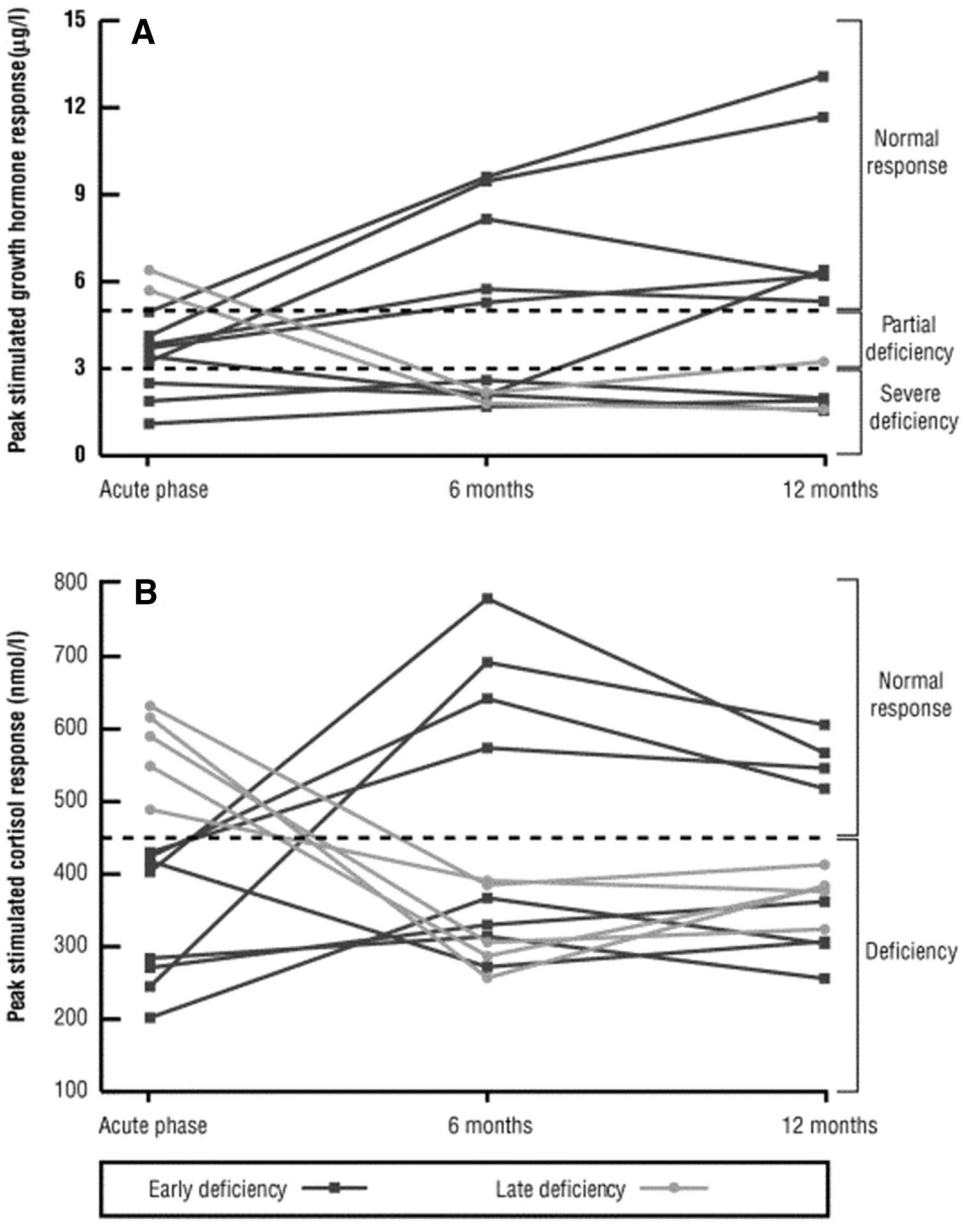

Fig. 1 Peak growth hormone (**a**) and cortisol (**b**) responses to glucagon stimulation in a prospective cohort of 50 patients following moderate to severe TBI demonstrating that acute pituitary dysfunction often improves over 12 months but new hormone deficiencies may also become manifest during follow up. Reproduced with permission from [10]

