MANAGEMENT OF ENDOCRINE DISEASE

Neuroendocrine surveillance and management of neurosurgical patients

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Abstract

Advances in the management of traumatic brain injury, subarachnoid haemorrhage and intracranial tumours have led to improved survival rates and an increased focus on quality of life of survivors. Endocrine sequelae of the acute brain insult and subsequent neurosurgery, peri-operative fluid administration and/or cranial irradiation are now well described. Unrecognised acute hypopituitarism, particularly ACTH/cortisol deficiency and diabetes insipidus, can be life threatening. Although hypopituitarism may be transient, up to 30% of survivors of TBI have chronic hypopituitarism, which can diminish quality of life and hamper rehabilitation. Patients who survive SAH may also develop hypopituitarism, though it is less common than after TBI. The growth hormone axis is most frequently affected. There is also accumulating evidence that survivors of intracranial malignancy, who have required cranial irradiation, may develop hypopituitarism. The time course of the development of hormone deficits is varied, and predictors of pituitary dysfunction are unreliable. Furthermore, diagnosis of GH and ACTH deficiency require dynamic testing that can be resource intensive. Thus the surveillance and management of neuroendocrine dysfunction in neurosurgical patients poses significant logistic challenges to endocrine services. However, diagnosis and management of pituitary dysfunction can be rewarding. Appropriate hormone replacement can improve quality of life, prevent complications such as muscle atrophy, infection and osteoporosis and improve engagement with physiotherapy and rehabilitation.

Introduction

Advances in the management of neurosurgical conditions such as traumatic brain injury (TBI), subarachnoid haemorrhage (SAH) and other neurosurgical catastrophes have led inevitably to improved survival rates. An increased focus on quality of life has led to the recognition that neurosurgical conditions are often complicated by neuroendocrine dysfunction, which can result either from the neurological insult or from the effects of
management with neurosurgery, post-operative fluid management or cranial radiation. Endocrinologists have traditionally been consulted about the neurohypophysial complications of TBI and SAH, and the management of diabetes insipidus (DI) and hyponatraemia in the post-neurosurgical recovery period has constituted part of the workload of endocrinologists for many years. However, over the last ten years, research studies have demonstrated that the adenohypophysis is also vulnerable to damage and dysfunction following a wide variety of neurosurgical events, which would not have traditionally been associated with pituitary involvement.

These new additions to the conditions causing hypopituitarism present significant logistic challenges to endocrine services. The time course of the development of hormone deficits is varied, predictors of pituitary dysfunction are unreliable and the need for dynamic testing to identify growth hormone (GH) and adrenocorticotropic hormone (ACTH) deficiency, all complicate the approach to the identification of neurosurgical hypopituitarism. The rewards of diagnosis are, however, attractive as appropriate hormonal replacement has significant potential to improve quality of life, prevent complications and increase the ability to respond to physiotherapy and rehabilitation medicine.

In this review, we will cover the spectrum and time course of pituitary dysfunction after common neurosurgical conditions and suggest strategies for screening patients.

**Traumatic brain injury**

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults. It is estimated that 823.7 persons per 100000 attend the emergency department, are hospitalised or die in USA as a result of TBI, with rates increasing over the past decade (1). Long-term sequelae in survivors of TBI include physical disability, cognitive, behavioural, psychological and social deficits. Some of these syndromes may reflect undiagnosed hypopituitarism. The first case of TBI-induced hypopituitarism was reported almost 100 years ago (2), but interest in this topic has developed exponentially over the past twenty years.

The pituitary gland is located within the bony sella turcica with the diaphragma sellae lying superiorly. Most of the blood supply to the anterior lobe of the pituitary is derived from the long hypophyseal vessels, which give rise to the hypophyseal portal system. These vessels are particularly vulnerable to either direct injury or occlusion as they traverse the diaphragma sellae compromising the vascular supply to the majority of the adenohypophysis. Several mechanisms of injury leading to hypopituitarism after TBI have been proposed, including direct mechanical injury to the hypothalamus, stalk or pituitary gland from skull fractures or shearing injury to the brainstem and indirect vascular damage due to compression of the pituitary gland and/or hypothalamus due to oedema and rising intracranial pressure (ICP) (3, 4, 5, 6, 7).

