Hypopituitarism in childhood and adolescence following traumatic brain injury: the case for prospective endocrine investigation

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Abstract
Pituitary dysfunction is now well recognised after traumatic brain injury (TBI) in adults; however, little except anecdotal evidence is known about this potential complication in childhood and adolescence. Histopathological evidence exists for both hypothalamic and pituitary damage, but few data specific to children have been published. We review the available paediatric data, which shows that after both mild and severe TBI, hypopituitarism may occur, with GH and gonadotrophin deficiencies appearing to be most common. Precocious puberty has also been documented. Road-traffic accidents, falls, sport and child abuse are the most common aetiological factors for paediatric TBI. There are no published data on the incidence or prevalence, neither within a population of children with TBI, of hypopituitarism, nor on its natural history or response to hormone replacement. We urge paediatric endocrinologists, in collaboration with adult endocrinologists, to perform formal prospective research studies in patients suffering from TBI to clarify these questions.

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Introduction
It is well recognised in the paediatric patient that abnormal pituitary function may be caused by developmental defects in the hypothalamic–pituitary region such as septo-optic dysplasia or by acquired lesions, such as hypothalamic or pituitary tumours, cranial irradiation or surgical intervention. Relatively, little attention has been paid to the possibility of acquired pituitary dysfunction caused by traumatic brain injury (TBI).

Although TBI-induced hypopituitarism in children has been reported in several individual cases, which are reviewed below, there is little knowledge of the incidence of this problem, its prevalence within a population of children suffering TBI, its natural history, its influence on morbidity and mortality, or the effects of replacement therapy.

In adults, a rapidly growing body of published data suggest that TBI-induced hypopituitarism has been an under-recognised and under-investigated disorder (1). We believe that it is important to draw attention to this potential problem in paediatric patients. The investigation and diagnosis of pituitary deficiency in a child can fundamentally change the outlook for growth and puberty development, in addition to problems related to potential central thyroid and adrenal deficiencies. Recovery from TBI could also be compromised by unrecognised hypopituitarism.

First, we review the pathological basis for abnormal hypothalamic and pituitary function following TBI, and summarise the evidence for TBI-induced hypopituitarism in adults, then describe the epidemiology of TBI in children followed by a review of the published evidence of a similar disorder in children or adolescents.

We finally propose a prospective diagnostic protocol and the formation of a multi-disciplinary network to aid referral, investigation and, where appropriate, treatment of affected patients.

Pathological evidence of hypothalamic and pituitary lesions following TBI
There is convincing histopathological evidence of lesions of the hypothalamus and pituitary following severe head trauma, however, although child patients have been included in a number of series of autopsies of TBI victims, no specific studies have been reported in children. Lesions of the hypothalamus have been carefully studied in a study of 106 consecutive autopsies.
following fatal closed head injury in patients ranging from infancy to old age (2). Lesions of the hypothalamus were present in 42.5% of autopsies and usually situated in the anterior hypothalamus. They were typically lesions of infarction and ischaemia. The ischaemia was consistent with shearing of small perforating blood vessels or venous engorgement secondary to raised intracranial pressure. Often they were associated with fracture of the middle cerebral fossa and in 28%, pituitary lesions were also present. A striking increase in hypothalamic lesions was seen in patients aged between 15 and 20 years following severe fatal head injury (2). Traumatic infarction of the anterior pituitary gland has also been documented (3). Harper et al. studied histopathological features of the pituitary gland in 100 autopsies from non-missile head injuries (4). The subjects were aged 0.7–85 years, however, no separate analysis of childhood victims was performed. In 38% of subjects, infarcts of the anterior lobe were present, sometimes associated with haemorrhage.

**TBI-induced hypopituitarism in adults**

In the last 5 years, the literature on adults diagnosed with hypopituitarism following TBI has grown considerably. Several recent reviews describe this subject in detail (1, 5, 6). It is now recognised that between 23 and 69% of adult patients demonstrate some degree of hypopituitarism during the first 12 months after TBI (7–10). The early phase after TBI is poorly investigated from an endocrine standpoint. The natural history of post-traumatic hypopituitarism has recently been studied and evidence reported 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 (11). Agha et al. studied 50 adult patients admitted to the intensive care unit and 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 hyperprolactinaemia (11). These results were confirmed by a study performed in similar conditions showing that 53% of patients demonstrated at least one deficient hormonal axis, hypoadrenalism and gonadal dysfunction being the most frequent (12). Growth hormone (GH) deficiency was also demonstrated, although GH resistance would be expected in this critical condition, low insulin-like growth factor-I levels were present associated with decreased GH secretion.

