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The role of autoimmunity in pituitary dysfunction due to traumatic brain injury

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Abstract

Purpose Traumatic brain injury (TBI) is one of the most common causes of mortality and long-term disability and it is associated with an increased prevalence of neuroendocrine dysfunctions. Post-traumatic hypopituitarism (PTHP) results in major physical, psychological and social consequences leading to impaired quality of life. PTHP can occur at any time after traumatic event, evolving through various ways and degrees of deficit, requiring appropriate screening for early detection and treatment. Although the PTHP pathophysiology remains to be elucitated, on the basis of proposed hypotheses it seems to be the result of combined pathological processes, with a possible role played by hypothalamic–pituitary autoimmunity (HPA). This review is aimed at focusing on this possible role in the development of PTHP and its potential clinical consequences, on the basis of the data so far appeared in the literature and of some results of personal studies on this issue.

Methods Scrutinizing the data so far appeared in literature on this topic, we have found only few studies evaluating the autoimmune pattern in affected patients, searching in particular for antipituitary and antihypothalamus autoantibodies (APA and AHA, respectively) by simple indirect immunofluorescence.

Results The presence of APA and/or AHA at high titers was associated with an increased risk of onset/persistence of PTHP.

Conclusions HPA seems to contribute to TBI-induced pituitary damage and related PTHP. However, further prospective studies in a larger cohort of patients are needed to define etiopathogenic and diagnostic role of APA/AHA in development of post-traumatic hypothalamic/pituitary dysfunctions after a TBI.

Keywords Brain trauma injury · Hypopituitarism · Antipituitary antibodies · Antihypothalamus antibodies · Hypothalamic–pituitary autoimmunity

Introduction

Encephalic brain injury or traumatic brain injury (TBI) is one of the most frequent disabling conditions involving the central nervous system following a cranial (or rather cranial-encephalic) localized trauma or among a more generalized traumatic event. It may be defined as any impairment of brain function or other evidence of brain pathology caused by external forces and it is a well recognized public health problem worldwide [1].

A substantial number of people with TBI are seen in emergency departments; the great majority, approximately 235,000 each year, are hospitalized because of non-fatal TBI and nearly 50,000 die according to reports from the USA. Furthermore, the overall annual incidence of TBI in the USA has been reported to be 506 per 100,000 in the general population [2]. Thus, there is no doubt that TBI is one of the most common causes of mortality and long-term disability among young adults and frequently results in devastating consequences, including death [3, 4]. The most frequent causes of TBI are road accidents (the main cause, which represents 50% of all cases) followed by falls, accidents related to violence, head injury linked to sport (hockey, football, soccer), combat sports (boxing and kickboxing) characterized by chronic repetitive head injuries and accidental war trauma, including explosion lesions [5–8].

The severity of the head injury is quantified on the basis of the Glasgow Come Score (GCS) which provides a score resulting from the sum of 15 clinical features related to

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ocular response, verbal and motor skills. In particular, mild trauma is identified by a GCS ranging between 15 and 13, moderate trauma by a GCS between 12 and 9 and severe trauma by a GCS < 8 [9]. Although TBI was previously considered a rare cause of hypopituitarism [10], an increased prevalence of neuroendocrine dysfunction in association with TBI has been reported during the last 15 years in many retrospective and prospective studies [11–21].

The reported prevalence of post-traumatic hypopituitarism (PTHP) differs significantly between the various studies, probably due to differences in inclusion/exclusion criteria (eg. severity of the TBI), variability in test protocols (eg. basal or dynamic tests), pituitary hormonal evaluation timing (in acute, medium and long-term phase), different diagnostic thresholds for considering hormone deficiencies [22, 23].

A meta-analysis of 14 studies reported the pooled prevalence of PTHP to be as 27.5%. When classified according to the severity of TBI based on the GCS score, pituitary dysfunction was assessed in 16.8% of patients with mild TBI, 10.9% with moderate TBI and 35.5% with severe TBI [10]. PTHP can result in major physical, psychological, emotional and social consequences leading to depression, reduced quality of life and poor rehabilitation outcome [24]. Our review is aimed at clarifying the role of autoimmunity in the development of PTHP and its potential contibution in the still open challenge of clinical management of this condition, also considering the data so far appeared in the literature on the post-TBI pituitary dysfunctions.

Post traumatic hypopituitarism: the cranial trauma as a chronic morbid process and not only acute event

Post-traumatic hypopituitarism is generally characterized by isolated anterior pituitary hormone deficiency rather than multiple hormone deficiencies. Impairment of growth hormone (GH) secretion and consequently of insulin-like growth factor 1 (IGF-1) concentrations seems to be the most common early disorder after TBI. Impairment of LH and FSH and less frequently, ACTH secretion, has been usually observed together or shortly after that of GH secretion.