by Tanriverdi et al. give important insights into the natural history of PTHP. In a study of 52 subjects following TBI they found, once again, that early neurohormonal disturbance often resolved during follow-up but approximately 50% of subjects had new pituitary hormone deficiencies 1 year after injury [16]. A re-evaluation of the same cohort, 3 and 5 years after injury, confirmed that the general trend in pituitary function was towards recovery over time [12, 24]. However, after 5 years 24% of subjects had persistent hypopituitarism. Both the studies by Klose et al .and Tanriverdi et al. were remarkable for a large subset of patients with mild TBI.

Prevalence of chronic hypopituitarism

In view of the dynamic nature of neurohormonal changes that can occur early following head injury and the findings of natural history studies discussed above we consider chronic hypopituitarism to be defined by hormonal evaluation 6 months or more post-injury. The combined results of several retrospective and prospective studies have reported a very broad range of chronic hypopituitarism from 5 to 76.4%. This wide range is clinically problematic but likely reflects the multiple confounding factors in the diagnosis of hypopituitarism in patients following TBI.

Estimating the true prevalence of pituitary dysfunction in the chronic phase after TBI is difficult due to differences in patient selection, timing of testing in relation to the injury and, importantly, the methodological differences with respect to the type of dynamic test used, whether abnormal results were confirmed or otherwise using a second test and the threshold used to define normality. The impact of methodological issues is illustrated in a study of GH deficiency (GHD) in a large Danish TBI cohort [13]. The investigators compared the insulin tolerance test (ITT) to the growth hormone releasing hormone (GHRH) and pyridostigmine (combined test). Rates of GHD were significantly higher—by a factor of 4—when the combined test was employed in comparison to the ITT. When both tests were used to confirm the diagnosis, the rate of GHD was substantially less than when either test was used alone. In addition, the use of a GH cut-off value, derived from a local, healthy cohort, for the GHRH and pyridostigmine test, resulted in a lower prevalence of GHD when compared to the use of a cut-off recommended in international guidelines. A systematic review found similar methodological bias in the diagnosis of ACTH deficiency after TBI [25]. The findings suggested that the broad range of chronic ATCH deficiency could be explained by the wide variety of test used including ITT, synACTHen (corticotrophin) stimulation, cortiotrophin releasing hormone (CRH) stimulation and basal cortisol measurement (Table 1).

The impact of patient selection on the reported prevalence of hypopituitarism is more controversial. Some researchers have found that patients with lower post-resuscitation Glasgow Coma Scale (GCS) scores (reflecting more severe TBI), hypoxia/hypotension and increased intracranial pressure are more likely to develop PTHP but this has not been a consistent finding [26–28]. Radiological features on cross-sectional imaging following head injury have been variably reported to predict hypopituitarism. These include base of skull fracture, diffuse brain swelling, petechial brain haemorrhage and focal cortical contusions [27, 29–31]. Recent research, suggests that decreased apparent diffusion coefficient (a marker of tissue ischaemia) may be a useful radiological predictor of PTHP and may help to stratify patients for biochemical screening. However, further prospective, longitudinal research is required [32]. A recent review article has discussed, in detail, the relative predictive power of these and other clinio-radiological features in post-traumatic hypopituitarism [33].

