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Traumatic brain injury induced hypothalamic-pituitary dysfunction: a paediatric perspective

Carlo L. Acerini · Robert C. Tasker

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Abstract In survivors of traumatic brain injury (TBI), impairment in anterior pituitary hormone function may be an important cause of long-term morbidity. Histopathological evidence from post-mortem studies suggests that the hypothalamic-pituitary structures are vulnerable to damage following head injury. Pituitary dysfunction, present months or years after injury, is now well recognised in adults, however, little evidence is known about this potential complication in children and adolescents. This article reviews the available paediatric data, which shows that hypopituitarism may occur after both mild and severe TBI, with growth hormone and gonadotrophin deficiencies appearing to be most common abnormalities. Central precocious puberty has also been documented. There are, however, few published data within a population of children with TBI on the incidence or prevalence of hypopituitarism, nor on its natural history or response to hormone replacement, and prospective studies are needed. Given the critical role of anterior pituitary hormones in the regulation of growth, pubertal and neurocognitive development in childhood, early detection of hormone abnormalities following TBI is important. We propose that a multidisciplinary approach to follow-up and endocrine assessment is required for the long-term management and rehabilitation of children and adolescents who survive moderate to severe head injury.

C. L. Acerini (✉) · R. C. Tasker
Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Level 8/Box 116, Cambridge CB2 2QQ, UK
e-mail: cla22@cam.ac.uk

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Introduction

Traumatic brain injury (TBI) is a major cause of mortality and morbidity in children. Disruption to the integrity and function of the hypothalamic-pituitary structures due to either closed or open head injury mechanisms can result in neuroendocrine dysfunction and may contribute to subsequent morbidity in survivors. The endocrine changes in the first few hours and days immediately after moderate to severe TBI have been reported in adults [1, 2] and share similarities to the changes in hypothalamic-pituitary-endocrine function observed in other critically ill patients [3]. The long-term significance of these acute abnormalities in endocrine function remain unclear, and it is uncertain whether they arise secondary to direct structural hypothalamic-pituitary injury, or reflect temporary adaptive changes to the underlying acute illness [4].

In contrast to our knowledge about the acute endocrine changes following TBI, much less is known about longer-term neuroendocrine function in survivors. Until recently, this area has received very little systematic study, although an increasing body of literature in adults suggests that TBI-induced hypothalamic-pituitary dysfunction may be an under recognised and under-investigated disorder. There is speculation that underlying deficits in anterior pituitary dysfunction may contribute to physical and neuropyschological morbidity experienced by many TBI survivors. Although TBI-induced hypopituitarism in children has been reported in several individual reports, which are reviewed below, little is known of the incidence of this

problem, its prevalence, its natural history, and its effects in children suffering TBI.

Epidemiology of TBI in childhood

In the UK it is estimated that ~180 children per 100,000-population sustain a closed head injury each year, with only 5.6 per 100,000 in the severest category requiring treatment in an intensive care unit (Table 1) [5]. Of those children admitted to intensive care almost one-third undergo neurosurgery for evacuation of subdural or epidural haematoma [6]. The estimated incidence of TBI doubles between the ages of 5 and 14 years and peaks in both males and females during adolescence and early adulthood with rates of ~250 per 100,000 population [7–9]. In adults, the severest category of TBI approaches 30 per 100,000—about five times the incidence in children. The causes of head trauma in children are more diverse and include child abuse, falls, pedestrian and road traffic accidents, and sports injuries. Non-accidental head injury in infancy (most frequently shaking injury) has an annual incidence of 24.6 per 100,000 in children younger than 1 year [10].