Instead, posterior pituitary dysfunction, represented by central diabetes insipidus (DI) or the syndrome of inappropriate antidiuretic hormone (SIADH), is typically transient (approximately > 1 month duration) [19, 25, 26]. Even if some post-TBI pituitary hormone deficiencies persist also in chronic phase, it has to be payed caution when interpreting the results of endocrine testing during the acute phase of TBI. In fact, some of the temporary hormone deficiencies evidenced in patients suffering from acute illness may reflect a normal adaptive endocrine response to the traumatic stress rather than transient hypopituitarism. This also considering that a temporary impairment of hormone secretion could be also related to a transient disruption of circadian system, as demonstrated in animals after spinal cord injury [27]. So, to test the pituitary function away from the head trauma, in order to perform a diagnostic and therapeutic reevaluation in the chronic phase, seems to be essential.

Disturbance of normal pituitary function appears to be transient in many patients, even if with rates of PTHP recovery over time and extent of pituitary dysfunction with marked variability among studies. Nevertheless, GHD and hypogonadotropic hypogonadism remain the two most commonly identified endocrine deficits both in acute and in chronic phase in adult patients, while less than 10% of patients manifest abnormalities of the ACTH-adrenal and thyroid-stimulating hormone (TSH)-thyroid axes in the longer term [25]. Children, instead, show a lower frequency of TBI-induced hypopituitarism, even if the occurrence of GH deficiency has been observed in several cases [28].

The different and often controversial results obtained from the studies carried out in patients with hypopituitarism post TBI, highlight the need to formulate a common and shared strategy of diagnostic and therapeutic management for patients with TBI both in the acute and the chronic phases, also for clarifying the pathophysiology and the risk factors for the development of PTHP. This also considering that the neuroendocrine disorders following TBI seem to play an important role in the development of neuropsychiatric sequelae, frequently seen after head trauma [y29].

Diagnostic and therapeutic aspects

Diagnostic aspects

The diagnosis of PTHP is frequently delayed and underestimated, because the clinical symptomatology is often vague and poorly specific, overlapping with those of TBI (post-concussional syndrome). Furthermore, uni or pluritropinic PTHP appears with varying degrees of severity, generally evolving over time.

In the complex, PTHP is associated with reduced quality of life, alteration of body composition and may delay neuropsychological recovery, since it may aggravate language and mood disorders, and reduce memory, attention and executive abilities. The early diagnosis of hypopituitarism is of fundamental importance because it could slow down or postpone rehabilitation treatment due to the presence of lethargy, muscle fatigue and poor exercise capacity, secondary to pituitary hormone deficiencies. Thus, the most important clinical challenge is to determine which TBI patients should be screened for pituitary dysfunction, to avoid unnecessary protocols with consumption of health care resources in the community. The first consensus guideline on screening for

hypopituitarism following TBI was published by Ghigo et al. in 2005 [30]. According to their conclusions, all patients who need hospitalization in neurosurgery units or intensive care units, regardless of the severity, should be screened for pituitary function in the acute phase, and monitored prospectively for the subsequent 12 months. Other authors suggest only the screening of patients who experienced moderate or severe injury and who have clinical signs and/or symptoms suggestive of hypopituitarism [23, 31–36], even because the evaluation of pituitary function in the acute phase can be difficult to perform in critically ill TBI patients. Moreover, most pituitary hormonal changes (particularly FSH/LH, growth hormone, and TSH deficiencies) are transient and may recover within 3–12 months from the injury [19, 37–41] and benefits of replacement therapy in acute phase in critically ill TBI patients with pituitary hormone deficiencies are uncertain [10, 23, 37]. Instead, the diagnosis and the replacement treatment of secondary glucocorticoid deficiency in this phase should not be missed because it is life-threatening [10, 42–45]. Tanriverdi and Kelestimur recommend assessing only ACTH deficiency by measuring morning basal cortisol levels during the acute phase (cut-off > 11 µg/dL to exclude deficiency), performing routine cortisol measurement on days 1–4 after TBI and on days 5–10 in the event of clinical suspicion of secondary hypoadrenalism [24]. Stress dose glucocorticoid replacement is mandatory in critically ill TBI patients with ACTH deficiency [41, 43].

As previously reported, post-TBI CDI and SIADH could be transient conditions (> 1 month). Tan et al. recommend that CDI should be suspected at an early stage in patients with TBI displaying hypernatraemia and hypotonic polyuria, whereas SIADH should be suspected in patients with euvolemic hyponatraemia, in whom it has been excluded/corrected renal, adrenal and/or thyroid dysfunction [25]. CDI is responsible for the early morbidity observed in TBI patients; however most cases are transient, recovering in the subsequent months, even if increased thirst with mild polyuria may persist for weeks or months after the trauma [46, 47]. The occurrence of CDI may instead be undiagnosed in some patients with neurological and cognitive disabilities responsible for hypodipsia, leading to dehydration and hyperosmolar state, a harmful condition for the life of these patients [48, 49]. Considering this, all patients presenting with features of diabetes insipidus following head trauma should be treated, and reevaluated in the post-acute phase off therapy to estabilish whether their condition was transient or stable, obviously excluding other interfering disorders of hydro-electrolytic metabolism [50].