Large neuropathological series have demonstrated hypothalamic and/or pituitary lesions in up to 86% of individuals who died as a consequence of TBI (4, 8, 9, 10, 11, 12); damage to the pituitary capsule was the most common abnormality seen (13). Kornblum and Fisher reported pathological lesions secondary to trauma in 62% of pituitary glands, with anterior pituitary necrosis demonstrated in 35% of 100 patients with fatal head injuries who survived at least 12h (10). In these cases, the pattern of pituitary necrosis reflected the vascular distribution of the long hypophyseal portal vessels, whereas tissue supplied by the short hypophyseal vessels was spared. In Crompton’s series (n=106), hypothalamic lesions were found in 42% of specimens, and pituitary lesions in 28% of those in whom the pituitary gland was examined (9). Harper demonstrated anterior pituitary infarcts in 38 of 100 consecutive individuals with fatal TBI; all of those with medium- or large-sized infarcts had evidence of raised ICP at some point (4). More recently, autopsy studies by Salehi et al. have demonstrated acute infarction of the pituitary in patients surviving between 3h and 7 days after fatal head trauma (12). In contrast, there was no histological evidence of vascular injury in the pituitary glands of those who died immediately. This suggests that secondary insults such as increased intracranial pressure, ischaemic and/or hypoxic damage may account for the pituitary lesions (14). It is thought that severed portal vessels can regenerate and grow down into viable anterior pituitary tissue with demonstration of mitotic figures in the surviving cells in early histopathological studies (15). This revascularisation may lead to the restoration of anterior pituitary function.

Magnetic resonance imaging studies of the pituitary gland have demonstrated enlarged glands compared with controls in the acute post-injury phase, with infarction, haemorrhage and heterogeneous signal intensities also seen (16). Pituitary volume loss, signal heterogeneity, perfusion deficits and loss of the posterior pituitary bright spot may be seen on neuroimaging in chronic hypopituitarism after TBI (17); Schneider demonstrated these pituitary gland abnormalities in 80% of patients with hypopituitarism after TBI vs 29% of those without (18).
Autoimmunity may also play a role in pituitary dysfunction after TBI. Tanriverdi found higher rates of hypopituitarism over a five-year follow-up period in individuals with positive anti-hypothalamic and anti-pituitary antibodies (19).

Growth hormone and gonadotrophins are the hormones most likely to be affected in post-TBI hypopituitarism, as gonadotroph and somatotroph cells are most vulnerable due to their anatomical site in the vascular territory of the long hypophyseal portal system. In contrast, corticotroph and thyrotroph cells are located ventrally and medially in the anterior pituitary and are supplied by short portal veins. These blood vessels are derived from the inferior hypophyseal arteries, which enter the sella from below the diaphragma sellae, and are therefore less susceptible to injury.

In a meta-analysis of 1015 TBI patients, the prevalence of anterior hypopituitarism at least five months after the injury was 27.5% (20), whereas in a systemic review of 2117 patients with TBI, 31% had long-term hypopituitarism after 12 months (21). Chronic hypopituitarism is therefore a significant problem after TBI.

**Acute hypopituitarism**

**Anterior pituitary**

Autopsy studies performed in patients who died within a week of serious road traffic accidents show that 43% have evidence of pituitary infarction (12). Vascular pituitary damage therefore occurs early after significant brain trauma. Patients who sustain TBI without pituitary trauma respond with a physiological increase in plasma cortisol concentrations (22, 23) with a return to normal over several days. Normalisation of serum cortisol concentration is predictive of good outcome (24). In contrast, patients with severe penetrating head injury may manifest hypocortisolaemia early after trauma (22). Random serum GH concentrations were reported to be elevated after TBI (25), with an exaggerated response to GHRH (26). However, impaired GH response to arginine has also been reported in patients with very severe TBI, with high mortality (27).

Our own prospective studies confirmed a robust physiological rise in plasma cortisol concentrations in most patients after TBI; 16% showed inappropriately low cortisol responses to glucagon in the first two weeks after TBI (28). In addition, 18% had subnormal GH responses to glucagon. Some of these patients presented with severe hypopituitarism, with hyponatraemia, hypotension and hypoglycaemia and responded rapidly to intravenous hydrocortisone (29). It is clear therefore that identification of acute ACTH/cortisol deficiency in the setting of acute TBI is potentially life-saving.

Our data also showed that 80% had gonadotrophin deficiency (28). Suppression of the hypothalamic–pituitary–gonadal axis has been reported in acute illness (30), and hypogonadism is likely to represent an adaptive response to injury rather than acute hypopituitarism. Secondary hypothyroidism was rare. Other workers have demonstrated low TSH and T3 concentrations after TBI, which seem to be adaptive changes rather than pituitary failure (22). Some studies have linked hypothyroidism to poor outcome from TBI (22, 31), though this association is not universally shared (26) and remains unproven.