In comparison with studies of late outcome in adults with TBI, the outcome in children is generally thought to be better. However, a recent prospective study of 330 children with moderate or severe TBI found that a considerable proportion of patients had measurable impairment of health-related quality of life scores at 3 months (42%) and 12 months (40%) after injury [11]. In a series of 112 children younger than 2 years of age at injury, most (67%) had an outcome of mild disability or better 2 years later, with 45% functioning at an age-appropriate level [12]. Many of the chronic morbidity symptoms experienced by TBI survivors are also common to patients with known deficiencies of one or more of the hormones regulated by the anterior pituitary gland and may in part explain the relatively high frequency of neurocognitive impairment and general ill health problems observed in the post-injury recovery phase [13, 14].

Table 1 UK (2001–2003) prevalence rates of severe traumatic brain in children aged 0–14 years children

Age group (years)	Prevalence rate (per $\times 10^5$ per year)	(95% CI)
0–4	5.1	4.4–5.9
5–9	4.8	4.1–5.5
10–14	6.9	6.0–7.7

Adapted from Parslow et al. [5]

TBI and neuroendocrine dysfunction: pathological mechanisms

The pituitary gland and its anatomical attachment to hypothalamic structures, or infundibular stalk, are vulnerable to injury following TBI, even though these structures are protected within a bony cavity, i.e. the sella turcica. The mechanism for this injury may be vascular. For example, a rich network of blood vessels serves the pituitary gland, with the most important blood supply originating from the superior hypophysial arteries, which arise from the internal carotids. The long hypophysial blood vessels and the dense network of capillaries that surround the pituitary and the infundibular stalk (*hypophysial-portal circulation*) are vulnerable to rupture and haemorrhage, leading to subsequent ischaemia and infarction of the anterior lobe of the pituitary gland. Pituitary lobe infarction may also result from tissue swelling and oedema causing compression of the hypophysial blood vessels within the restrictive space of the sella turcica.

There are few studies directly linking TBI with disruption and damage to hypothalamic-pituitary structures. However, the available data provide convincing histopathological evidence that lesions occur in this part of the brain as a result of severe TBI. For example, post-mortem studies in a series of 106 fatal closed head injury cases revealed hypothalamic lesions in almost 43% [15]. Lesions were typically suggestive of infarction and ischaemia, and consistent with either shearing of small perforating blood vessels or with venous engorgement secondary to raised increased intracranial pressure. In 28% of cases, pituitary lesions were also present and often associated with fracture of the middle cerebral fossa. Others have reported traumatic infarction of the anterior pituitary gland [16, 17]. Histopathological examination of the pituitary gland in 100 autopsies showed that 38% had infarcts of the anterior pituitary lobe, often in association with haemorrhage [17].

Historical perspective

The association between TBI and the development of pituitary hormone deficiency is long established, with the first case reports published nearly 90 years ago [18]. Since then, there have been many other reports describing chronic pituitary hormone deficiencies, occurring in a variety of combinations, following different mechanisms of head injury [19, 20]. In a comprehensive review of the literature reported over a 28-year period between 1970 and 1998, Benvenga and colleagues identified a total of 367 cases where anterior pituitary dysfunction was reported following head injury survival [21]. Analysis of these case reports suggested that deficiencies in the hypothalamic-

pituitary-gonadal axis were very common (i.e. 100%) in those undergoing evaluation of this system (n = 166). Deficiencies in the other hypothalamic-pituitary-endocrine axes were less frequent (thyroid 90%; adrenal 58%; GH 24%) and in most of the cases, multiple hormone dysfunction was a consistent feature. The majority of patients described in this series presented within 1 year of injury, but in ~30% of cases presentation did not occur until much later [21].

TBI and pituitary dysfunction: contemporary adult studies

The literature regarding adults diagnosed with hypopituitarism following TBI has flourished since 2000, and the findings of the key studies are discussed below and summarised in Table 2. Several recent reviews also describe this subject area in detail [22, 23].