Notwithstanding the confounding elements described above, a number of studies among unselected patients have helped to define the prevalence of hypopituitarism among long term survivors of TBI and the main ones are summarised in Table 1. In one of the earliest studies, Aimaretti and colleagues (n = 70) reported anterior hypopituitarism in 22.7% of patients [34]. This was followed by Tanriverdi et al. and Schneider et al. who described a prevalence of 51% and 36% in long-term survivors respectively [16, 35]. Klose et al., in a study of 104 patients, found a lower prevalence of 15% at 1 year [26]. A similar, large retrospective study from Ireland among 102 TBI survivors of moderate or severe TBI diagnosed hypopituitarism in 28% of subjects [14]. The last two studies used confirmatory dynamic tests. Most recently, in a study of 100 consecutive patients, Hannon et al. reported that 34% had pituitary hormone deficiency [18]. Finally, two systematic reviews, one in 2007 and another in 2014, have examined the heterogeneity between various studies and reported a pooled prevalence of 27.5% and 31.6% respectively following TBI [8, 36].

Neurohypophyseal damage

Cranial diabetes insipidus (DI) is common following moderate to severe head injury and typically becomes manifest within the first 3 days. In general, DI is easily diagnosed following head injury and, therefore, the prevalence rate is less affected by methodological bias. Prospective studies have detected acute DI in 16–28% of patients following TBI [17, 37–40]. Lower rates, reported by other investigators, have been derived from smaller retrospective studies and are likely to be an underestimate of the true prevalence [41, 42]. There is a correlation between severity of TBI and likelihood of developing DI [38]. Also, DI is associated with cerebral

Table 1 Summary of selected studies evaluating anterior pituitary function in adult survivors of TBI 12 months or more after injury

Study	Patient No. 12 months follow-up	TBI Severity	Timing of test post TBI (months)	Overall hypopituitary %	LH/FSH deficiency %	GH deficiency %	TSH deficiency %	ACTH deficiency %
Hannon et al. (2013) [18][a]	32	Moderate–severe	6–24 (median 14)	34	3.1	18.8	0	18.8
Kozlowski et al. (2012) [78][b]	55	Mild–severe	At least 12	76.4	3.6	40	21.8	27.3
Kokshoorn et al. (2011) [15][c]	112	Mild–severe	1–144 (median 36)	5.4	0.9	2.7	0	1.8
Krahulik et al. (2010) [79][d]	89	Moderate–severe	12	21	5.6	13.5	N/R	N/R
Berg et al. (2010) [80][e]	246	Moderate–severe	4–47 (mean 12)	21	9	11	12	1
Kleindienst et al. (2009) [81][f]	23	Mild–severe	24–36	N/R	0	35	0	43.4
Klose et al. (2007) [26] [g]	104	Mild–severe	Median 13	15	2	15	2	5
Klose et al. (2007) [11][h]	46	Mild–severe	12	11	2	11	2	6.5
Schneider et al. (2006) [35] [i]	70	Mild–severe	12	36	28.5	14.3	4.3	12.9
Tanriverdi et al. (2006) [16] [j]	52	Mild–severe	12	51	41.6	20.4	5.8	9.8
Agha et al. (2005) [10] [k]	48	Mild–severe	12	N/R	13	8.3	18.8	2.1
Aimaretti et al. (2005) [34] [l]	70	Mild–severe	12	22.7	11.4	38.6	5.7	7.1
Leal-Cerro et al. (2005) [82][m]	99	Severe	> 12	42.4	29.2	10	10.1	11.1
Agha et al. (2004) [14][n]	102	Moderate–severe	6–36 (median 17)	28.4	11.8	10.7	1.0	12.7
Bondanelli et al. (2004) [83][o]	50	Mild–severe	12–64	54	14	8	10	0
Popovic et al. (2004) [84][p]	67	Moderate–severe	12–264	34.3	9	14.9	4	7

Rate of GH deficiency is reported as severe GH deficiency unless stated otherwise

N/R not reported

Cross-sectional study. ACTH deficiency was diagnosed using 08:00 h serum cortisol