Therapeutic aspects

The multifaced and often beneficial role of inflammation following TBI suggests caution against aggressive treatments. A nonspecific, high dose immune suppression seems to be detrimental during the first weeks after TBI, as demonstrated by the CRASH trial [51]. However, selected anti-inflammatory therapeutic agents (progesterone, statins, erythropoietin, minocycicline, heparinoids) seem to show promising even if still controversial results in both preclinical and clinical phases [52–57] Therapeutic hypothermia induced 2 or 4 h post TBI gave promising results improving neurological outcomes, reducing edema and inflammation but the best effects were achieved with hypothermia induced 15-min post injury, a protocol not easily feasible in clinical practice [58]. Obviously, in patients with post TBI hypopituitarism, single or multiple pituitary hormone deficits, chronically consolidated, have to be corrected with appropriate replacement therapy.

Replacement tailored therapy reverses symptoms and normalizes the risk factors associated with hormone deficiencies. Thus, patients who experience TBI, should be followed-up carefully and evaluated for pituitary dysfunction to ensure that early appropriate hormone replacement therapy can be provided, if needed [59].

Pathophysiology

The pathophysiological basis of hypopituitarism secondary to traumatic brain injury is still discussed. The cause of the damage could be the hypoxic-ischemic insult, with subsequent oxidative stress and cytotoxicity leading to the death of neuronal cells by apoptosis or necrosis. Prospectively, in addition to the primary mechanical event, secondary insults (i.e., hypotension, hypoxia, hyperthermia and increased intracranial pressure due to skull fractures, edema and hemorrhage) and changes in cerebral flow and metabolism can contribute to hypothalamic–pituitary damage [60] and trigger a neuroinflammatory and autoimmune process, which can contribute to perpetuate pituitary dysfunction. A possible genetic predisposition to the development of autoimmune processes could contribute to its evolution.

Role of direct post-traumatic hypothalamic–pituitary injury

Due to anatomical reasons, the anterior lobe is more frequently affected than the posterior lobe. Indeed, blood supply to the posterior lobe is mostly provided by hypophyseal arteries, arising from the supraclinoid portion of the internal carotid artery, while the anterior lobe is vascularized by the hypophyseal portal vessels, passing through the diaphragma sellae, and the portal capillaries in the pituitary stalk, particularly vulnerable to mechanical compression and direct stalk injury [60, 61]. PTHP seem to be the result of a combination of pathological processes [62]. Among them, the most widely accepted theory ascribes it to an ischaemic insult to the pituitary gland [62, 63]. In fact, TBI can

be associated with direct damage to the hypophyseal portal veins, [64, 65] direct trauma to the gland [66, 67] or transection of the pituitary stalk [64, 68]. These alterations, in association with the hypotension, hypoxia and brain swelling that frequently accompany TBI, lead to pituitary ischaemia and infarction [69]. These assumptions are supported by postmortem findings in patients with TBI showing pathological features including capsular haemorrhage around the pituitary, posterior lobe haemorrhage, anterior lobe and stalk necrosis [65, 70]. In a significant proportion of patients ischaemic/haemorrhagic lesions may affect the hypothalamus [66]. Several other factors have also been implicated in the pathogenesis of PTHP. The pituitary gland is susceptible to direct mechanical impact in TBI, particularly in those with a fracture of skull base. Acceleration/deceleration forces may cause shearing of white matter tracts connected to the pituitary gland. It has been suggested that impairment of GH and gonadotrophin secretions is the most commonly pituitary disorder occurring post-TBI due to the more laterally location of somatotrophs and gonadotrophs [13, 71]. In vivo, imaging techniques in patients with moderate-to-severe TBI demonstrated pituitary enlargement in the acute phase [68]. Over time, patients with TBI may exhibit loss of pituitary volume or an empty sella, abnormal enhancement, perfusion deficits and/or lack of the posterior pituitary signal [72].

