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The history of pituitary dysfunction after traumatic brain injury

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Abstract
Purpose To estimate the total number of articles on traumatic brain injury (TBI)-related hypopituitarism and patients (including children and adolescents) with such disorder that were published until now, particularly after the author's review published on April 2000.
Methods Review of the literature retrievable on PubMed.
Results TBI-related hypopituitarism accounts for 7.2% of the whole literature on hypopituitarism published during the 18 years and half between May 2000 and October 2018. As a result, the total number of patients with TBI-related hypopituitarism now approximates 2200. A number of patients, both adults and children, continue to be published as case reports. Articles, including reviews and guidelines, have been published in national languages in order to maximize locally the information on TBI-related hypopituitarism. TBI-related hypopituitarism has been also studied in animals (rodents, cats and dogs).
Conclusions The interest for the damage suffered by anterior pituitary as a result of TBI continues to remain high both in the adulthood and childhood.

Keywords Head trauma · Traumatic brain injury · Pituitary · Anterior hypopituitarism

Introduction

This paper can be considered an update of the article [1] that appeared on December 2005 in a special issue of this journal (Brain injury-induced hypopituitarism, by G. Aimaretti and E. Ghigo). That article made the point after four fundamental reviews on post-head trauma anterior hypopituitarism, also termed traumatic brain injury (TBI)-related anterior hypopituitarism [2–5].

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Impact of reference no. 5

With 20 articles, three of which being the first ones from an ad hoc study group of a National Society of Endocrinology [6–8], 12 reviews, and the first consensus guideline [9] that were published after May 2000 and prior to the said 2005 special issue of Pituitary, the review of Benvenga et al. published on April 2000 [5] clearly generated much interest on the endocrine consequences of head trauma as a result of the damaged secretion of one or more adenohypophyseal hormones. Illustrative examples of the value attributed to that review [5] by other authors [10–18] are given in Table 1. In contrast, over the threefold longer period of time between the April 2000 review [5] and the September 1986 review [4], only 11 articles and one short review in Japanese [19] were published. As summarized in the subsequent paragraph, the review of April 2000 [5] was followed by decreased attention on the damaged secretion of the antidiuretic hormone (ADH) secretion in favor of increased attention on the damaged secretion of the anterior pituitary hormones.

After the review of April 2000 [5] and through October 16, 2018, 326 items (81/326 [24.8%] being reviews) were retrieved in PubMed upon entering the string "head trauma AND hypopituitarism", while 4495 items were retrieved

Table 1 Illustrative examples of the value attributed by other authors to the review by Benvenga et al. published in April 2000 [5]

References	Authors and year	Statement
[10]	Aimaretti and Ghigo, 2005	"One particular study that alerted endocrinologists of the relationship between TBI and hypopituitarism was published in 2000 by Salvatore Benvenga and colleagues and included 367 patients with TBI-induced hypopituitarism together with new data from 15 patients from their own center. (ref.)"
[11]	Medic-Stojanoska et al. 2007	"Although data emerging after 2000 demonstrate the relevance of the problem, in general there is a lack of awareness in the medical community about the incidence and clinical repercussions of the pathology."
[12]	Maiya et al. 2008	"TBI has largely been ignored as a cause of hypopituitarism. However, there has been a growing body of literature over the last 6 years recognising the contribution of anterior pituitary dysfunction in TBI outcomes [ref.]"
[13]	Hohl et al. 2009	"However, the diagnosis of post-TBI hypopituitarism became more consistent just in the last decade (ref.)"
[14]	Heather and Cutfield, 2011	"After early reports [ref.], post-traumatic hypopituitarism received little attention until the last decade. Benvenga et al summarized the literature on post-traumatic hypopituitarism, locating a total of 367 cases reported individually or in small series [ref.]"
[15]	Javed et al. 2015	"… anterior-pituitary dysfunction is more common than posterior-pituitary dysfunction in survivors of TBI [ref.]"
[16]	Scranton and Baskin, 2015	"Hypopituitarism is an underdiagnosed sequela of TBI. It was previously thought to be rare, comprising 0.7% of cases of hypopituitarism [ref.], but is increasingly recognized [refs.]"
[17]	Tanrivedi and Kelestimur, 2015	"Until recently, neuroendocrine dysfunction after TBI was recognized as an uncommon abnormality, and only 367 cases of hypopituitarism due to TBI were reported before 2000 [ref.]. Since then, the relation between TBI and neuroendocrine changes has become one of the hot topics mainly in endocrinology and neurosurgery, and more data exist at the present time."
[18]	Reifschneider et al. 2015	"Case reports showing association between TBI and hypopituitarism were originally published in the early 1900s. A pivotal clinical article by Benvenga [ref.] further confirmed the relationship of TBI-induced hypopituitarism."

upon searching for "hypopituitarism". Thus, TBI-related hypopituitarism accounts for 7.2% of the whole literature on hypopituitarism published during the 18 years and half between May 2000 and October 2018. By comparison, the corresponding proportion for the 100 years between January 1900 and April 2000 was 1.5% (90/6117).