Kelly and co-workers were the first to systematically study the frequency of TBI-related hypopituitarism in a cohort of adult survivors (n = 22), assessed between 3 months and 23 years after injury. They found that 36% had subnormal responses in at least one hypothalamic-pituitary-endocrine axis, with deficiencies in the gonadal and growth hormone (GH 18%) axes being the most common [24]. In a subsequent prospective cohort screening study of 70 adult survivors of TBI (age 18–56 years), dynamic tests of anterior pituitary function up to 23 years after the injury revealed a high prevalence of previously undetected deficiencies in the GH (15%), adrenal (16%) and thyroid (22%) hormone axes [25]. In total, 68% of subjects had evidence of deficiency in at least one endocrine axis, and in 17% of cases the deficiency involved multiple hormones. In contrast to the historical case reviews of post-traumatic hypopituitarism, no deficiencies in either the gonadal axis or in posterior pituitary function were observed [25]. In 2004, Bondanelli and colleagues also observed a high frequency of pituitary dysfunction (59%) in survivors (n = 50) of severe TBI up to 5 years from the traumatic event, especially GH deficiency that was either partial or severe in 24% of subjects [26]. In addition, Aimaretti and co-workers identified some degree of pituitary dysfunction in 35% of 100 subjects after trauma or subarrachnoid haemorrhage; severe GH deficiency was the most common defect (25%), with the gonadal (17%), thyroid (5%) and adrenal (8%) axes less frequently affected [27].

These observations have been supported by a series of recent findings reported by Agha et al. [28]. In a study of 102 TBI survivors assessed at a median of 19 months following moderate to severe injury, deficiencies in the GH, gonadotrophin and adrenal axes were detected in 11, 12 and 13% of patients, respectively. At least 28% had at least one pituitary hormone deficit, but panhypopituitarism was a rare occurrence (1%) [28]. The same group has also studied the natural history of post-traumatic hypopituitarism and evidence suggests that neuroendocrine abnormalities in the acute phase following severe or moderate TBI may be transient, whereas some abnormalities present later during the course of rehabilitation [29]. Fifty adult patients admitted for intensive care following TBI demonstrated a high frequency of early post-traumatic endocrine abnormalities, in particular low basal cortisol levels with subnormal cortisol responses to a glucagon test, hypogonadism and hyperprolactinemia [29]. These results

Table 2 Prevalence of late occurring hypopituitarism following traumatic brain injury in adults

Study/year	Design	Subjects (n)	Interval TBI-diagnosis	Total hypopituitarism (%)	GH axis (%)	Gonadal axis (%)	Thyroid axis (%)	Adrenal axis (%)
Kelly et al. [24]	R, Sc	22	0.3–23 years	36	18	23	5	5
Lieberman et al. [25]	R, Sc	70	0.1–23 years	69	15	–	22	7
Agha et al. [1, 28, 47]	R, Sc	102	6–36 months	28	18	12	1	23
Bondanelli et al. [26]	P	50	12–64 months	54	28	14	10	–
Leal-Cero [51]	R, Sc	99		42	23	30	10	11
Aimaretti et al. [52]	P, L	70	12 months	23	20	11	6	7
Agha et al. [29]	P, L	50	12 months	–	10	13	2	19
Tanriverdi et al. [30]	P, L	52	12 months	51	33	8	6	19

Summary of contemporary adults studies 2000–2006

R retrospective, *Sc* screening *P* prospective *L* longitudinal, *GH* growth hormone

were confirmed by a study performed in similar conditions; 53% of patients demonstrated at least one deficient hormonal axis, hypoadrenalism and gonadal dysfunction being the most frequent [30]. GH deficiency was also demonstrated, although GH resistance would be expected in such a critical condition. Low plasma insulin-like growth factor-I (IGF-I) levels were also observed in association with decreased GH secretion.

In most of these studies no relationships were observed between the occurrence of pituitary dysfunction and time since TBI, severity and type of injury or later outcome [25, 27, 28]. These findings imply that other factors related to the characteristics of the trauma (e.g. vascular changes) are likely to be involved.

