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A case of post-traumatic isolated ACTH deficiency with spontaneous recovery 9 months after the event

Survivors of traumatic brain injury (TBI) often suffer from significant adverse physical, neuropsychological, and social sequelae. TBI may pose significant risks to pituitary function;[1–5] untreated hypopituitarism may aggravate these adverse consequences. Studies on the natural history of post-TBI hypopituitarism are lacking, and the reversibility of hormone deficits remains uncertain.

We describe a case of a man who suffered a transient period of secondary hypoadrenalism after a serious TBI. This is the first reported case of reversible isolated adrenocorticotrophic hormone (ACTH) deficiency following head trauma.

CASE REPORT

An 18 year old man was assaulted on 14 September 2003 and immediately admitted to the local accident and emergency unit with a Glasgow Coma Scale (GCS) score of 3/15 and constricted pupils. Brain computed tomography (CT) revealed multiple small bleeds involving the basal ganglia, left cerebellum, and midbrain, and a left maxilla linear fracture. No other serious injuries were found. He was ventilated on admission, supported in the intensive care unit, and 4 days later transferred to a trauma ward with an unaltered brain CT. Over the next 7 weeks, his GCS remained reduced (6–11/15) with a marked improvement after this time. During his acute recovery phase, no hypotensive insults were recorded, but he had episodes of hypoxia and increased intracranial pressure (ICP). He was admitted to a neurological rehabilitation unit on 24 November 2003 with dysathria, dysphagia, ataxia, increased muscle tone, and impairments in concentration, executive functioning, and visuospatial perception. His post-traumatic amnesia lasted several weeks. He consented to participate in a research project on post-TBI pituitary dysfunction.

He had no history of diabetes insipidus (DI) (permanent or temporary). Evaluation of the anterior pituitary in January and February 2004 showed optimum growth hormone (GH) secretory reserve, and normal thyrotroph and gonadotroph function; prolactin levels were normal. A short synacthen test (250 µg intramuscularly) in January 2004 indicated sub-optimum cortisol response, confirmed by a glucagon test (1 mg intramuscularly) 1 month later. The ACTH at this time was 16.9 ng/l (normal range 0 to 46); the patient had not been on steroids during the acute or post-acute phase. He had no classical signs or symptoms of hypoadrenalism and his blood electrolytes were normal. Treatment with hydrocortisone at times of stress was suggested. During the following months, he did not show clinical features of pituitary dysfunction. A short synacthen test repeated in June 2004 demonstrated recovery of the corticotroph axis (table 1). Upon discharge (July 2004), he was significantly improved in all aspects of neurological function, and brain CT was reported as normal.

DISCUSSION

TBI may pose significant risks to pituitary function, owing to its bony encasement within the sella turcica, delicate infundibular hypothalamic structure, and vulnerable vascular supply.[2] Autopsy studies after head trauma show necrosis or haemorrhage of the pituitary stalk or gland in 3.8–42% of cases.[1] Possible pathophysiological mechanisms include direct damage during the traumatic event, compression due to subsequent increased ICP (by haematomas or oedema), decreased cerebral perfusion pressure and/or vasospasm during the recovery phase, and trauma to the stalk and/or hypothalamus during neurosurgical interventions.[2] In contrast to the corticotroph and thyrotroph cells mainly found in the more protected territory of the short hypophyseal portal system, the majority of somatotroph and gonadotroph cells is located in the vulnerable vascular area of the long hypophyseal portal system.[2] This anatomical arrangement appears to translate into a hierarchy of hormone failure, with GH and FSH/LH deficiencies usually being the first deficits to appear in cases of pituitary damage.[2] Studies assessing patients 3–36 months after TBI suggest GH deficiency in 11–21%, FSH/LH deficiency in 13–17%, ACTH deficiency in 8–12%, TSH deficiency in 1–5% and DI in 4–6% of subjects, with the initial post-resuscitation GCS or CT appearances not related to the presence of anterior pituitary deficits.[3–5] Rarely, exceptions to this pattern with isolated ACTH deficiency have been reported, as in the case we present; notably, in a multicentre study of 100 patients assessed 3 months after the injury, isolated ACTH deficiency was diagnosed in only 1%.[3] Although the pathophysiological mechanism has not been clarified, this finding suggests that in TBI patients the absence of GH or FSH/LH deficiency cannot rule out other pituitary hormone deficits and therefore, systematic neuroendocrine evaluation may be necessary.