A prospective study by Tanriverdi found a lower incidence than we did of ACTH deficiency (9%), based on a single estimation of plasma cortisol during the first day of ITU admission (32). However, the true prevalence of acute ACTH/cortisol deficiency after TBI may be underestimated. In a prospective study of 100 consecutive patients, with moderate or severe TBI, daily measurement of plasma cortisol demonstrated that 78% of patients had at least one plasma cortisol value less than 300nmol/L during the first ten days. In contrast, all patients recovering from major abdominal surgery had sustained elevation of plasma cortisol during an equivalent follow-up period (33). Interestingly, all the 15% of patients who developed hyponatraemia responded to treatment with intravenous hydrocortisone suggesting that the SIADH seen in patients recovering from TBI may be partly a reflection of glucocorticoid deficiency.

**Posterior pituitary**

Dysnatraemias are the commonest biochemical abnormalities occurring early after TBI (34). One study of 38 patients five weeks after TBI defined 8 patients (21%) as having DI, on the basis of paired plasma and urine osmolalities (35). However, the methodology and the cutoffs used for identifying DI were not robust (36) and the high rate of DI was in marked variance with the clinical impression of most experienced observers. Our data in the acute phase after TBI showed that 26% of patients developed diabetes insipidus in the acute phase of TBI (28). A subsequent larger prospective study of 100 patients showed higher rates of DI, with 51% of patients developing hyponatraemia associated with hypotonic urine; in 2% of the total cohort, DI persisted until hospital discharge (33). This suggests a much lower rate of permanent DI than that found in Bohnen’s study (35).
One key finding in this study was that failure to recover vasopressin secretion was associated with a considerable increase in mortality; 9 of the 11 patients who did not recover from DI died. Persistent DI in the setting of TBI may be a strong indicator of rising intracranial pressure and therefore of poor outcome.

Although DI is usually self-limiting after TBI, it is important to be aware of the triple-phase response. This uncommon variant is characterised by polyuria occurring in the first few days after TBI, spontaneous resolution after two or three days, progressing to hyponatraemia due to SIADH. It is hypothesised that the initial stalk contusion causes DI, but in some cases, the initial contusion injury is complicated by unregulated vasopressin release from damaged neurons producing SIADH. After several days of hyponatraemia caused by release of the pre-formed vasopressin, gliosis of the damaged neurons occurs, with the development of permanent DI – the triple-phase response.

Hyponatraemia occurs in approximately 15% of patients after TBI (28, 37). Most cases have been attributed to SIADH (38) though recent data have shown that a significant proportion of hyponatraemic patients have low plasma cortisol concentrations, particularly for stressed patients (33). This has led to a speculation that much of the SIADH seen after TBI would respond to steroid replacement rather than traditional management with fluid restriction (39, 40), though this hypothesis has not been tested by randomised control trials. Our current practice, based on our research findings, is to measure plasma cortisol concentration in all hyponatraemic patients and to treat empirically with hydrocortisone if the concentration is less than 300 nmol/L, on the assumption that this is inappropriately low for a patient in the intensive care unit (41).

Although hyponatraemia after TBI is usually due to SIADH or acute ACTH/cortisol deficiency, excessive intravenous fluids or diuretic therapy should also be excluded. Cerebral salt wasting has been reported after TBI, but we did not find a single case in our large prospective series (33) and a recent literature review concluded that this phenomenon remains very rare (42).

**Chronic hypopituitarism**

*Anterior pituitary*

It is well recognised that posterior pituitary dysfunction, manifested as diabetes insipidus or SIADH, is transient after TBI with few long-term sequelae. However, it seems that anterior pituitary hormone deficiencies are also often transient. Studies from Italy (43) and Spain (44) independently demonstrated that acute hypopituitarism could recover in the first few months after brain injury. Occasional later recovery has also been reported (19, 44, 45). Interestingly, new hormone deficiencies can also develop in the first six months after recovery from TBI. In a prospective study of 50 patients followed up with glucagon stimulation studies, some patients with normal pituitary function in the immediate aftermath of TBI were shown to subsequently develop hypopituitarism. We also confirmed recovery of normal GH secretion in two-thirds of patients who were deficient immediately after TBI, and recovery of cortisol secretion in one-half of deficient patients (45). The dynamic nature of pituitary hormone secretion in the months after TBI has important implications for screening, which will be discussed in later sections.