Role of autoimmunity

The first question to be satisfied is whether TBI may favour the development of autoimmune process. Several studies reported the role of traumatic brain injury in triggering neuroinflammatory and autoimme process. In particular, some years ago Ankeny and Popovich underlined the potential mechanisms for CNS trauma-induced B cell activation and discussed the potential consequences of these injury-induced B cell responses. They concluded hypothesizing that a subset of autoimmune B cell responses initiated by CNS injury could play a pathogenic role, thus suggesting that a targeted inhibition of B cell could improve recovery in cases of brain and spinal cord injury [73]. In the subsequent years, Zhang et al. reported their results in searching for the identification of serum autoantibody responses to brain-specific protein after TBI in humans. They found that TBI-evoked antibodies showed predominant immunoreactivity against a cluster of bands from 35 to 50 kDa on human brain immunoblots, which were identified as glial fibrillary acid protein (GFAP) and GFAP breakdown products. These antibodies showed an increase by 7 days after injury and were of IgG subtype predominantly. Changes in autoantibody levels were negatively correlated with outcome as measured by GOS-E score at 6 months, suggesting that TBI patients with greater anti-GFAP immune-responses had worse outcomes [74]. The role of antibodies against GFAP in acute and chronic phases of TBI was subsequently further clarified by Wang et al. opening also the way to possible therapy [75]. However, not only negative effects have been attributed to TBI-evoked neuroinflammation and consequent autoimmunity. In fact, post-traumatic neuroinflammation may promote also brain recovery through the production of new neurons from neuronal stem/progenitor cells (NPCs) as demonstrated by experimental TBI in animals [76]. In fact, the neurogenic process is particularly stimulated by cytokines in some regions of the brain. In the hippocampus, for example, TBI robustly increases NPC proliferation, whereas injury-induced neuronal differentiation and survival of new neurons is far less pronounced [77]. Anyhow, a spontaneous cognitive recovery has been shown to be associated with granule neurons produced after TBI [78]. Moreover, a possible protective role had been also attributed to the TBI-evoked autoimmunity by previous studies [79]. In particular, a reduced neuronal loss favoured by a neuroprotective T cell-dependent response evoked by CNS injury had been demonstrated in animals by Yoles et al. in 2001. They found that in transgenic mice overexpressing T cell receptors, ganglion cell survival after injury was higher [80].

Association between hypotalamic-pituitary autoimmunity and TBI induced hypopituitarism

As described in the previous paragraph a linkage between TBI, neuroinflammation and autoimmunity has been suggested by several studies. A review recently appeared in the literature has recounted the research evidence supporting the multifaced roles of neuroinflammation in the injured brain following trauma. The authors summarize the data fluctuating from the protective and detrimental properties that cytokines, chemokines, leucocytes and glial cells play in the acute and chronic stages of TBI. They, moreover, discuss the way by which early and chronic inflammation may amplify some clinical conditions of affected patients, ranging from acute neurological, pshychiatric and neuroendocrine disorders to chronic traumatic encephalopathy [52]. With regards to the events leading to the post-TBI hypothalamic–pituitary deficiencies, it may be speculated that head trauma may trigger an ongoing cascade of vascular and histopathological alterations (necrotic, ischemic, and hypoxic changes) affecting both hypothalamus and pituitary and involving precociously GHRH and corticotropin-releasing hormone (CRH) neurons at hypothalamic level and somatotropic and gonadotropic cells at pituitary level with consequent impairment of the respective hormone secretions [15, 19, 26, 81–85]. Mediators of inflammatory process may favour the activation of the immune system, through the acceleration of neuronal cell necrosis [71, 83, 85], which allows to unmask sequestered

pituitary or hypothalamic antigens and consequent production of respective autoantibodies, that may contribute to late hypothalamic–pituitary dysfunction in TBI patients. However, a unifying hypothesis suggesting that, in these patients, vascular injury is responsible for early pituitary hormone deficits while autimmunity for late pituitary hormone deficits, has to be still confirmed.

A possible role of autoimmune process involving the hypothalamic–pituitary region triggered by head trauma has been suggested by studies conducted in animals, showing the occurrence of IgG autoantibodies against dying neurons [86] and increased expression of interleukin IL-1b and glial fibrillary acidic protein in the cerebral cortex, hypothalamus and anterior pituitary [87] of the injured brain of adult rats.

Therefore, based on the currently available data it is tempting to speculate that persistent neuroinflammation may be involved in the pathogenesis of the long-term after TBI pituitary dysfunction, particularly in individuals who have a genetic predisposition [86–88]. In a recent study involving 93 patients with TBI due to various causes, it has been shown that apolipoprotein E (APO E) polymorphisms are associated with the development of TBI-induced pituitary dysfunction, and that the APO E3 genotype decreases the risk of hypopituitarism after TBI [88]. APO E is a key protein in enhacing lipid transport and metabolism within the nervous system and it has a role in neuronal repair and maintenance. In human beings, there are three common alleles of APO E gene (e2, e3 and e4) which encode the three isoforms of the protein (E2, E3, and E4) [89]. Several studies have demonstrated the association of APO E polymorphism with traumatic hematoma volume [90], coma duration [91], neurobehavioral recovery and seizures [92, 93] after TBI. In addition, Jordan et al. have demonstrated the relation of APO E4 allele with the chronic traumatic encephalopathy in boxing [94]. APO E is the primary apolipoprotein synthesized within the central nervous system, including the hypothalamo-pituitary region, and it is upregulated following injury [95]. After the initial head trauma, secondary neuronal injury is associated with a neuroinflammatory response, resulting in the release of reactive oxygen species and inflammatory cytokines, such as tumor necrosis factor (TNF), IL-1, and IL-6 [96]. APO E has also been demonstrated to reduce the neuroinflammatory response in vitro and in vivo in an isoform-specific fashion [97]. The APO E4 isoform has been shown to be less effective than the APO E3 isoform at downregulating inflammatory cytokines, both in the peripheral circulation and in the brain [98]. In several studies, it has been reported that homozygosity for APO E e3 allele in humans reduces the risk for the development of Alzheimer's desease [99] and may protect against vascular morbidity [100]. Based on these previous data and our findings, we could suggest that the trauma-induced neuroinflammatory response and individual variations in APO E-related neuronal repair mechanisms may have an impact on the pathogenesis of TBI-induced hypopituitarism [88].