TBI and pituitary dysfunction: paediatric perspective

The literature concerning children and adolescents with post-TBI induced hypothalamic-pituitary dysfunction is much less detailed. To date, very few comprehensive retrospective or prospective studies have been reported on this subject. A recent systematic review of the literature identified only a few case reports or small case series highlighting a link between TBI and the occurrence of hypothalamic-pituitary hormone abnormalities [31].

The literature suggests that post-TBI induced hypothalamic-pituitary dysfunction may be observed in children after a variety of different mechanisms. Road traffic accidents, falls and sport related trauma appear to be the most common causes of head injury in children reported to have resulted in pituitary dysfunction, and these events are often associated with loss of consciousness, subdural haematoma or skull fracture [32–35]. Post-TBI induced hypopituitarism has also been reported after severe birth trauma and it has been suggested that that some cases of idiopathic congenital hypopituitarism may be due to brain injury sustained during a traumatic birth, e.g. breech delivery [36]. In a seminal paper on hypopituitarism, child abuse was the reported mechanism of injury in three children who had been taken into care following severe physical abuse in infancy [37]. These children all suffered acute brain trauma associated with loss of consciousness and subdural haematoma and were diagnosed with multiple pituitary hormone deficiencies several years after the initial insult.

The presenting characteristics and hypothalamic-pituitary investigations have been described in some detail in 20 paediatric cases (Table 3). These cases clearly represent a highly selected group of patients and provide no information on the incidence of pituitary deficiency or its prevalence within a population of post-TBI survivors. Delay in the diagnosis of hypopituitarism appears to be a frequently

Table 3 Summary of clinical details and pituitary hormone deficiencies following paediatric traumatic brain injury

Author	Cases (*n*)	Sex	Age at TBI (years)	Type of injury	GH	TSH	ACTH	LH/FSH	ADH	Symptoms at presentation	Interval injury-Diagnosis (years)
Benvenga et al. [40]	4	F, M, M, NS	7–16	Fall, RTA, RTA, Fall	2	4	1	4	–	Apathy, libido, Amenorrhoea	5, 41, 42, 22
Elchler [53]	1	M	12	NS	1	–	–	–	–	Growth	1
Paxson and Brown [32]	1	F	14	RTA, Skull[#]	1	1	1	1	–	Puberty	1.2
Girard and Marelli [33]	1	M	3	RTA	1	1	1	–	–	Growth	3.1
Miller et al. [37]	3	F, M, M	0.1–0.3	Abuse	3	2	3	3	–	Growth × 3	12, 12, 6
Mariani et al. [41]	3	F, M, M	2, 8, 9	RTA, Judo, Fall	2	2	2	2	2	Growth, Puberty	10, 1, 5
Barbeau et al. [39]	3	M, M, F	0.5–3	NS	3	2	2	2	–	Growth × 3	5, 5, 1
Grossman and Sanfield [34]	1	F	0.8	RTA	1	1	1	1	–	Puberty	16
Yamanaka [38]	2	M, M	3, 11	Fall × 2	2	1	–	2	–	Growth × 2	6.5, 2
Valenta and De Feo [35]	1	F	16	Skull[a]	1	1	–	1	–	Puberty	2
Total (*n*)	20				17	15	11	16	2		
Percentage					85	75	55	80	10		

Data from literature review 1976–2006. Adapted from Acerini et al. [31]

NS not specified, *RTA* road traffic accident, # fracture, *Growth* poor growth, *Puberty* delayed puberty

observed characteristic [34, 38–40]. Analysis of these 20 cases reveals that diagnosis of pituitary deficiency was made after a median interval of 5 years (range 1–43 years) from the initial TBI event. The diagnosis of pituitary dysfunction was established during childhood and in adolescence in 17 of 20 patients and in adult life in the remaining three. Growth failure was the presenting concern and the reason for endocrine evaluation in 11 of the patients diagnosed before the end of adolescence and was invariably associated with evidence of GH deficiency. Delayed or arrested pubertal development, secondary amenorrhea and reduced libido were additional presenting features [32, 34, 35, 41]. The frequency of anterior pituitary hormone deficiencies was high in this series of cases (GH axis 85%; LH/FSH 80%; thyroid 75%; adrenal 50%), but no clear pattern linking the mechanism of head injury to the cause of hypopituitarism is evident. In six cases, multiple pituitary hormone deficiencies were documented after relatively mild head injury without loss of consciousness [38, 40, 41]. Brain imaging demonstrated pituitary stalk transection in several cases [38, 39, 41].