[a]Prospective study. One hundred consecutive patients with TBI underwent endocrine evaluation following TBI. Twenty-one died during follow-up and 32 attended for follow-up endocrine testing. ACTH deficiency was diagnosed using the insulin tolerance test (ITT). In cases where ITT was contraindicated the glucagon stimulation test was used and the diagnoses confirmed using a short synACTHen test

[b]Cross-sectional study. ACTH deficiency was determined using an ITT

[c]Multicenter cross-sectional study. A variety of methods were used to diagnose ACTH deficiency including the ITT, short synACTHen test (1 µg and 250 µg) and the corticotrophin releasing hormone (CRH) test

[d]Prospective study of 186 subjects following TBI of whom 89 were still under observation at 12 months following injury. ACTH deficiency was defined by measurement of basal serum cortisol and ACTH

[e]Multicenter cross-sectional study in which 330 survivors were screened and 246 underwent endocrine testing. ITT was used to diagnose ACTH deficiency if basal serum cortisol was less than 7 µg/dL

[f]Prospective study of consecutive subjects admitted following TBI. Twenty-three returned for long-term follow up. ACTH deficiency determined by failure of adequate response to short synACTHen test

[g]Cross-sectional study. ITT was used to diagnose ACTH deficiency or short synACTHen test when contraindicated. Insufficiencies were confirmed by retesting

[h]Prospective study. ITT was used to diagnose ACTH deficiency or short synACTHen test when contraindicated

[i]Prospective study of 78 consecutive patients following TBI. Seventy were re-evaluated at 12 months. ACTH deficiency was diagnosed using a short synACTHen test

Table 1 (continued)

[j]Prospective study of 52 patients following TBI. ACTH deficiency was confirmed using a low-dose (1 µg) synACTHen test

[k]Prospective longitudinal study of 50 patients. At 12 months, 48 patients underwent repeat hormonal evaluation. The glucagon test was used to evaluate ACTH reserve

[l]Prospective study. ACTH deficiency was diagnosed using 09:00 h serum cortisol and 24 h urine free cortisol

[m]Cross-sectional study. A total of 170 survivors of severe TBI responded to a mailed questionnaire of whom 57 (33%) did not report any symptoms of hypopituitarism. Fourteen patients declined pituitary testing. Therefore, 99 subjects underwent biochemical evaluation for hypopituitarism. ACTH deficiency was confirmed using ITT

[n]Cross-sectional study. ACTH deficiency was diagnosed using the glucagon stimulation tests and confirmed with ITT (or short synACTHen test if ITT contra-indicated)

[o]Cross-sectional study. One hundred and twenty-eight patients were invited to participate of whom 76 volunteered. Fifty patients completed the research study protocol. ACTH deficiency was diagnosed using by measuring 08:00 h cortisol and ACTH

oedema and predicts a higher mortality rate following head injury [18, 38, 43]. The general trend is towards improvement with a prevalence of 7% in long term survivors in a large series [37].

Hypopituitarism following concussion

Most of the published data concerning PTHP is derived from patients admitted to hospital following TBI. In most studies, at least half of subjects have moderate to severe TBI when graded according to post-resuscitation GCS scores. However, there is considerable overlap between the symptoms of hypopituitarism and the post-concussive syndrome, sometimes referred to as chronic traumatic encephalopathy. Some authors have reported that patients exposed to repeated concussion may be at risk of long term hypopituitarism, particularly GH deficiency, with rates ranging from 18 to 27% of subjects [44–47]. Kelestimur and colleagues demonstrated the risk of pituitary dysfunction among retired boxers who suffered repeated concussion [45]. They have subsequently elaborated on these findings by reporting hypopituitarism in kickboxers and highlighting the clinical implications of pituitary hormone deficiencies in these athletes [44, 48, 49]. More recently, Kelly et al. robustly evaluated pituitary function in retired National Football League players [46]. They selected a high-risk cohort who reported a poor quality of life and found pituitary hormone dysfunction in 23.5% of subjects overall. Isolated hormone deficiency, typically growth hormone, is the most common abnormal finding following concussion. A minority of subjects have multiple pituitary hormone deficiencies. An important confounder, in studies of pituitary function in athletes, is the impact of current or prior use of performance enhancing drugs such as anabolic steroids. The true prevalence of drug doping can be difficult to ascertain and steroid use can have a prolonged impact on pituitary function if used at high dose or for a long duration.