The possible triggering role of neuroinflammation and autoimmunity in the occurrence of pituitary dysfunction was also supported by the results of our studies in collaboration with other researche groups investigating the autoimmune pattern of TBI patients [21, 101, 102]. The first clinical study demonstrating the presence of antipituitary antibodies in these patients 3 years after head trauma was published in 2010 by Tanrivedi et al. in collaboration with our group of immunoendocrinology [101]. Twenty-nine patients with TBI, mainly due to road traffic accidents, were included in that study; the occurrence of pituitary dysfunction was found significantly more frequent in APA-positive (46.2%) than in APA-negative (12.5%) patients ($P < 0.04$). There was a significant association between the detection of APA and hypopituitarism due to TBI [101]. We re-analyzed the sera of these 29 TBI patients to evaluate the possible association between the detection of antihypothalamus antibodies (AHA) and the occurrence of hypopituitarism, but we could not find any significant association (unpublished data). Subsequently, we performed a 5 years prospective follow-up of autoimmune hypothalamic–pituitary pattern and anterior pituitary function in 25 patients (20 men, 5 women) with mild, moderate and severe TBI, investigated at one, three and 5 years after TBI. We showed, for the first time, close strong associations between the presence of high titers of APA and/or AHA and hypopituitarism at the fifth year [21]. Impaired GH secretion was the most constantly observed pituitary hormone deficiency along all the time span of observation after TBI. Some pituitary hormone deficiencies, diagnosed at the first observation, recovered over time, but other ones persisted until the fifth year with different prevalence (28% GH, 4% ACTH, and 4% gonadotropin deficiencies), especially in strongly AHA- and APA-positive (titers > 1/16) patients. However, all patients with severe TBI and ACTH and GH secretion deficiencies at the first year after TBI, constantly showed persistence of these deficiencies until the fifth year [21]. Futhermore, in a collaborative study on the effect of chronic repeatitive head trauma with low intensity in boxers and kickboxers, investigating their autoimmune pattern, we showed for the first time the presence of AHA and APA, thus suggesting that autoimmunity may play a pathogenic role also in the pituitary dysfunction frequently occurring in these subjects [8]. Interestingly, while the hypopituitarism observed in patients with other causes of TBI was significantly associated with the presence of APA [101], that occurring in boxers was only significantly associated with the presence of AHA. A further interesting point emerging from our data was the high prevalence of GH and/or ACTH deficiency and the absence of diabetes insipidus in all AHA-positive patients. This seems to indicate that these antibodies may be directed toward GHRH- and

CRH-secreting cells more than toward AVP-secreting cells [102]. Moreover, the presence of APA and AHA has been shown in patients with Sheehan's syndrome even many years after the onset of hypopituitarism, thus suggesting that an autoimmune process involving both the hypothalamus and pituitary gland, triggered by cellular damage caused by ischemia, may contribute to late pituitary dysfunction also in women with this syndrome [103]. A similar process leading to hypopituitarism can be hypothesized as consequence of vascular pituitary alterations following a TBI. Although the nature and the clinical significance of these autoantibodies are still discussed, the results of these studies suggest that they may be considered as markers and risk factors of pituitary impairment, especially when detected at high titer, as they are undetectable (< 1:8) in healthy control subjects [104, 105].

Methodological concerns

The role of antipituitary and antihypothalamus antibodies is still discussed owing to methodological difficulties and also because the findings on the true pituitary antigen(s) are still debated. In spite of the diffuse use of the immunofluorescence method, the results so far appeared in the literature are often conflicting, particularly due to the use of different human or animal substrates. In our studies, APA and AHA were evaluated by simple indirect immunofluorescence method on cryostat sections of young baboon pituitary and hypothalamus glands, respectively. In particular, fluorescein isothiocyanate conjugated with goat antihuman immunoglobulins was used to detect the presence of APA and AHA; they were considered positive starting at dilution of 1:8. Figure 1 show a sample positive for APA (a) and Fig. 2 a sample positive for AHA (a) by immunofluorescence, compared to two negative control samples (Figs. 1b and 2b, respectively).