Hypopituitarism may not be the only manifestation of hypothalamic-pituitary dysfunction following TBI in children. Activation of the hypothalamic-pituitary-gonadal axis leading to central (gonadotropin dependent) precocious puberty has been reported in at least ten cases [42–45], occurring at mean interval ranging from 0.4 to 1.6 years after TBI [44].

Posterior pituitary dysfunction leading to abnormalities in water homeostasis, and resulting in either cranial (central) diabetes inspidus (DI) or the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion, are commonly observed following brain injury due to neurosurgery and subarachnoid haemorrhage [46]. These neuroendocrine complications are also well recognised after head injury. In the majority of cases, perturbations in water balance are transient and resolve within a few days or weeks of the TBI event [47]. In adults, recent prospective data suggest that the incidence of DI may be as high as 26% in the acute phase immediately following TBI, although up to 70% of cases fully recovery from DI within 12 months [29]. Overall the incidence of DI persisting beyond 3–12 months after TBI appears to be in the range of 7–8% in adult survivors, with many cases exhibiting a partial form of DI with mild, subclinical symptoms which may be overlooked and undiagnosed [29]. Central DI has very rarely been reported in childhood survivors of TBI [41]. The occurrence of DI in the immediate phase after TBI may be a poor prognostic factor for survival post-TBI, and in one series of 19 children (aged 4 months to 15 years) with acute DI secondary to severe brain injury (trauma $n = 12$), only three patients survived the acute ictus [48].

The first two systematic studies of childhood related post-TBI induced hypothalamic-pituitary dysfunction have been published recently. In the first, Einaudi and colleagues used a mixed retrospective and a prospective study design and reported an overall prevalence of TBI induced pituitary dysfunction of 10.4% [49]. In the prospective longitudinal component of the study ($n = 30$), seven patients (23%) had abnormalities in thyroid or water homeostasis in the acute post-TBI phase, which after 6 months had completely resolved. In contrast to this, but in keeping with some of the adult TBI studies, two patients with normal pituitary function immediately post-TBI subsequently developed evidence of pituitary dysfunction (one-hypoadrenalism and one-GH deficiency) after 12 months [49]. In the second, a retrospective screen in a cohort of children and adolescents TBI survivors ($n = 26$) there was a much higher prevalence of abnormalities of hypothalamic-pituitary dysfunction (61%) after a mean interval of 30 months (range +/– 8 months), with 42% (12 of 26) meeting the diagnostic criteria for GH deficiency [50].

The paucity of clinical reports relating to children with post-TBI induced hypothalamic-pituitary dysfunction suggests that this phenomenon might be less common than that observed in adults. A recent analysis of results complied over a 20-year period (1986–2006) from the Pfizer International Growth Database [Kabi International Growth Study (KIGS)] lends some support to this hypothesis. Over this time period only 141 cases were registered as having GH deficiency secondary to TBI compared to 23,722 registered with idiopathic GH deficiency (IGHD) (KIGS unpublished data, 2006). Nevertheless, there may be several explanations for this observation, including differences in the epidemiology and nature of head injury in children and differences in the pathological mechanisms underlying the development and natural history of hypothalamic-pituitary dysfunction. A lack of awareness and failure to diagnosis pituitary hormone deficits in childhood survivors of TBI, particularly where the latter may be evolving with time and initially subclinical in nature, may also be contributory.