The risk of pituitary dysfunction after a single, typical concussion is more difficult to estimate as such cases rarely receive long term medical follow up. Studies of military personnel who suffered concussion following explosive, blast related injuries suggests that the long term risk of hypopituitarism may not be insignificant. Wilkinson and colleagues estimated that approximately 20% of combat personnel may have clinically significant pituitary dysfunction after a blast-related concussion [47, 50]. Similarly, a small study of UK male soldiers who suffered blast-related TBI reported a high prevalence (approximately 30%) of chronic anterior pituitary dysfunction [51].

Cranial DI is extremely rare following a single concussion, although isolated case reports have suggested that this may occur [52]. A greater degree of brain damage is probably required to cause clinically detectable hypothalamic/posterior pituitary dysfunction. However, emerging research suggests that concussion may result in hypothalamic injury detectable with novel imaging techniques [53].

Pituitary dysfunction after childhood TBI

Children and young people deserve special consideration. Non-accidental injury is estimated to occur in 20 per 100,000 infants per year [54]. The rate of TBI increases throughout childhood and young adult life and, by age 25, approximately 1/3 of the population has experienced a head injury [55]. However, children are particularly vulnerable to the consequences of PTHP which could impair linear growth and/or delay pubertal development. Precocious puberty has also been described following head injury.

Research data on the prevalence of PTHP in children is subject to the same confounders and bias as the adult literature discussed above. However, studies in early childhood suggest that hypopituitarism following TBI is rare. A study of 198 survivors of structural TBI, less than 2 years of age, found no clinically significant pituitary hormone deficiencies [56]. Casano-Sancho et al., in a prospective study of 37 children with TBI found no evidence of hypopituitarism in patients under 6 years of age [57]. However, isolated GHD was quite prevalent in older children at a rate of 34% at 1 year. This rate fell sharply to 3.8% if only patients with a low height velocity had been assessed. The utility of

auxological measurement, as a guide to the likelihood of pituitary hormone deficiency, was highlighted in a recent study in which the investigators demonstrated that height velocity less than the 25th centile 1 year after TBI, was a useful screening tool for persistent growth hormone in children [58].

A prospective study of 30 children (mean age 13 years) admitted to hospital following TBI (50% mild) again found a low rate of hypopituitarism after 1 year—only one child had biochemical and auxological evidence of GH deficiency [59]. Similarly, Personnier et al., in a study of childhood survivors of severe TBI, reported an 8% prevalence of PTHP [60]. Finally, a prospective study from the United States followed 21 children (mean age 11.8) for 1 year post TBI. One child (5%) had GHD, 2 (9%) had central hypothyroidism and 3 (14%) had precocious puberty [61].

The literature on TBI in childhood, when considered in its entirety, reports a highly variable prevalence of long-term pituitary dysfunction [62]. However, when the analysis is confined to prospective studies, recruiting unselected consecutive patients (discussed above) it appears that the risk of PTHP may be lower in children compared to that reported in adults.

Diagnosis of pituitary dysfunction after TBI

Acute phase

Diagnosing anterior hypopituitarism in the acute phase following head injury is very challenging. Many neuroendocrine perturbations are felt to be physiological adaptive responses to critical illness or caused by medications (e.g. sedation,opiates, anaesthesia) and will resolve spontaneously if the patient survives. ACTH deficiency, however, is potentially life threatening. Therefore, the focus during the acute phase should be on detecting and managing glucocorticoid deficiency.