The literature contains reported rates of chronic hypopituitarism post-TBI which range from 15% to 69% (3, 19, 32, 33, 43, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59). Published cohort studies vary widely in methods of patient selection, severity of head injury and the timing and methods of testing for hypopituitarism (Table 1). The screening test selected to define hypopituitarism accounts for significant variability in reported prevalence rates of hypopituitarism. Lieberman found subnormal morning plasma cortisol levels in 46% of 70 adults studied at a median of 13 months after TBI, but only 7% failed Synacthen testing, which casts doubt on the high proportion of ACTH/cortisol deficiency reported in this study (46). In contrast, Klose et al. used the gold standard insulin tolerance test to define ACTH/cortisol deficiency and reported a prevalence of ACTH deficiency of only 5% in 104 patients, tested a median of 13 months after head trauma (51). However, the figures for this study need to be carefully interpreted as the low prevalence rates for hypopituitarism that they report may reflect their inclusion of significant numbers (40% of the total) of patients with mild TBI, a group excluded by almost every other series. When patients with moderate or severe TBI are included, their figures are comparable to most other published series. In fact, 88% of those with hypopituitarism had moderate-to-severe injury (51).

*Posterior pituitary*

Our own series show that although 26% of patients develop diabetes insipidus in the early period after TBI, prospective follow-up over a one-year period (60) shows that most survivors of TBI show recovery of DI within the
first six months. A study of a large cohort of long-term survivors of TBI, tested formally with water deprivation, showed that 7% have evidence of permanent diabetes insipidus (61). However, in most cases, the DI is partial and only 2% of the entire cohort needed desmopressin therapy to control polyuria (61). An in-depth prospective study of a large cohort of patients in the early period after TBI suggested a higher figure for DI of 51%; most cases were transient, but the data showed that persistence of DI was a strong predictor of mortality (33). As a consequence, we regard persistent DI, particularly in an unconscious or ventilated patient, as a poor prognostic sign.

Adipsic DI has been reported in a single case after TBI (62). Hypernatraemia in the setting of clear consciousness and adequate access to water should alert the clinician to this possibility, as adipsia needs careful management of fluid intake as well as desmopressin therapy, to avoid swings in plasma sodium concentration.

### Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH), most often due to a ruptured aneurysm of the circle of Willis, occurs with an incidence of six cases per 100 000 patient years (63). The pathogenesis of SAH-induced hypopituitarism relates to the proximity of the circle of Willis to the hypothalamic–pituitary complex. Several mechanisms have been proposed including increased intracranial pressure, ischaemia and/or infarction of the hypothalamus, iatrogenic insult as a result of treatment of the aneurysm, hydrocephalus and direct compression of the hypothalamic–pituitary complex by the aneurysm (20, 64, 65, 66).

The first structured study evaluating pituitary function after SAH, in 1969, showed abnormal diurnal variation of plasma cortisol in 65% and subnormal urinary steroid response after metyrapone in 44% of cases, with improvement after one month (67). Since then, widely conflicting results have been published in the literature, and the true prevalence of pituitary dysfunction remains debatable.

### Acute hypopituitarism

In the immediate period after aneurysm rupture, the clinical priority is the prompt detection and treatment of ACTH deficiency and disorders of water balance.

### Anterior pituitary

Published data on the rate of ACTH deficiency in the acute phase after SAH is conflicting. Klose found that 3/26 (11.5%) patients had 09:00 h plasma cortisol values below 276 nmol/L at a median of 7 days after SAH (68). Tanriverdi reported much higher rates of ACTH deficiency of 23% (5/22 patients) based on a single 09:00 h plasma cortisol below 193 nmol/L measured within 24 h of SAH (69), whereas Parenti reported an incidence of 7% (4/56 patients) within 72 h of SAH using the same criterion (70).

