Long-term neuroendocrine dysfunction following traumatic brain injury: an overview

Paul E Goodwin[*] and Richard PG Morris[**]

[*]Institute of Neuroscience, University of Nottingham, Queen's Medical Centre, Nottingham. [**]Headway—the brain injury association, 4 King Edward's Court, Nottingham.

Introduction

Neuroendocrine dysfunction as a consequence of traumatic brain injury (TBI) has been widely documented since it's initial identification early in the twentieth century (Cyran, 1918). In recent months there has been a resurgence of reviews, opinions, seminars and clinical studies of the condition.

A recently published viewpoint, (Aimaretti and Ghigo, 2007), a Lancet seminar (Schneider, *et al*, 2007) and a review and comment (Nishi and Lifshitz, 2007) all restated the need for correct recognition and treatment of neuroendocrine dysfunction in a wide population of TBI survivors.

This poster provides a brief overview of post-TBI neuroendocrinopathy and aims to bring this, much under-diagnosed, condition to the attention of a wider audience.

The nature of traumatic brain injury

There are no reliable data for the number of TBI patients treated in the UK. Tennant (2005) provides the most recent statistics. Using ICD-10 codes S00.0-S09.9, Tennant's study reveals that 112,718 head injury patients were admitted to English hospitals during 2001-02, giving a hospital incidence rate of 229 per 100,000 population. Whilst Tennant gives no breakdown based on the severity of the injury, another study by Miller and Jones (1985) shows that, of the 1919 traumatic brain injury patients treated in Edinburgh Royal Infirmary in 1981, 84% were classified as minor injury, 11% as moderate, and 5% of patients were classified as severe injury (Figure 1). Although reliability of data is often compromised by differing criteria for TBI used by clinicians across the UK, it is clear that the population today includes a large number of TBI survivors, many of whom are left with long-term neurological and physical disabilities.

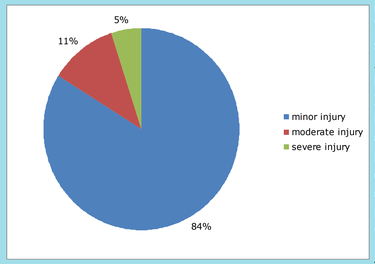

Figure 1. Severity of head injury diagnosed in patients admitted to Edinburgh Royal Infirmary for head injury during 1981 (data from Miller and Jones, 1985)

The usual indicators for recovery from brain injury are the Glasgow Coma Scale (GCS); intracranial fluid pressure; length of loss of consciousness; the period of post-traumatic amnesia; and CT and MRI scans. Although useful in the prognosis of TBI, none are reliable indicators of neuroendocrine dysfunction (Shin, *et al*, 2001). Hormonal sequelae to the initial injury have no fixed criteria for investigation and problems are treated by clinicians if and when they are diagnosed.

The type of tissue injury that occurs in TBI often depends on the nature of the initial assault. Penetrative injuries tend to produce localised focal damage; whereas closed injuries, such as road traffic accidents, falls and impact with a blunt instrument, produce more diffuse injuries including axonal shearing and tearing from acceleration forces, ischaemia and infarction due to swelling or haemorrhage (Sandel, *et al*,1998).

Traumatic injury to neuroendocrine structures

There is long-standing evidence, from both imaging and post-mortem investigations, that neuroendocrine structures are vulnerable to damage following TBI (for examples see Daniel, *et al*, 1959 and Ceballos, 1966).

Unless directly pierced in a penetrative assault, neuroendocrine structures in the brain are most susceptible to diffuse shearing and tearing forces, and ischaemic and haemorrhagic damage.

The fine network of blood vessels that make up the hypothalamic-pituitary portal system are at high risk from haemorrhage (Daniel, *et al*, 1959).