Clinical features of secondary hypoadenalism, such as hypotension, a higher than expected vasopressor requirement, hyponatremia and hypoglycemia may be helpful in identifying patients with ACTH deficiency [63]. However, these complications can occur for other reasons following moderate to severe TBI and are not specific for glucocorticoid deficiency. Conversely, patients with hypoadrenalism may exhibit no overt haemodynamic or metabolic instability. Stimulation tests of the hypothalamic-pituitary adrenal axis are contraindicated (in the case of ITT) or unreliable (short corticotropin test) during the acute phase following TBI. Therefore, most endocrinologists rely on early morning serum cortisol during the acute phase. The appropriate serum cortisol concentration in head injury victims is difficult to define as it depends on the severity of the injury (or injuries), presence or absence of sepsis, and other factors. Importantly, in the absence of sepsis, total serum cortisol appears to be an accurate reflection of free cortisol in the early days following injury, despite concerns about alterations in the concentration of serum binding proteins [64]. In the acute phase, following moderate to severe TBI, morning serum cortisol ≤ 10 µg/dL is deemed inappropriately low, based on data from non-TBI surgical patients in critical care [18, 65] and justifies glucocorticoid replacement although clinical judgement should apply.

International guidelines do not universally recommend routine monitoring of serum cortisol in all patients admitted to hospital following TBI [65–67]. The highly dynamic nature of serum cortisol in the days following TBI can make individual measurements difficult to interpret. Also, further research about the impact of replacement glucocorticoids, in the absence of clinical features of hypoadrenalism, is necessary.

Cranial diabetes insipidus is easily recognisable in the acute phase. In adults, a 24 h output in excess of 3.5 L of hypotonic urine in the presence of serum sodium > 143 mmol/L strongly supports the diagnosis [68]. Despite preservation of thirst, hypernatremia is common due to clouding of consciousness and consequent inability to drink. The treatment is to administer parenteral Desmopressin, as required and hypotonic intravenous (or enteral) fluids guided by the urine output and the plasma sodium.

Chronic phase

Case detection

The very common occurrence of head injury makes it impractical to screen every case for hypopituitarism without consuming an enormous amount of healthcare resources. Severity of head injury has been proposed as a screening tool to identify those most likely to suffer from PTHP [65]. Some studies in the field, including two systematic reviews, have shown a correlation between severity of injury and risk of hypopituitarism [8, 11, 26–28, 30, 36].

Severity of head injury can be assessed clinically by the post-resuscitation, pre-intubation GCS. Scores between13-15 are indicative of mild TBI, 9–12 of moderate while ≤ 8 indicate severe injury. However, there is inter-individual variation in calculation of GCS and other factors such as drugs/alcohol can confound accurate measurement. One scheme proposed by the Veterans Administration/US Department of Defence suggests a multi-category score to judge severity of head injury [69]. This includes GCS as well as alteration/loss of consciousness and post-traumatic amnesia. TBI severity can also be graded according to the degree of abnormality on cross-sectional imaging of the head which

may be useful when initial GCS score is not available or inconsistent [70].

Current UK guidance recommend that patients hospitalised for more than 48 h following TBI should subsequently undergo screening for pituitary dysfunction [66]. Other clinical and radiological features may help to risk stratify patients e.g. mechanism of injury, post-traumatic seizure, length of ICU stay, diffuse axonal injury or base of skull fracture [16, 26, 30, 36].

Recent research supports the contention that patients with less severe TBI presenting to the emergency department have a low prevalence of endocrine dysfunction when strict diagnostic criteria are used and perhaps should be considered for endocrine evaluation only if they develop clinical features suggestive of pituitary deficiency [71]. Similarly, patients who have suffered repetitive concussion and who have persistent post-concussive symptoms, unresponsive to conventional treatment, should be screened for PTHP [9].