Klose’s cohort (68) was treated by either coiling or clipping, whereas all of Tanriverdi’s (69) patients were treated with neurosurgical clipping so the two cohorts were different. Furthermore, Klose (68) excluded 66 of the initial 226 patients who died between study initiation and follow-up; as these were the sickest patients, the rates of ACTH deficiency may have been underestimated.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Median duration (months)</th>
<th>n</th>
<th>HPit (%)</th>
<th>GH (%)</th>
<th>ACTH (%)</th>
<th>Gn (%)</th>
<th>TSH (%)</th>
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<tbody>
<tr>
<td>(3)</td>
<td>26</td>
<td>22</td>
<td>36</td>
<td>18</td>
<td>5</td>
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<td>5</td>
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<td>17</td>
<td>102</td>
<td>28</td>
<td>8</td>
<td>13</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>(48)</td>
<td>12–64*</td>
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<td>54</td>
<td>8</td>
<td>0</td>
<td>14</td>
<td>10</td>
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<td>(49)</td>
<td>3</td>
<td>100</td>
<td>35</td>
<td>21</td>
<td>8</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>(50)</td>
<td>12</td>
<td>70</td>
<td>23</td>
<td>20</td>
<td>7</td>
<td>11</td>
<td>6</td>
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<tr>
<td>(51)</td>
<td>12</td>
<td>52</td>
<td>50</td>
<td>33</td>
<td>19</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>(52)</td>
<td>13</td>
<td>104</td>
<td>15</td>
<td>11</td>
<td>5</td>
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</tr>
<tr>
<td>(53)</td>
<td>3</td>
<td>77</td>
<td>56</td>
<td>9</td>
<td>19</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>(54)</td>
<td>40</td>
<td>166</td>
<td>31</td>
<td>10</td>
<td>9</td>
<td>21</td>
<td>3</td>
</tr>
</tbody>
</table>

*value represents range.

GH, growth hormone; Gn, gonadotrophin; HPit, hypopituitarism. *value represents range.
These three prospective studies are relatively small, with analysis of cortisol dynamics taking place at only a single time point. In a prospective cohort study of 100 patients after SAH, serial measurements of 09:00-h plasma cortisol for twelve days after haemorrhage demonstrated a rate of ACTH/cortisol deficiency of 14% based on a cut-off of 300nmol/L (71), whereas a recent prospective study by Takala reported a rate of 11% based on a cut-off of 276nmol/L on six measurements over fourteen days (72). Importantly, Hannon’s data showed that ACTH deficiency is often transient after SAH; therefore, a single estimation of plasma cortisol at one time point may miss the diagnosis.

Posterior pituitary

Diabetes insipidus occurs acutely in 15% of cases of SAH and is associated with poorer outcome (73). Hyponatraemia seems a much more accurate predictor of mortality than hyponatraemia in this setting. Most DI recovers spontaneously. Adipsic DI has been occasionally reported after clipping of anterior communicating artery aneurysms (62, 74, 75, 76). The osmoreceptors for thirst appreciation are situated in an area of the anterior hypothalamus, which derives its blood supply from small perforating branches of the anterior communicating artery. It is thought that the adipsic DI in this scenario occurs after infarction of osmoreceptor cells after clipping of the anterior communicating artery (77). Adipsic DI has not been reported following coiling of the anterior communicating artery. Adipsic diabetes insipidus is usually permanent, though cases of complete recovery have been reported (77, 78). If a patient does have adipsic DI, they may also develop other hypothalamic abnormalities, such as obesity and obstructive sleep apnoea, which can complicate management (79).

Hyponatraemia is extremely common after SAH (80). In a retrospective case note analysis of 316 patients admitted with SAH to our institution over a 20 month period 57% developed mild hyponatraemia (<135 mmol/L) and 20% developed moderate-to-severe hyponatraemia (<130 mmol/L) (Table 2) (81). SIADH was adjudged to be the commonest cause of hyponatraemia, accounting for 62% of cases, though the retrospective nature of the study meant that diagnostic accuracy was compromised by poor ascertainment of essential diagnostic parameters. Hyponatraemia was associated with longer hospital stay but had no effect on mortality. In a more recent prospective cohort study of 100 patients with SAH admitted to our neurosurgical unit, we confirmed the high rate of hyponatraemia (50% of patients <135 mmol/L). With prospective collection of key clinical and biochemical diagnostic criteria we were able to demonstrate that the most common cause of hyponatraemia was SIADH (71.4%) followed by excessive intravenous fluids (10.2%), hypovolemia (10.2%) and acute glucocorticoid deficiency (8.2%) (71). We were unable to identify any cases of cerebral salt wasting.

Hyponatraemia was not associated in our studies with any particular aneurysm site and was independent of method of aneurysm management. A recent retrospective review identified old age was associated with hyponatraemia and smoking habit predicted longer duration of hyponatraemia (82).