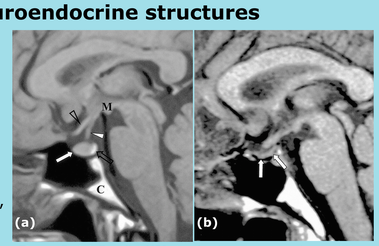

Figure 2. (a) Saggital MRI showing the normal anatomy of the sella turcica and juxtasella region. The anterior pituitary —thick arrow, posterior pituitary —open arrow, infundibulum— thick arrowhead, optic chiasm—open arrowhead, mamillary body—M and clivus—C are all indicated. **(b)** Saggital MRI of 17 year old TBI survivor showing transection of the infundibulum and resulting atrophy of the hypophysis (thick arrows) (reproduced with permission from Shin, *et al*, 2001)

Neuronal processes within the infundibulum are particularly prone to shearing and tearing damage as the pituitary lies within the hard pituitary fossa, part of the sella turcica of the sphenoid bone (Shin, *et al*, 2001). Magnetic resonance images of surviving patients have revealed extensive neuroendocrine damage including infundibulum transection and pituitary atrophy (Figure 2). Lesions have been noted in both the hypothalamus and pituitary during autopsy of TBI fatalities (Daniel, *et al*, 1959).

Clinical consequences of neuroendocrine trauma

Figure 3 illustrates the links between the hypothalamus and pituitary structures. Direct neuronal connections exist between the supraorbital and paraventricular nuclei in the hypothalamus and the posterior pituitary (or neurohypophysis). Neurones originating in the paraventricular nucleus carry oxytocin to the neurohypophysis, whereas neurones whose cell bodies lie in the supraoptic nucleus carry anti-diuretic hormone (ADH) to the neurohypophysis. Damage to the hypothalamic nuclei, the neurohypophysis or the infundibulum may result in central or cranial diabetes insipidus (cDI). Central diabetes insipidus often occurs in the acute phase of TBI recovery and usually resolves itself. cDI is rarely a chronic condition as the result of TBI (Shin, *et al*, 2001). Rare cases of long-term post-TBI cDI are managed successfully with medication (Shin, *et al*, 2001).

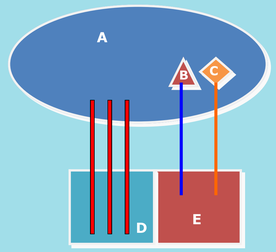

Figure 3. Diagram of the hypothalamic-pituitary axis. A—Hypothalamus; B—Paraventricular nucleus; C—Supraoptic nucleus; D—Anterior pituitary; E—Posterior pituitary; blue line—paraventricular oxitocinergic neurones; orange line—supraoptic ADH neurones; red lines—portal vessels

The hypothalamus is also connected to the anterior pituitary (or adenohypophisis) by a fine network of blood vessels, the hypothalamic-pituitary portal system. The hypothalamic-pituitary portal vessels carry hypophysiotrophic hormones from the hypothalamus to the adenohypophisis.

Disruption of the hypothalamic-adenohypophyseal axis can result in much more serious long-term consequences for the patient.

Lesions within the hypothalamus, damage to the anterior pituitary or disruption of the hypothalamic-hypophyseal portal vessels can result in hypopituitarism, the insufficiency of one or more adenohypophyseal hormones (Aimaretti and Ghigo, 2005). Some of the clinical consequences of hypopituitarism are given in table 1.

Table 1. Hypophysiotrophic hormones originating in the hypothalamus, the effected hormones within the adenohypophisis and clinical consequences of their dysfunction

Hypothalamic hypophysiotrophic hormones	*Adenohypophyseal trophic hormones*	*Some possible clinical consequences of dysfunction*
Corticotrophin-releasing hormone (CRT)	Adrenocorticotrophic hormone (ACTH)	Secondary adrenalism
Thyrotrophin-releasing hormone	Thyroid-stimulating hormone (TSH)	Secondary hypothyroidism
Growth hormone releasing hormone (GHRH)	Growth Hormone (GH)	Growth hormone deficiency (stunted growth in children)
Growth hormone release-inhibiting hormone (GHRIH)	Growth hormone (GH)	
Prolactin release-inhibiting hormone (PIH)	Prolactin	Hyperprolactinaemia
Gonadotrophin-releasing hormone (GnRH)	Luteinizing hormone (LH) and Follicle stimulating hormone (FSH)	Precocious puberty, Amenorrhea

A full review of the substantial amount of literature relating to post-TBI hypopituitarism is beyond the scope of this presentation, however we outline a number of important clinical studies to give an indication of the percentage of TBI survivors affected by long-term hypopituitarism. Comparisons between studies should be made with extreme caution as variables between the TBI survivor populations studied were wide-ranging. Factors such as age, body mass index (BMI), severity of the initial insult, and clinical practice during the acute stage of recovery, are all significant variables between the studies.