A significant proportion of patients are left with permanent multiple anterior pituitary hormone deficits (1). GH deficiency, which is usually severe (5), occurred most frequently (> 20% of cases) followed by gonadotrophin deficiency (1), then adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) deficiencies.

Consequently, a protocol for prospective endocrine assessment of patients at risk of hypopituitarism is a necessary component of post-TBI management (1, 13). No data exist to demonstrate that pituitary dysfunction influences clinical recovery from TBI, however, significant pituitary defects were demonstrated 12 months after the initial injury (10, 13). There are hitherto few reports of pituitary hormone replacement in adults. However, beneficial effects influencing recovery and possibly cognitive function are anticipated and awaited (14).

**Epidemiology of TBI in children and adolescents**

In the acute phase after an accident, the severity of injury is categorised as mild, moderate or severe according to the glasgow coma scale (GCS) score and any features in the history. The range in GCS scores is from a minimum of 3 (completely unresponsive with no eye opening, verbal and motor response to painful stimulus) to a maximum of 15 (appropriate and normal eye opening, verbal and motor responses). Mild (or ‘minor’) head injury should have a GCS score of ≥13. Such an injury will have been caused by a blunt blow to the head in which post-traumatic amnesia lasts for <1 h. If there was an initial loss of consciousness at the time of injury, then it would have been <15 min duration and there is an absence of focal neurological signs (15). Children with a GCS ≤8 have severe head injury. Children with moderate severity head injury have a GCS of 9–13.

This three-layered stratification is important in epidemiology, since it helps with relating injury to outcome. However, the distinction between what is truly a moderately severe versus a severe injury is becoming difficult to assess. Children are now being intubated and mechanically ventilated at a much earlier stage in resuscitation (16), and it is probable that a GCS of 10 in a pre-verbal child has a different significance to a similar score in a 13-year-old (17).

Approximately, 180 children per 100 000 population sustain closed head injury each year with only 5.6 per 100 000 in the severest category, requiring treatment on an intensive care unit (18). Of those children admitted to intensive care, almost one-third undergo neurosurgery for evacuation of subdural or epidural haematoma (19). 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 (20–22). In adults, the severest category of TBI approaches 30 per 100 000 – about five times the incidence in children. The causes of brain trauma in children 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 children younger than 1 year (23).

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 (24). 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 (25).

Evidence for abnormal pituitary function after TBI in children and adolescents

The literature is much less detailed concerning post-TBI defects of hypothalamic or pituitary function in paediatric, compared with adult, patients. No comprehensive review exists on this subject. However, individual case reports or small published series of patients, present an overall picture that shows that hypopituitarism is a potential long-term complication of TBI in paediatric patients. Pituitary deficiency has been reported after severe brain trauma, often associated not only with loss of consciousness, subdural haematoma or skull fracture (26–29), but also following relatively mild head injury without loss of consciousness (30–32). A recent preliminary retrospective and prospective analysis of paediatric and adolescent patients also confirmed the risk of pituitary dysfunction (33).

A seminal paper on hypopituitarism following child abuse reported three children who had been taken into care following severe physical abuse in infancy (34). The 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. Delay in the diagnosis of hypopituitarism has frequently been reported (28, 30, 32, 35, 36).

Characteristics of hypopituitarism

Detailed investigations of pituitary function have been reported in 20 cases (Table 1). These patients, 12 males, 7 females and 1 sex unspecified, were aged from infancy to 16 years at the time of injury and investigated between 1 and 42 years after the initial episode of TBI. They clearly represent a highly selected group of patients and give no information on the incidence of pituitary deficiency after TBI or its prevalence within a population of post-TBI survivors. All the patients had multiple anterior pituitary hormone deficiencies except one, who had isolated GH deficiency (37).
The frequencies of deficient hormones were GH: 85%, luteinizing hormone (LH), follicle-stimulating hormone (FSH): 80%, TSH: 75% and ACTH: 50%. No clear pattern emerges from these case reports about the prediction of which type of injury is likely to cause hypopituitarism. However, it was notable that in six cases, multiple deficiencies were documented after relatively mild head injury without loss of consciousness (30–32). In several cases, evidence was presented that the hypopituitarism was of hypothalamic origin (28–30). In these patients, responses of pituitary hormones to gonadotrophin-releasing hormone or thyrotrophin-releasing hormone (TRH) or growth hormone-releasing hormone and elevated prolactin were demonstrated. Magnetic resonance imaging (MRI) also demonstrated pituitary stalk transaction in several cases (30, 31, 35).