Our data showed that hyponatraemia was a bigger predictor of mortality than hyponatraemia, results which were supported by a prospective study from Asia (83) and a recent meta-analysis (84). However, inadequate management of hyponatraemia is responsible for one in six readmissions after hospital discharge after SAH (85), so correct therapy remains important.

A meta-analysis of steroid therapy in SAH, with either fludrocortisone or hydrocortisone showed that lower rates of hyponatraemia occurred with supplementation (86). Authors concluded that this reflected mineralocorticoid activity, though an alternative interpretation could be that hydrocortisone had replaced post-SAH deficiencies.

**Chronic hypopituitarism**

A systematic analysis of five studies by Schneider et al. in 2007 concluded that hypopituitarism is present in 47% of patients in the chronic phase after SAH (20). In contrast, a recent meta-analysis reported pooled

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**Table 2** Incidence of significant hyponatraemia (plasma sodium <130nmol/L) in patients admitted to the neurosurgical unit in Beaumont Hospital between January 2002 and September 2003.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of patients with plasma sodium &lt;130nmol/L</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>187</td>
<td>1698</td>
<td>11</td>
</tr>
<tr>
<td>SAH</td>
<td>62</td>
<td>316</td>
<td>19.6</td>
</tr>
<tr>
<td>Tumour</td>
<td>56</td>
<td>355</td>
<td>15.8</td>
</tr>
<tr>
<td>TBI</td>
<td>44</td>
<td>457</td>
<td>9.6</td>
</tr>
<tr>
<td>Pituitary surgery</td>
<td>5</td>
<td>81</td>
<td>6.2</td>
</tr>
<tr>
<td>Spinal</td>
<td>4</td>
<td>489</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Adapted from M. Sherlock et al. Incidence and pathophysiology of severe hyponatraemia in neurosurgical patients. Postgraduate Medical Journal 2009 85 171–175 (38); with permission.
frequencies of 0.31 and 0.25 for hypopituitarism at 3–6 months and over six months after SAH (87). These meta-analyses share the limitations of the original studies. The variation in prevalence rates across individual studies can be explained by methodological differences in endocrine assessments, time-points of assessment, surgical methods used and inclusion and exclusion criteria. When gold standard dynamic testing is used to confirm a pituitary hormone deficiency, reported rates of hypopituitarism are much lower. In Klose’s follow-up of 62 patients 1–2 years after SAH (68), initial basal pituitary testing was abnormal in 13% of patients. However, none of these patients had hypopituitarism on subsequent dynamic testing. In a well-designed study by Gardner, using two different confirmatory tests for GHD adjusted for body mass index (BMI), 12% of patients had hypopituitarism at 12 months (88). GH deficiency is most common pituitary hormone deficiency reported after SAH (49, 69, 89).

Pituitary hormone deficiencies after SAH recover in the majority of cases. For instance, in a prospective study of 100 SAH patients, 14% had acute glucocorticoid deficiency defined by inappropriately low plasma cortisol concentrations (89). However, only two of 41 (5%) had long-term ACTH deficiency and four of 41 (10%) had GHD when formally tested, with either insulin hypoglycaemia or, if contraindicated, glucagon or Synacthen testing, at a median of 15 months (89). None were hypothyroid or gonadotrophin deficient. However, new deficiencies can also occur for the first time after the acute phase. In Aimaretti’s study of 32 patients with SAH, two patients with single hormone deficiency at three months progressed to multiple hormone deficits at twelve months (43). In Tanriverdi’s study four of five ACTH-deficient patients in the acute phase recovered after twelve months, whereas ACTH deficiency detected at 12 months was new in onset in two of three patients (69). In a three-year follow-up study including 20 patients from Tanriverdi’s cohort, Karaca found four cases of GHD, three of whom had normal GH reserve at one year (90). It is clear from these studies that although pituitary dysfunction is less common after SAH than it is after TBI (91), pituitary function is dynamic and may change after the acute period.

DI occurring after SAH is transient in the majority of cases (43) but can persist up to three months after discharge in up to 8% of patients (49) although DI in this study was not confirmed by water deprivation testing.

Cranial radiotherapy

Screening for hypopituitarism after irradiation of pituitary adenomas is an accepted component of endocrine practice. However, there is accumulating evidence that irradiation of intracranial tumours not derived from pituitary tissue may also cause pituitary hormone deficits. Therapeutic cranial radiation for non-pituitary malignancy causes hypothalamic–pituitary (HP) dysfunction in survivors of childhood cancer (92), and there are good data on hypopituitarism after radiotherapy for nasopharyngeal cancers (93) and skull base tumours (94).