Hormonal evaluation

Figure 2 suggests an algorithm for the assessment of pituitary function in the chronic recovery phase following TBI which is in keeping with the proposed advice from opinion leaders in the field [33]. It is recommended that initial assessment, including a detailed history and physical examination, takes place between 3 and 6 months after injury [65, 66, 72]. Assessment for hypogonadism, one of the most common pituitary deficiencies after moderate/severe TBI, is undertaken with paired measurement of serum gonadotrophins and testosterone in men (menstural history in premenopausal women). Central hypothyroidism, which is uncommon after TBI, can be diagnosed on baseline thyroid function test with a low serum free T4 concentration in the presence of a low or inappropriately normal serum TSH.

Early morning serum cortisol is often used to assess the adrenal axis. Serum concentration ≤ 3 µg/dL is diagnostic of ACTH/cortisol deficiency and a level ≥ 18 µg/dL indicates sufficient ACTH reserve [30, 65, 66]. However, intermediate values require further testing, either with repeat sampling of basal cortisol values or a stimulation test. The short synACTHen (corticotrophin) test is a safe, convenient and clinically reliable test in this setting [73].

Assessment of GH reserve in adults should probably be deferred until 1 year post injury as recovery of growth hormone secretion may occur over many months. Children who exhibit retardation of linear growth may require earlier assessment. Low serum IGF-1 concentration in a patient with multiple pituitary hormone deficiencies (MPHD) is highly suggestive of GHD. However, in the absence of MPHD, serum IGF-1 measurement lacks sensitivity for the diagnosis of GHD. If the patient is a candidate for replacement then a GH stimulation test is required in most cases to make the diagnosis with confidence. The ITT is the most reliable test—a peak serum GH <3 µg/dL is used to diagnose severe GH deficiency in adults [74]. This test is contra-indicated in those with a history of seizures or heart disease—the former a common complication of TBI. GHRH + arginine (combined test) is a potent stimulus of GH in lean subjects but the response is highly BMI dependant [75]. GHRH is not readily available in the United States and, therefore, the glucagon stimulation test is another alternative for assessing GH (and ACTH) reserve. Traditionally, similar GH cut off values have been used as with ITT. However, the glucagon test is sensitive to BMI and there is high risk of a false positive in obese individuals. Recently, however, lower GH cut offs for diagnosing GHD in obese individuals have been proposed when using a glucagon stimulation test [76].

Central diabetes insipidus

Survivors of brain injury who report polyuria or polydipsia should be assessed for the possibility of persistent DI. A 24 h urine volume greater than 40 mL/kg/24 h warrants further investigation. Measurement of serum glucose, adjusted calcium and potassium will out-rule other common causes of polyuria. The water deprivation test may be needed to confirm the diagnosis, particularly in the case of partial cranial DI. Peak urinary concentrating ability <700 mOsm/kg with normal renal function in the presence of concentrated serum, is suggestive of DI [77].

Conclusion

A large body of evidence has now demonstrated that patients who suffer TBI are at risk of hypopituitarism. However, despite the publication of many detailed prospective and retrospective clinical studies, the true prevalence of PTHP remains a matter of debate. The dynamic nature of pituitary function after head injury, the confounders and practical difficulties of studying endocrine function in the early days following major trauma, the limitations of the diagnostic biochemical tools as well as the overlap between post-TBI/post-concussive symptoms and hypopituitarism have posed major challenges to researchers in the field.

The value of routine screening for hypopituitarism during the acute phase after TBI is controversial. However, emerging evidence has shed new light on cortisol dynamics in the days following injury and emphasises the need for clinicians to be vigilant for ACTH deficiency. Screening for pituitary dysfunction during the chronic recovery phase requires consideration of patient and injury-related factors. Severity of TBI currently provides a reasonable guide as to who requires pituitary evaluation after injury. Other TBI survivors, including those who have suffered