Conclusions and recommendations for pediatric practice

Studies in adult survivors of TBI have established that the hypothalamic-pituitary structures are vulnerable to injury and dysfunction following brain trauma. The extent and characteristics of this potential complication in children are unknown and well-designed prospective studies are needed. However, it appears likely from the evidence that post-TBI hypopituitarism is a neglected phenomenon in children. The impact of undiagnosed partial or complete

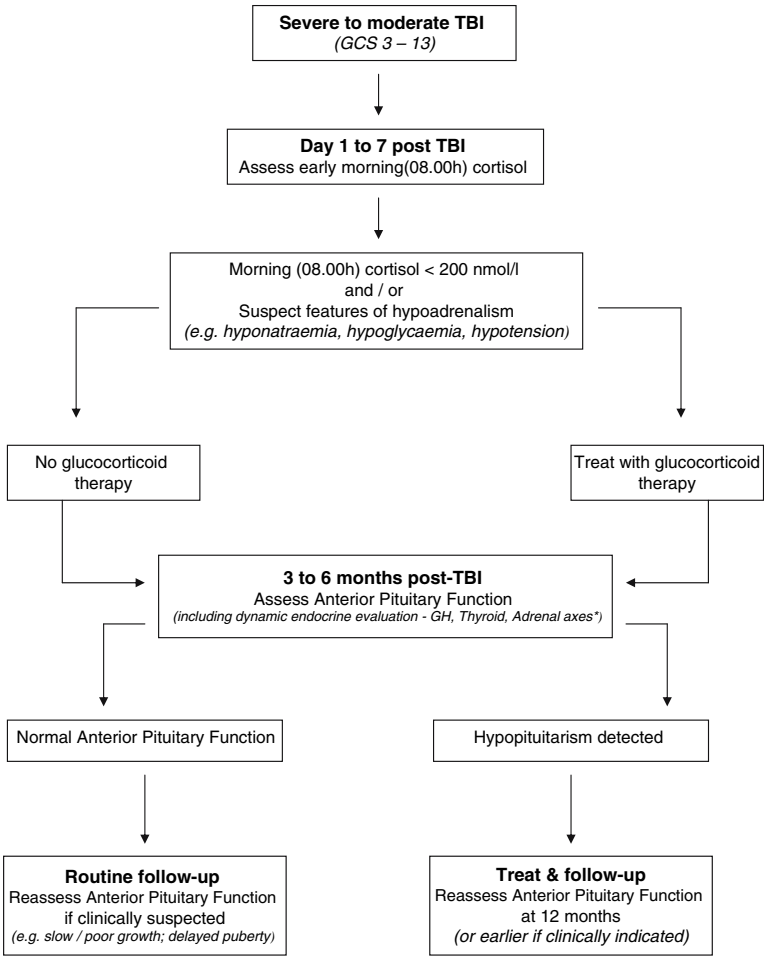

Fig. 1 Algorithm for the endocrine assessment and follow-up of children and adolescent survivors of traumatic brain injury. Modified from Agha and Thompson [22]. *GCS* glasgow coma scale, GH growth hormone. (*) represents the choice of stimulation test for GH and adrenal axis should be based on preference/experience of unit performing test

deficiency in any one of the hormone systems regulated by the pituitary gland has significance not only for growth and pubertal development, but also with regard to brain development and neurocognitive function. The case reports in children highlight extreme delay in diagnosis in many patients. We therefore consider that hypopituitarism must be identified early in the post-TBI period, so that the child has a chance of recovery in an optimum endocrine environment. A multidisciplinary protocol is required since these children benefit from the skills of paediatric endocrinologists, intensivists, neurologists and rehabilitation experts. In adults, follow-up and endocrine assessment has recently been proposed [22], and it seems logical that a similar approach should be used in children surviving severe to moderate brain injury (Fig. 1) until such time as new data informs us differently.

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