Hypopituitarism after radiotherapy (RT) has traditionally been attributed to direct damage to hypothalamic cell nuclei, with subsequent pituitary atrophy. This hypothesis has been used to explain the delayed onset of deficiency, as cells of slowly dividing tissue die during mitosis. This theory is also supported by the common occurrence of hyperprolactinemia after irradiation, which is considered to result from a reduction in hypothalamic release of dopamine (95) although there is also evidence to suggest that cranial radiation causes direct pituitary damage (96). Direct pituitary damage is also suggested by the observation that stereotactic radiotherapy, which spares the hypothalamus, also causes hypopituitarism (97). The somatotroph axis is the most vulnerable to the effects of RT. Therefore, GHD is the most common deficit seen followed by deficiencies in gonadotrophins, ACTH and TSH (98, 99, 100).

There are considerable variations in the reported rates of hypopituitarism after cranial radiotherapy. A systematic review of 18 studies with a total of 813 patients treated for nasopharyngeal or intracerebral tumours reported a point prevalence of any degree of hypopituitarism of 0.66; follow-up ranged from 4 months to 30 years (100). In the largest cohort of adult-onset brain tumours studied to date, 88.8% of 107 adults followed up for a median of 8 years following cranial radiotherapy developed hypopituitarism (99). The frequency of GH, gonadotrophin, ACTH and TSH deficiencies was 86.9% (severe GHD 64.5%, partial GHD 22.4%), 34.6, 23.4 and 11.2% respectively. ACTH deficiency was not always clinically significant, necessitating glucocorticoid replacement in only 10.3%; the disparity was hypothesised by the authors to reflect the use of the GST to diagnose ACTH deficiency, which carries a 8% false-positive rate (101). Entirely normal pituitary function after cranial radiotherapy was only seen in 11.2% of the patient group (99).
We have demonstrated lower rates of hypopituitarism, in 41% of 56 adult patients who received external beam radiotherapy for primary non-pituitary brain tumours (98). Our follow-up was slightly shorter, varying from 12 to 150 months after RT, which may account for differences in the incidence of hypopituitarism. However, a key difference between the two studies is that the Leeds group studied patients who were already attending an endocrine service, presumably because of clinical suspicion of endocrine symptoms, whereas the Dublin series was recruited de novo from the radiotherapy services, and therefore, had no bias introduced by symptoms suggestive of hypopituitarism. In the Dublin series, 16% had single hormone deficiencies and 25% had multiple deficiencies including 7% with panhypopituitarism. Hypopituitarism was significantly associated with longer time interval from RT and greater biological effective dose (BED) (98). Radiation-induced hypopituitarism therefore increases in incidence and severity the longer the duration of follow-up. In Kyriakakis’s study, the prevalence of hypopituitarism doubled between year 2 and 7 of follow-up, with new deficits occurring as late as ten years after radiation (99).

The neurohypophyseal tissue is less sensitive to radiation compared with the adenohypophysis, and DI does not seem to occur as part of the spectrum of post radiotherapy hypopituitarism (102).

**Non-pituitary brain tumours**

Pituitary dysfunction may occur following surgical resection of brain tumours that do not originate from the pituitary. Our own small published series of twenty radiation naïve patients suggested that hypopituitarism is uncommon in patients with extrasellar tumours; we identified a single case of GH deficiency, which occurred in a patient who had extensive debulking of a para-sellar astrocytoma. All patients passed dynamic testing of the HPA axis and had normal gonadal and thyroid function (98).

In contrast, Schenider et al. reported rates of hypopituitarism of 38% in 68 adult patients who underwent neurosurgery (NS) either alone or in combination with RT or chemotherapy (CT) for intracranial tumours (103). Although it could be argued that RT and CT could contribute to this rate of hypopituitarism, the authors found that the prevalence was higher in patients who underwent NS only. Not surprisingly, the prevalence and severity of pituitary dysfunction was higher in patients with tumours located close to the sella turcica. Impairment of gonadotrophins and GH were more common than ACTH and TSH. DI occurred in 4.4%, all of whom had panhypopituitarism. This study, however, did not comment on surgical approach, and it is not clear whether those treated with NS alone underwent more radical surgery. A similar paper from Italy demonstrated hypopituitarism in 8 of 37 patients twelve months after resection of non-pituitary intracranial tumours (104). More data are needed in this area.