**Presenting features of hypopituitarism**

The diagnosis of pituitary deficiency was made during childhood and adolescence in 17 out of the 20 patients and during adult life in the remaining 3. In those diagnosed before the end of adolescence, growth failure was the presenting symptom in 11 patients. All these patients were shown to have GH deficiency. The second key presenting symptom was delay or arrested puberty, secondary amenorrhoea or reduced libido. Delay in the diagnosis was extreme in many cases and hypopituitarism was clearly not considered as a possible complication of the TBI, until defects of growth or reproductive function became obvious.

Unrecognised hypopituitarism might be suggested by the presence of low serum cortisol in the acute post-TBI phase (1). After the acute phase, hypopituitarism may contribute to lack of energy, reduced lean body mass, muscle fatigue, decreased exercise capacity and reduced bone mineral density. These features could be particularly marked following prolonged immobilisation.

Results, compiled in 2006, from the Pfizer international growth database (KIGS), reporting children with GH deficiency following TBI, demonstrated that this may be a relatively infrequent cause of GH deficiency. The cases registered were 141 (66% males), compared with 23 722 with idiopathic GH deficiency (IGHD) during the same time period (unpublished data). Interestingly, in the TBI patients, mean height velocity (3.8 cm/year) and peak GH after stimulation (3.6 mU/l) were significantly reduced ($P<0.001$) compared with values of 4.3 cm/year and 6.0 mU/l respectively in the patients with IGHD. In the TBI patients, isolated GH deficiency was much less common (59%) than in the IGHD patients (87%). Associated deficiencies of ACTH, TSH and gonadotrophins in the TBI patients ranged from 17 to 36%.

**Hypopituitarism following perinatal insults**

It has been suggested that some cases of idiopathic congenital hypopituitarism may be due to brain injury sustained during a traumatic birth, e.g. breech delivery (38). The evidence for this is at best circumstantial and largely based on clinical case reports reporting an association between traumatic perinatal events and the occurrence of hypothalamic–pituitary dysfunction in later childhood (39). More recent case series studies have consolidated this view, including observations by Maghnie and colleagues (40) who examined the perinatal histories of 22 children with congenital anterior pituitary hypoplasia and posterior pituitary ectopia and found an excess frequency of breech delivery (68 vs 4%) compared with the background population. Similarly, in a study comparing children with congenital severe isolated GH deficiency due to a mutation in the GH-1 gene with those with isolated GH deficiency of unknown aetiology, the incidence of breech birth delivery history (0 vs 38%) and of demonstrable pituitary abnormalities on MRI scan (38 vs 100%) was found to be significantly higher in the later group (41).

**Diabetes insipidus following TBI**

Abnormalities in water homeostasis, resulting from either cranial diabetes insipidus (DI) or the syndrome of inappropriate anti-diuretic hormone secretion, are commonly observed following brain injury events such as neurosurgery and subarachnoid haemorrhage (42). These neuro-endocrine complications are also well recognised after head injury (1) and in the majority of cases perturbations in water balance are usually transitory and resolve within a few days or weeks of the TBI event (1). 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 in up to 70% of cases complete recovery from DI was achieved within 12 months (43). Overall, the incidence of DI persisting beyond 3–12 months after TBI appears to be in the region of 7–8% in adult survivors, with many cases exhibiting a partial form of DI with mild, subclinical symptoms, which are at risk of being overlooked and undiagnosed (6, 44). Post-TBI related DI may also be related to the severity of head injury event, with those patients the lower GCS ratings being more likely to develop permanent DI (44, 45).

There are no comparable data relating to post-TBI induced DI for the paediatric age group and only a small number of case reports have been published to date (31, 42). The occurrence of acute onset DI may be a poor prognostic factor for survival post-TBI. In one series, 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 (43). Mariani et al. described three cases of post-traumatic hypopituitarism (aged 2, 8 and 9 years respectively at time of TBI), of which two developed DI within days of their injury. In one patient, the DI was an isolated defect, whereas in the other, it occurred in association with other pituitary hormone deficits (GH, thyroid and hypogonadism) (49). Analysis of the KICS database (compiled 2006, unpublished data) found a significantly higher prevalence of DI in those children with GH following TBI compared with IGHD patients (9 vs 0.7%, P < 0.001).