In contrast, only 159 items (38/159 [23.9%] being reviews) were retrieved upon entering the string "head trauma AND diabetes indipidus". The situation was the opposite prior to April 2000, with 88 items (5/88 [5.7%] being reviews) related to the search on "head trauma AND hypopituitarism", as compared to 188 items (9/188 [4.8%] being reviews) related to the search on "head trauma AND diabetes indipidus". Of the mentioned 81 reviews that were published between April 2000 and October 2018, 19 (23.5%) appeared in the year 2005. Twelve reviews were published in national languages (viz. French, Spanish, Czech, Hungarian, Polish, Danish, Swedish and Japanese) [20–31], indicating the intention to maximize locally the information on TBI-related hypopituitarism.

Further to the papers by the study group of the Italian Society of Endocrinology [6–8], only after the 2000 review [5] there were studies from other national societies or studies based on national databases [32–44]. The aforementioned first consensus guideline [9] was followed by other guidelines or recommendations at either national or international level [29, 33, 45–47].

After the 367 patients in the literature reported up to the April 2000 review [5], another approximately 1800 patients with post-TBI hypopituitarism could be retrieved in the liteature retrievable on PubMed search as of October 16, 2018 [string entered "head trauma AND hypopituitarism"]. Thus, the total number of such patients becomes almost 2200. Of these, 32 patients (1.5%) were described as case reports, with 5/32 being children or adolescents.

Before moving to the next section, which deals with particular forms of TBI-related hypothyroidism [34, 48–71], including animals [72–79], it is appropriate to remind the importance of some original papers [80–84] whose messages were echoed in some reviews [85–89]. These articles are worthy of note because have focussed on the decreased quality of life of patients with TBI-related hypopituitarism, including impairment of cognitive, behavioral, neuropsychological and even cardiorespiratory fitness. These consequences were essentially the results of a more or less severe GH deficiency, and could be managed by appropriate GH replacement therapy. Another article [89] has historical value for the setting of the screening for TBI-related hypopituitarism (that is, subjects recruited from a community-based postacute residential rehabilitation facility for patients

with a history of acquired brain injury), and having detected an unexpectedly high frequency of central hypothyroidism (approximately one in ten patients) or, as shown by serum concentration of both TSH and free T4 levels below the corresponding midnormal levels, high frequency of subtle disturbance of the hypothalamus-pituitary thyroid axis (approximately nine in ten patients).

Particular forms of TBI-related hypopituitarism

Children and adolescents

Of the 81 reviews published between April 2000 [5] and through October 16, 2018, 11 (13.6%) concerned children and adolescents [48–58].

The review by Acerini et al. in 2006 [49] collected a total of 20 patients in whom TBI had occurred in the pediatric age (0.1–16 years), 1–42 years before the diagnosis of post-head trauma hypopituitarism. With three exceptions (interval between TBI and diagnosis = 22–42 years), in the remaining 17 patients the diagnosis occurred in the pediatric age. These 20 patients were published in 10 papers. Four papers, which described six children/adolescents, were published prior to the Edwards and Blake review [4], precisely between 1976 and 1980; five papers, which reported another six chidren/adolescents, were published between that review [4] and the review by Benvenga et al. [5]. The remaining paper, which also described 4 patients with TBI in childhood/adolescence, was published in 2004 [59]. It should be noted that the Acerini et al. review [49] missed two children/adolescents with isolated or multiple pituitary hormone deficiencies following TBI [60, 61].

After the 2000 review [5], there were another 74 cases of post-TBI hypopituitarism with this diagnosis made, and trauma occurred in the pediatric age; these cases were reported in 15 papers. Based on the Acerini et al. review [49], the frequencies of hormone deficiencies were: 55% for ACTH, 80% for FSH/LH, 85% for GH, and 75% for TSH. Based on the review by Soliman et al. [57], rates were 2–43% for ACTH, 6–16% for FSH/LH, 6–48% for GH, and 2–33% for TSH. In the same review, the corresponding frequencies reported for adults were 1–60%, 2.2–41%, 2–37.5%, and 2.2–22% [57].