Pituitary insufficiency has serious consequences, which may contribute to long-term physical, cognitive, and psychological disability following TBI. ACTH deficiency can be life threatening but may also present with fatigue, muscle weakness, and altered mental activity. GH deficiency is associated with decreased muscle mass and strength, central obesity, fatigue, compromised quality of life, reduced bone mineral density, and impaired lipid profile. FSH/LH deficiency causes decreased muscle mass and strength, diminished mood and wellbeing (men), premature atherosclerosis (women) and osteoporosis (both sexes). TSH deficiency is associated with fatigue, muscle weakness, and neuropsychiatric disorders.[6] Early diagnosis and treatment of these abnormalities is important for the prevention of life threatening consequences (as with ACTH deficiency), and for the possible beneficial effects of hormone replacement therapy on recovery and rehabilitation potential.

The natural history of TBI attributed hypopituitarism is largely unknown. Although spontaneous recovery of DI is well recognised,[5] the data are less clear for anterior pituitary hormone deficits. Three cases of transient post-TBI anterior hypopituitarism have been published to date; a possible mechanism is regeneration of the damaged portal vessels permitting resumption of pituitary function.[1] To our knowledge, our case is the first of spontaneous recovery of isolated ACTH deficiency (not attributed to glucocorticoid therapy during the acute or post-acute recovery phase), and it demonstrates the need for periodical neuroendocrine evaluation in patients diagnosed with deficits, in order to avoid unnecessary hormone replacement. Unfortunately, an established protocol for the timing of these assessments does not exist due to the lack of published evidence.

In conclusion, our case shows that TBI may result in pituitary hormone deficits not following the commonly recognised pattern

Table 1 Assessment of pituitary function

Date	GH axis	ACTH axis	FSH/LH axis	TSH axis	PRL
Jan 2004		Peak cortisol in short synacthen test at 30 min: 481 nmol/l*	FSH 8.5 IU/l (3 to 8) LH 5.3 IU/l (3 to 8) testosterone 22 nmol/l (9 to 42)	TSH 0.9 mU/l (0.5 to 6.0) T3 2.4 nmol/l (1.0 to 2.5) fT4 24.2 pmol/l (9.0 to 25.0)	173 mU/l (0 to 450)
Feb 2004	Peak GH in glucagon test: 52.0 mU/l‡ IGF-I 21.5 nmol/l (12.5 to 67.5)	Peak cortisol in glucagon test: 243 nmol/l†			
June 2004		Peak cortisol in short synacthen test at 30 min: 609 nmol/l*			

Figures in parentheses are normal ranges. Normal responses: *> 580 nmol/l; †> 580 nm/l; ‡> 6 mU/l. IGF-I, insulin-like growth factor I; FSH, follicle stimulating hormone; LH, luteinising hormone; TSH, thyroid stimulating hormone; PRL, prolactin.

of hormonal failure; spontaneous recovery can occur. Prospective studies clarifying the natural history of hypopituitarism associated with head trauma and allowing the development of appropriate guidelines for the follow up and management of these patients are needed.

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An aspirin responsive non-progressive chronic chorea

Chronic generalised chorea is a physically and socially disabling symptom with few effective treatments. We present a case of long standing neurologically isolated non-progressive chorea which resolved almost completely after the introduction of aspirin therapy.

Case report

A 41 year old female presented with chronic generalised chorea since she was 10 years old. Onset had been over several weeks and was preceded by recurrent sore throats. There was no family history of neurological disease.

Since onset, the chorea had fluctuated slightly over time but had never progressed or resolved. It was slightly worse during the patient's menstrual periods but was severely disabling during her pregnancies. Her first pregnancy ended with an intra-uterine death after 31 weeks. Her second pregnancy ended as a miscarriage after 8 weeks. A third pregnancy resulted in a son being delivered at 34 weeks. However, the chorea had become so severe during this pregnancy that the patient decided to undergo sterilisation. Between pregnancies, the chorea settled back to its previous levels.