TBI in adolescence and during the transition phase from adolescence to adult life

Adolescents and young adults are particularly vulnerable to TBI due to road-traffic accidents, violence and sports injuries (46). Recent attention on the transitional period between adolescence and complete physical maturity has stressed the importance of normal pituitary function for both somatic and bone development (47). Aimaretti et al. have studied the consequences of TBI on pituitary function in 23 patients, aged 16–25 years (48). At 3 months post-TBI, hypopituitarism was present in 35% of subjects. Total, multiple and isolated deficits were present in 8.6, 4.3 and 21.7% respectively. DI was present in 8.6% of patients. When the patients were studied again at 12 months, evidence of hypopituitarism remained in 30%. GH deficiency and hypogonadism were the two most prominent features. This study emphasises the vulnerability of this age group in terms of post-TBI pituitary deficiencies. Physical signs such as lack of progression through puberty, with decrease in testicular volume and libido could suggest the presence of unrecognised hypopituitarism. Careful investigation and monitoring is necessary to unmask and treat such hormone deficiencies in the transition phase.

Precocious puberty

Central (gonadotrophin-dependent) precocious puberty has been reported following TBI in at least ten cases (49–52). In the largest series, precocious puberty, defined as onset at age <8.5 years in females and <9.0 years in males, occurred with an interval ranging from 0.4 to 1.6 years after the TBI (51). In most cases, the status of other anterior pituitary hormones was not investigated in these patients. In one case, associated symptoms of hyperphagia, defective thirst and temperature instability, with a normal TSH response to TRH were present suggestive of a hypothalamic lesion (49).

Strategy for improved diagnosis of hypopituitarism after paediatric TBI

It appears likely, from the evidence in the literature, that hypopituitarism is being neglected in post-TBI children and adolescents. Health professionals involved at all levels of care of post-TBI patients need to be aware of the possibility of unrecognised pituitary deficiencies. Inappropriately, slow recovery, lack of muscle power and marked lethargy are markers of possible endocrinopathy. Not only is this diagnosis important for optimal growth and puberty prospects, but also its treatment would almost certainly contribute to the process of rehabilitation. There are two basic ways that paediatric endocrinologists can address this question of probable under-diagnosis.

Improved history-taking in the child with short stature or delayed puberty

Head injury appears in the standard list of causes of GH deficiency. However, it is likely that direct questions about previous minor or major TBI are not asked in the majority of cases of children or adolescents referred with short stature or delayed puberty. Yet, these two clinical features appear most often as markers of pituitary dysfunction following TBI. The omission of such enquiries is further evidence of the general lack of knowledge and awareness of paediatric TBI as an important cause of pituitary deficiency. This article aims to educate clinicians about the subject.

Prospective studies of pituitary function in post-TBI survivors

The adult literature has now established both the prevalence of hypopituitarism after TBI and its natural history in terms of onset, evolution and duration of individual anterior and posterior pituitary hormone deficiencies (1). It is essential that similar prospective studies are performed in children. This requires considerable organisation as specialists in many different disciplines such as neurosurgery, neurology, rehabilitation and developmental paediatrics, in addition of course to endocrinology, are involved in the care of such patients. However, only when such collaborative studies have been performed will the extent of the neglected field of post-TBI endocrine investigation become clarified.

Conclusions

Studies in adults have established that the hypothalamus and pituitary, two key organs that are essential for childhood and adolescent development, are vulnerable to injury and dysfunction following brain trauma. The extent and characteristics of this potential
complication in the paediatric age range is presently
unknown. The vulnerability of these two organs in
the child may be reduced, similar or increased compared
with the adult. There is no published data on this.

It is not acceptable to argue that patients with
pituitary deficiency will present with abnormal growth
or puberty and thus be identified and treated. The
impact of undiagnosed pituitary deficiency may be more
far-reaching than this with potential consequences on
other systems, including adverse effects on body
composition and bone health. In addition, the effects
on brain growth and neuro-cognitive function during a
time of continuing brain development must be a
concern. Case reports have demonstrated the extreme
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