We used as substrate cryostat sections of young baboon, due the difficulty to have human substrates in our disposal. This suggests caution against generalization of our results. However, we think that improvement of specificity and sensitivity of the method may be obtained, considering a predetermined cut-off of the titre and a particular kind of immunostaining, thus excluding the low titres and counfounding immunostaining patterns. This procedure may allow reliable results for diagnosing pituitary immunity, also by using animal substrates, especially when the results are validated by a second step with four-layer double immunofluorescence [105–108]. In fact, this method allows not only to detect APA and/or AHA but also to identify the different cell lines targeted by these autoantibodies and predict a possible specific hormonal deficiency. Concerning this, since 2005, we

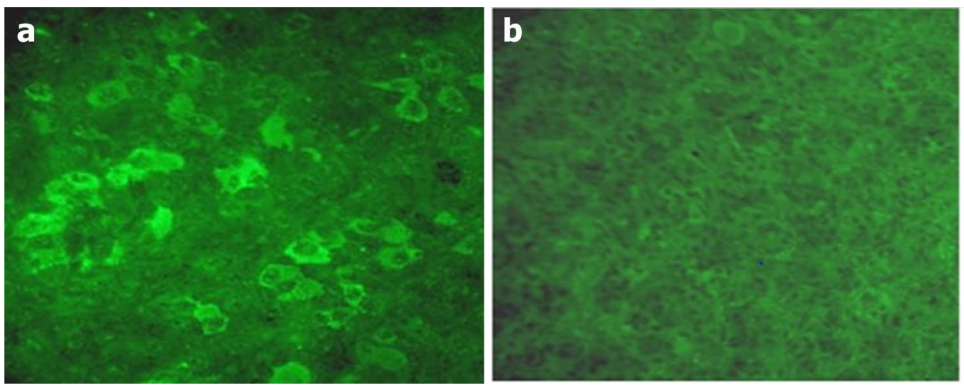

Fig. 1 Antipituitary antibodies (APA) detected by immunofluorescence method: **a** positive serum sample showing intracytoplasmatic immunofluorescence of pituitary cells; **b** negative control serum

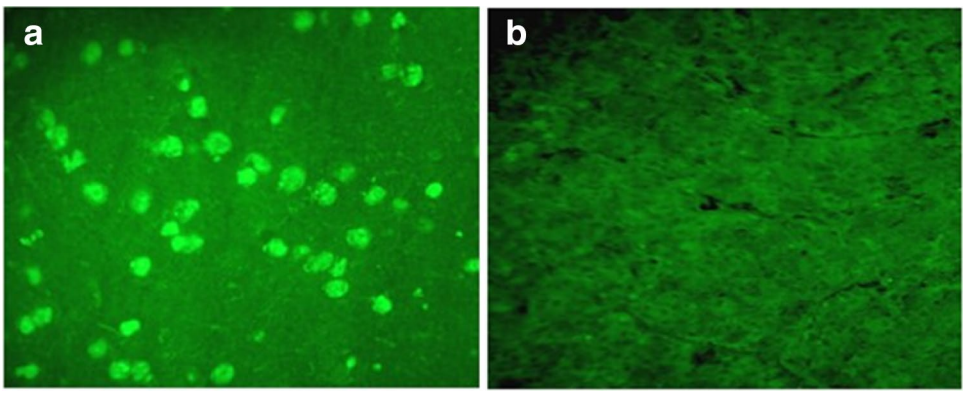

Fig. 2 Antihypothalamus antibodies (AHA) detected by immunofluorescence method: **a** positive serum sample showing intracytoplasmatic immunofluorescence of hypothalamus cells; **b** negative control serum

used a double four-layer immunofluorescence method in a study aimed at characterizing the pituitary-secreting cells targeted by antipituitary antibodies in APA positive children with idiopathic GH deficiency and in children with idiopathic short stature [105]. Using this method, the same pituitary section from young baboon was tested in a first step against the patient's serum and then fluorescein isothiocyanate (FITC) goat anti-human immunoglobulin sera and in the second step, against rabbit anti-sera, anti-GH, -ACTH, -TSH, -PRL, -FSH and -LH, separately followed by rodamine goat sera anti-rabbit IgG. The different color of anti-Ig conjugate against human sera and animal serum (green for FITC and red for rodamine), allowed for direct assessment of whether the patient's serum and the animal's sera stained the same or different pituitary cells. By this procedure, we were able to demonstrate that, in GH-deficient patients, positive for APA at high titre, GH-secreting cells were the main target of these antibodies [104, 105] (Fig. 3). Combined evaluation of these methods also in TBI patients may allow identifying those at higher risk for pituitary autoimmune dysfunction, thus requiring a strict pituitary surveillance to disclose a preclinical phase of hypopituitarism and interrupt, if possible, therapeutically the progression to clinically overt disease.

Guaraldi et al. reviewing the literature until 2015, assessed the association of pituitary autoimmunity and pituitary dysfunction in patients with TBI. They affirmed that the detection by immunofluorescence of anti-hypothalamus and antipituitary antibodies at high titers in patients with acute and chronic TBI, may be considered a risk factor for the onset and persistence of TBI-induced hypopituitarism, in the context of chronic neuroinflammation. However, highlighting the limitations of the previously published studies on this topic, they concludeded that hypothalamic–pituitary autoimmunity seems to contribute to TBI-induced pituitary damage, but major methodological issues need to be overcome and larger studies are warranted to confirm these preliminary data [109, 110]. In this connection, by searching in the literature data published since 2000 (Table 1), we found that among all studies appeared on this topic, only very few studies had been addressed at performing an autoimmune evaluation searching for specific autoantibodies in affected patients after months of TBI (Table 1A).