Over the years, the following investigations were negative or normal: clotting studies, haemoglobin, white cell count, C-reactive protein, erythrocyte sedimentation rate, serum urea and electrolytes, liver function tests, creatinine kinase, lactate, protein electrophoresis, thyroid function tests, amino acid profile, white cell enzymes, antistreptolysin O titre, C_3 and C_4 complement, serum caeruloplasmin and urinary copper, blood film for acanthocytes, syphilis serology, rheumatoid factor, autoantibody screen, anticardiolipin IgG and IgM, anti-β_2-glycoprotein-I IgG and IgM, anti-basal ganglia antibodies, genetic testing for mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), chest *x* ray, ECG, EEG, CT and MRI brain, and nerve conduction studies. A low platelet count of 106×10^9/l (normal range: 150–400) was noted during the first pregnancy and persisted thereafter. Giant platelets on the blood film and bone marrow biopsy changes were consistent with peripheral platelet consumption.

At the age of 41 the patient presented to the neurology clinic because she still found that the chorea was interfering with her daily life. She had generalised bilateral chorea affecting her arms, legs, tongue, and speech. Higher cognitive function was intact. Previous treatments had been of little or no benefit. Tetrabenazine and diazepam provided some improvement. Propranolol and sulpiride had no effect. A trial of steroids (prednisolone 60 mg) seemed to improve her chorea for 2 weeks but had to be discontinued due to intolerance of the adverse effects.

She was commenced on aspirin 75 mg each morning because of the suspicion of antiphospholipid syndrome (APS), although antibody testing was repeatedly negative. This resulted in a marked immediate improvement in her chorea, such that it became almost unnoticeable. She noticed that the chorea appeared to return towards the end of the day. She was advised to stop treatment during menstruation because of heavy periods. However, stopping the aspirin was also associated with a return of the chorea towards the end of the week. The aspirin was increased to 150 mg once a day. The chorea disappeared almost completely at all times of the day. This improvement has been maintained for over 2 years. She tries not to stop taking aspirin for longer than 1 week in case the chorea returns.

Discussion

We report the case of a patient with long standing chorea which improved after aspirin was given. In a literature review we found only one previous case of chronic chorea that had been reversed with aspirin alone.[1]

We suspect our patient has APS because of the history of chorea, miscarriages, placental thrombosis, and thrombocytopenia. However, none of the laboratory criteria are met and therefore a definitive diagnosis cannot be made.

Seronegative APS patients are described and are presumed to have other, as yet unidentified, circulating antibodies causing thrombosis.[2] Alternatively, it is possible that the patient has persistent Sydenham's chorea (SC), although throat swabs and the antistreptolysin O titre were both normal at presentation and anti-basal ganglia antibodies were negative. However, anti-basal ganglia antibodies are positive in only ~69% of chronic SC which does not usually respond to aspirin.[3]

APS and SC are both thought to be antibody mediated. In APS, antiphospholipid antibodies may affect phospholipid binding proteins causing hypercoagulability. However, antibodies in APS may also activate endothelial cells and up regulate adhesion molecules, cytokines, and prostacyclins. This generates an inflammatory vasculopathy, resulting in ischaemic injury with microthrombosis to the basal ganglia. There is also laboratory evidence of APS antibodies binding directly to the brain.[4]

Aspirin is widely used in APS for its presumed antiplatelet properties. Activated platelets have been observed in APS with neurological manifestations but not in patients without neurological features. However, aspirin also inhibits the formation of inflammatory cytokines. Aspirin has been shown to down regulate prostaglandin E2, which is produced by brain endothelial cells in vitro, and prostacyclin receptors have been identified in the striatum. It has also been shown to exert a protective effect on endothelial brain cells by decreasing leucocyte adhesion molecule expression at the cell surface.[5] In the absence of a measurable coagulopathy, these mechanisms may explain the benefit of aspirin therapy in our patient. Alternatively, the aspirin may have a modulatory platelet effect independent of endothelial cells.

While it could be argued that aspirin therapy coincided by chance with an improvement in the chorea, this seems unlikely. The patient had chronic chorea for 30 years and her symptoms never improved spontaneously as they did immediately after starting aspirin. A placebo effect is unlikely as other treatments had provided no significant benefit. Moreover, her chorea returns if she does not take the aspirin for a week. However, she is unwilling to stop taking aspirin for longer and we believe it would be unethical to advise this. To address the question definitively, a multi-centre randomised controlled trial would be required, but this might be impractical in such an uncommon condition.

In conclusion, aspirin may be useful in the treatment of some patients with chronic non-progressive chorea.

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Patient consent: the patient gave her written informed consent. However, we have not included any identifying details in this case report.

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