Sports

Only after the 2000 review [5], with its Table 1 summarizing 2 of the 15 patients from the personal experience having had TBI-related hypopituitarism after diving, sports were investigated in more detail, though the interest was for the contact/combative types. The first paper was published in 2004 [62]. The study concerned 11 actively competing or retired male boxers with a mean age of 38.0 ± 3.6 years and seven age-, sex- and BMI-matched healthy non-boxing controls. Peak GH levels in 5 (45%) boxers were found to be lower than 10 μg/L and considered as severe GH deficient. Mean IGF-1 levels (367 ± 18.8 ng/ml) were significantly lower than in controls (237 ± 23.3 vs. 367 ± 18.8 ng/ml). All the other pituitary hormones were normal, including ADH. Other original articles or reviews from the same Turkish group appeared subsequently [63–66], including the most recent review on hypopitutarism subsequent to sports-related TBI [66]. It was in the setting of sports-related hypopituitarism that an autoimmune pathogenesis was elaborated [67]. In a total of 61 male boxers (competing, n = 44; retired, n = 17; mean age = 26 years, range 17–53) and 60 controls, serum anti-hypothalamus antibodies (AHAs) and anti-pituitary antibodies (APAs) were measured. AHAs were detected in 13 of 61 boxers (21.3%), and APAs were detected in 14 of 61 boxers (22.9%), but in none of the normal controls. Pituitary dysfunction was significantly higher in AHA-positive boxers than in AHA-negative boxers (46.2% vs. 10.4%) [67].

Blast

Only after the 2000 review [5], which reminded of bullets and explosions as the causes of TBI-related hypopituitarism in approximately 5% of the 147 cases of TBI-related hypopituitarism of the literature in whom a cause could be identified, the first paper dealing with hypopituitarism occurring after blast exposure did appear in the literature [68]. This paper from USA was soon followed by a paper from England [34], both evaluating individuals who had suffered TBI at least 1 year earlier. Worthy-of-note, in the year 2010, endocrinologists at the Walter Reed Army Medical Center in Washington, DC, USA, alerted that there were no data on TBI-related hypopituitarism in the military population, and that combat veterans could be at risk [69]. Two years earlier (April, 2008), not so far from Washington, DC, the National Institutes of Health convened a workshop [70]. A multidisciplinary group of neuroscientists, engineers, and clinicians were invited to share insights on blast-induced traumatic brain injury (bTBI), specifically pertaining to: physics of blast explosions, acute clinical observations and treatments, preclinical and computational models, and lessons from the international community on civilian exposures. Of interest, endocrine consequences of bTBI were totally ignored, with not a single citation among the 70 papers appearing in the bibliography.

The American paper evaluated 26 male veterans of combat in Iraq or Afghanistan who had reported experiencing at least one blast exposure in the war zone [68]. The control group consisted of seven veterans of deployment to Iraq and/or Afghanistan who did not experience blast trauma. The

authors found that 42% of the 26 blast-exposed veterans, but none of the control veterans, had anterior pituitary hypofunction involving one or more hormones. In another paper by the same research team on a larger number of veterans [71], 12 of 39 veterans (31%) in the study group and 3 of 20 (15%) in the control group had pituitary dysfunction.

The English paper included 19 male soldiers who had suffered moderate to severe brain injury caused directly by a single exposure to a blast between December 2009 and March 2012, and who were considered representative of the 183 UK soldiers who had survived a moderate to severe blast TBI in Afghanistan during this 27-month period [34]. The control group consisted of 39 patients after nonblastTBI. This represented all the patients seen in our multidisciplinary Traumatic Brain Injury clinic at Charing Cross Hospital, London, United Kingdom between August 2009 and March 2012. In this study [34], the rate of anterior pituitary dysfunction was 32% in the study group, significantly more than the 2.6% rate in the control group. No hypothalamic–pituitary abnormalities were seen on MRI brain scans in any soldiers in the blast TBI group [34], a neuroradiological evaluation that was not performed in the American study [68].

Animals

Studies were conducted in mice [72], rats [73–75], cats [76, 77], and dogs [78, 79]. The studies in male rodents showed impaired GH secretion and, when investigated [75], gonadotropin secretion. At a mechanistic level, repeated brain trauma caused vascular permeability of the pituitary gland [74], chronic inflammation of the pituitary and hypothalamus [73]. Furthermore, the distributions of claudin-1 and zonula occludens-1 between tanycytes in the median eminence were disorganized, suggesting tight junction disruptions [72].

The case reports in cats showed diabetes insipidus and central hypothyroidism, with the additional presence of hypocortisolism and low levels of IGF-1 in one of the two felines [76], while the canine case report described isolated hypocortisolism [78]. The retrospective study on 17 dogs referred to four centers for non-fatal TBI showed this order of frequency for deficiencies of these anterior pituitary axes: 41% (GH/IGF-1), 23% (TSH/T4), 12% (ACTH/cortisol) [79].

Conclusions

The interest for the damage suffered by the anterior pituitary gland as a result of TBI continues to remain high both in the adulthood and childhood, clearly outnumbering the interest for the damage suffered by the posterior pituitary.

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