Conclusion and future research

Post traumatic hypopituitarism (PTHP) results in major physical, psychological and social consequences leading to impaired quality of life and poor rehabilitation. It is important to find a shared diagnostic and therapeutic management of PTHP.

Knowing the pathogenesis and molecular mechanism could be determinant to prevent development of pituitary dysfunction after TBI and to detect and treat it early.

Hypothalamic–pituitary autoimmunity seems to contribute to TBI-induced pituitary damage and development of PTHP; however, data so far appeared in the literature suggest caution against generalization of this assumption. In this regard, a recently published paper reviewed the latest articles and compiled the evidence which suggests for or against the role of autoimmunity in post-TBI hypopituitarism or which defines the strength to which autoimmunity has been established as a cause of this dysfunction [121]. Also considering the conclusions of this paper, further data from long-term, case control, prospective studies in larger cohorts, performed with an optimized immunofluorescence method, such as double four-layer immunofluorescence, are warranted to validate these preliminary results and, if possible, define the etiopathogenic role, if any, of APA and/or AHA in the occurrence of PTHP. Furthermore, it would be interesting to analyze the role of autoimmunity in children suffering from post-TBI GH deficiency, but APA and AHA negative at the first observation, through the evaluation

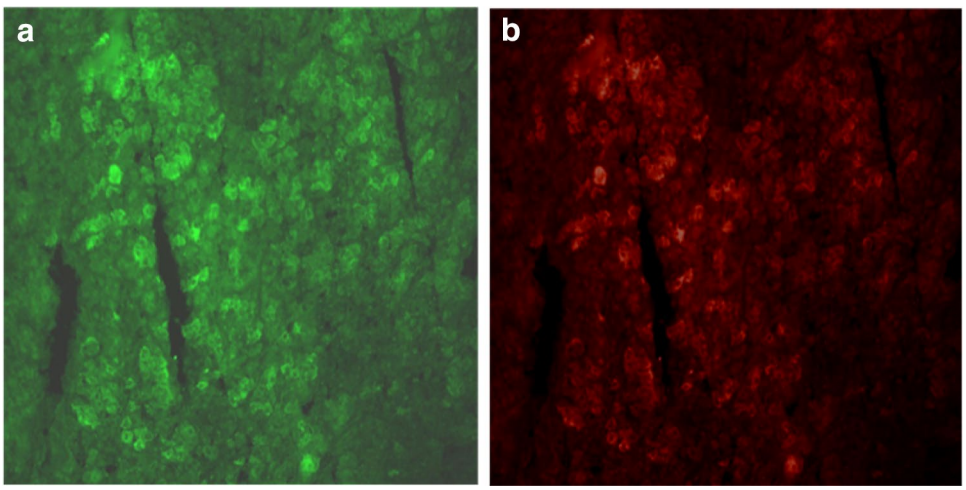

Fig. 3 Characterization of pituitary-secreting cells targeted by antipituitary antibodies (APA) by four-layer double immunofluorescence: **a** first step showing some pituitary cells targeted by APA; **b** second step showing that the cells targeted by APA correspond to GH-secreting cell

Table 1 Summary of the studies assessing the occurrence of anterior hypopituitarism after months from traumatic brain injury (TBI)