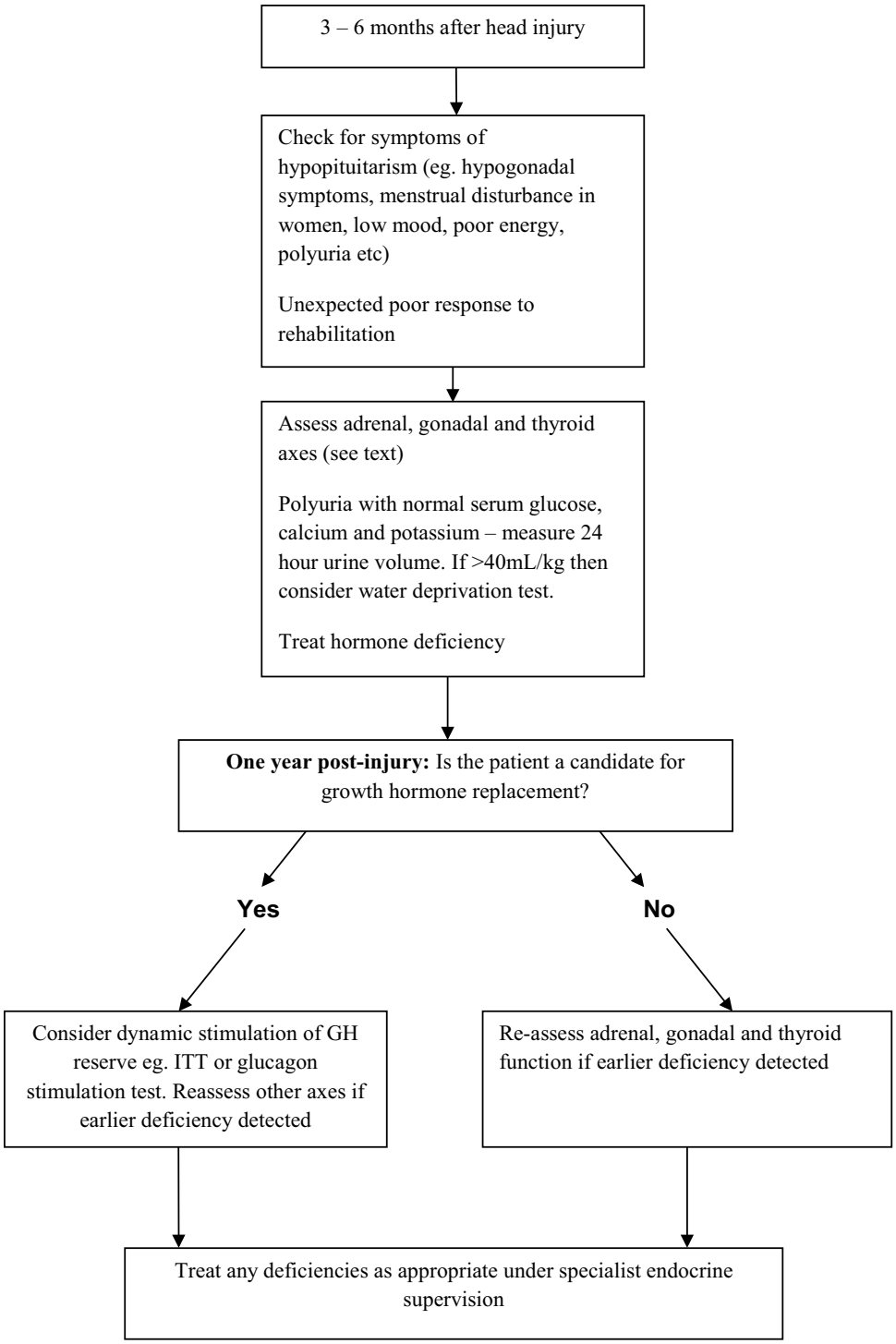

Fig. 2 Suggested algorithm for the evaluation of post-traumatic hypopituitarism in the post-acute phase

concussion, should be considered for screening if they display any clinical features of hypopituitarism.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interests.

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