An important longitudinal study by Schneider, *et al* (2006) examined TBI survivors for hormone deficiencies at 3 and 12 months after the initial injury. At the TBI +3 month test 56% had at least one hormone deficiency. Of these, 32% had gonadotrophic hormone deficiency; 19% corticotrophic hormone; 9% GH deficient and 9% thyrotrophic deficiency. At 12 months post TBI, 36% of patients had hormonal impairments. Of these, 21% were gonadotrophic; 10% GH; 9% corticotrophic and 3% thyrotrophic. It is important to note that, at the 12 month post-TBI test stage, some patients had developed *de novo* hormone deficiencies (Schneider, *et al*, 2006).

A 2006 survey and deficiency-testing of 170 TBI patients discharged from hospital between 1998 and 2002 (i.e. 4-8 years post-TBI), revealed that 42 of them (24.7%) had hypopituitarism. Of these, 10 patients were TSH deficient; 11 ACTH deficient; 29 were GH deficient and 15 showed multiple hormone deficiencies (Leal-Cerro, *et al*, 2006)

Another clinical research study, undertaken in 2005 by Amar Agha *et al* at the Beaumont Hospital in Dublin, investigated hypopituitarism in TBI patients during the acute phase of recovery and at 6 and 12 months after injury They found that, at 12 months post-TBI, 10% of the patients had GH deficiency; 18% had ACTH deficiency including one *de novo* case; 12.5% were gonadotrophin deficient and 2% were deficient in TSH. 12.5% of the patients also exhibited hyperprolactinaemia at 12 months post-TBI (Agha, *et al*, 2005) .

Conclusion: screening, therapy and rehabilitation

It is clear from the evidence that long-term neuroendocrine dysfunction is not uncommon and may remain undiagnosed in many survivors of TBI. Despite the wealth of clinical studies and case reports, the authors are not aware of any establishment in the UK that routinely performs endocrine function tests in survivors of traumatic brain injury.

A consensus statement on screening for neuroendocrine dysfunction following TBI was published by Ghigo *et al* in 2005, and numerous calls for greater screening have been made in literature targeted at brain injury specialists and clinical endocrinologists. Yet, outside of the clinical studies and case reports, little is done to identify and treat those TBI survivors at risk or suffering from long-term neuroendocrinopathies. Few clinicians are aware of the potential for long-term neuroendocrine sequelae to TBI, and few rehabilitation units employ the skills of clinical endocrinologists.

Any number of proposals for neuroendocrine screening (e.g. Ghigo, *et al*, 2005; and Agha, *et al*, 2005) will not help sufferers of long-term TBI-induced neuroendocrine dysfunction unless they are agreed upon and implemented. Undoubtedly, financial limitations and cost effectiveness mean that screening should be targeted at the most 'at-risk' population, but this population is difficult to identify as severity of TBI does not indicate the potential for neuroendocrinopathy (Shin, *et al*, 2001). Screening for neuroendocrine dysfunction must be applied more widely to mild, moderate and severe TBI survivors bearing in mind that some neuroendocrinopathies can occur *de novo* many months, even years, after the initial trauma (Agha, *et al*, 2005; Leal-Cerro *et al*, 2005).

Rehabilitation after TBI can be a very difficult time for both patient and caregiver. It is crucial for the physical and psychological well-being of the patient to ensure recovery and rehabilitation can occur in the optimal endocrine settings; and many previously unidentified patients may benefit from the correct hormone replacement therapies.

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