Author	No. patients	GCS	Time from injury	Hormone deficiency (anterior hypopituarism)	Number of patients APA+ (%)	Number of patients AHA+ (%)
A (papers investigating the association between post-traumatic hypopituitarism and hypothalamic–pituitary autoimmunity)						
Tanriverdi et al. [20]	17	3–15	3 years	Total%: 23; GH%:23	8 (47%)	9 (53%)
Tanriverdi et al. [21]	25	3–15	5 years	Total%: 32; GH%: 28; FSH/LH%: 4	12 (48%)	15 (60%)
Tanriverdi et al. [102]	61	NA	NA	Total%: 18.4; GH%: 14.8; ACTH%: 8.2	14 (23%)	13 (21%)
Tanriverdi et al. [101]	29	3–15	3 years	Total%: 27.6; GH%: 20.7; ACTH%: 6.9	13 (44.8)	Not evaluated
Author	No.	GCS	Time from injury	Hormone deficiency (anterior hypopituarism)		
B (papers investigating only the occurrence of post-traumatic hypopituitarism)						
Alavi et al. [111]	47	3–15	> 6 months	Total%: 21.3; FSH/LH%: 21.4; ACTH%: 4.3; Multiple%: 12.8		
	22	3–15	> 12 months	Total%: 9.1; GH%: 9.1		
Kopczak et al. [112]	340	–	< 1 month to 39 years	Total%: 36.5; GH%: 7.8; FSH/LH%: 40; ACTH%: 1.2; TSH%: 5.6; Multiple%: 5.6		
Hannon et al. [43]	100	< 14	Median 14 months	Total%: 34.4; GH%: 18.8; FSH/LH%: 3.1; ACTH%: 18.8; Multiple%: 3.1		
Ulfarsson et al. [113]	51	< 9	2–10 years	Total%: 27.5; GH%: 21.6; FSH/LH%: 3.9; TSH%: 2		
Kozlowski Moreau et al. [114]	55	Lowest GCS 8.8	> 1 year	Total%: 76.4; GH%: 63.6; FSH/LH%: 3.6; ACTH%: 27.3; TSH%: 21.9		
Kokshoorn et al. [36]	112	–	Mean 4 years	Total%: 5.4; GH%: 2.7; FSH/LH%: 0.9; ACTH%: 1.8		
Schneider et al. [115]	825	–	> 5 months	Total%: 37–38		
Berg et al. [116]	246	< 13	Average 12 months	Total%: 21; GH%: 5; FSH/LH%: 9; ACTH%: 1; TSH%: 12; Multiple %: 3		
Krahulik et al. [40]	186	3–14	12 months	Total%: 21; GH%: 13.5; FSH/LH%: 5.6		
Kleindienst et al. [37]	71	3–15	24–36 months	GH%: 35; ACTH%: 61		
Wachter et al. [69]	55	3–15	1–4 years	Total%: 25.4; GH%: 1.8; FSH/LH%: 12.7; ACTH%: 3.6; TSH%: 1.8; Multiple%: 1.8		
Klose et al. [117]	104	3–15	Median 13 months	Total%: 15; GH%: 15; FSH/LH%: 2; ACTH%: 5; TSH%: 2; Multiple%: 3.8		
Klose et al. [39]	46	3–15	12 months	Total%: 10.9; GH%: 10.9; FSH/LH%: 2.1; ACTH%: 6.5; TSH%: 2.1; Multiple%: 6.5		
Herrmann et al. [118]	76	< 8	Median 20 months	Total%: 24; GH%: 8; FSH/LH%: 17; ACTH%: 2; TSH%: 2; Multiple%: 6.6		

Table 1 (continued)

Author	No.	GCS	Time from injury	Hormone deficiency (anterior hypopituarism)
Schneider et al. [18]	78	3–15	12 months	Total%: 36; GH%: 10; FSH/LH%: 20; ACTH%: 9; TSH%: 3; Multiple%: 4,3
Tanriverdi et al. [19]	52	3–15	12 months	Total%: 59; GH%: 32; FSH/LH%: 7.7; ACTH%: 19; TSH%: 6; Multiple%: 9.6
Leal-Cerro et al. [16]	170	< 8	> 12 months	Total%: 24.7; GH%: 5.8; FSH/LH%: 17; ACTH%: 6.4; TSH%: 5.8; Multiple%: 8.8
Aimaretti et al. [12]	70	3–15	12 months	Total%: 22.7; GH%: 18.6; FSH/LH%: 11.4; ACTH%: 7.1; TSH%: 5.7; Multiple%: 10
Agha et al. [11]	102	3–13	Median 17 months	Total%: 28; GH%: 10.7; FSH/LH%: 11.8; ACTH%: 12.7; TSH%: 1; Multiple%: 5.9
Agha et al. [38]	50	8–13	12 months	GH%: 10.4; FSH/LH%: 12.5; ACTH%: 18.8; TSH%: 2.1
Bondanelli et al. [119]	50	3–15	12–64 months	Total%: 54; GH%: 28; FSH/LH%: 14; TSH%: 10; Multiple%:12
Popovic et al. [17]	67	9–13	Median 44 months	Total%: 34; GH%: 15; FSH/LH%: 9; ACTH%: 7; TSH%: 4; Multiple%: 10.4
Liebermann et al. [120]	70	–	Median 13 months	Total%: 68.5; GH%: 14.6; FSH/LH%: 1.4; ACTH%: 45.7; TSH%: 21.7
Kelly et al. [15]	22	3–15	Median 26 months	Total%: 36.4; GH%: 18.2; FSH/LH%: 22.7; ACTH%: 4.5; TSH%: 4.5

ACTH adrenocorticotropic hormone, *FSH* follicle-stimulating hormone, *GCS* Glasgow Coma Scale, *GH* growth hormone, *LH* luteinising hormone, *TBI* traumatic brain injury, *TSH* thyroid-stimulating hormone

over time of these antibodies, following-up their trend after months and years from the trauma. Finally, even if some therapeutic choices have been so far indicated, the results are still controversial. In particular, it should be investigated the possibility of interrupting the cascade of events leading to PTHP closely linked to the TBI-evoked neuroinflammation/autoimmunity, by a tailored appropriate therapy, thus possibly avoiding to reach an overt stable hypopituitarism. Of course, at this time, in patients with single or multiple post-traumatic pituitary hormone deficiencies, a replacement therapy is absolutely necessary.

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Compliance with ethical standards

Conflict of interest The authors have nothing to declare.

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