**How should we screen for hypopituitarism?**

Screening for pituitary disease in non-pituitary conditions presents significant logistic and resource difficulties. This reflects the large patient numbers, and the need for dynamic testing for ACTH and GH deficiency. Although we know when to optimally screen for pituitary disease, which groups to screen – or not to screen – remain elusive. The organisational and fiscal challenge of identification of pituitary dysfunction that would benefit from hormonal replacement is daunting.

**Traumatic brain injury**

**Acute hypopituitarism**

The clinical imperative in acute TBI is to identify pituitary dysfunction that requires urgent treatment. Acute ACTH and AVP deficiency should not be missed, as both are predictive of mortality (33), and both are potentially treatable. In addition, hyponatraemia is important to identify, diagnose and monitor; some cases of apparent SIADH may be manifestations of acute ACTH deficiency, and although most hyponatraemia does resolve spontaneously, occasional progression to neurological sequelae such as seizures can occur.

In the acute phase after TBI, dynamic tests of ACTH/cortisol reserve are impractical. The Synacthen test depends upon secondary adrenal failure and will not render an abnormal result with acute ACTH deficiency. Insulin hypoglycaemia risks seizure activity in a damaged brain, and the glucagon test is unwieldy. In practice, we use a 09:00-h plasma cortisol measurement; although in critical illness, the normal diurnal variation of cortisol is usually lost, we have used a 09:00-h sample for routine screening for research standardisation. However, if there is a need for urgent treatment on clinical grounds, the timing of diagnostic sampling is not critical. Defining a cut-off value for basal cortisol levels requires a high
sensitivity due to the potential consequences of a missed diagnosis. Therefore, we have adopted a diagnostic plasma cortisol concentration of <300 nmol/L, in an unwell neurosurgical patient, as suggestive of ACTH insufficiency, and empiric glucocorticoid replacement is administered until dynamic testing is appropriate (33, 71). Plasma cortisol concentrations of between 300 and 500 nmol/L may not exclude acute ACTH deficiency, and we consider empiric glucocorticoid cover if there is supplementary clinical suspicion of hypoadrenalism, such as hypotonia, hypoglycaemia or profound hypotension (41).

DI can be picked up by monitoring daily plasma sodium concentration and fluid balance. The diagnosis of acute post-operative DI can be made using the Seckl and Dunger criteria; if plasma sodium exceeds 145 mmol/L in the presence of hypotonic (urine osmolality <300 mosmol/kg) polyuria (>300 mL/h for two consecutive hours or >3 litres per day) (41). Other potential causes of polyuria should be ruled out such as steroid induced hyperglycaemia, renal impairment or administration of diuretics or mannitol before the diagnosis is made.

Testing for TSH deficiency is less important in the acute setting due to the relatively long half-life of T4. There is no role for testing the gonadotrophin or growth hormone axes in the acute setting as deficiencies may be transient, and there is no evidence that replacing these hormones improves outcomes in the short term.

**Chronic hypopituitarism**

**Who to test?** There are a number of criteria that have been suggested to aid selection of patients for post-TBI testing, and there are some useful suggestions from Aimeretti and Ghigo (105). They recommended reserving routine testing for patients with moderate or severe TBI, as defined by the Glasgow Coma Scale rating on hospital admission. A meta-analysis of 1015 TBI patients by Schneider (20) showed pooled prevalence rates of hypopituitarism in mild, moderate and severe TBI of 17, 11 and 35% respectively. Therefore, although the risk of hypopituitarism is the highest in those with severe TBI, the risk is not negligible in those with less severe injury. It should be noted however that all patients with mild TBI included in this meta-analysis required hospitalisation and neurosurgical intervention (20). Certainly, the Danish cohort of patients with mild TBI did not display hypopituitarism with sufficient frequency to justify recommending routine screening in this group (51).

A number of guidelines (105, 106, 107, 108) have suggested the use of symptoms suggestive of hypopituitarism as a criterion for targeted screening. We adopted these suggestions into routine surveillance programmes and recently published the results of an audit of the use of symptoms as predictors of hypopituitarism. We showed that symptoms of hypogonadism, such as menstrual dysfunction, erectile dysfunction or loss of libido are strongly predictive of hypopituitarism, but nonspecific symptoms such as weight loss and anergia are no more predictive than unselected screening in identifying pituitary hormone deficits (109).

It seems sensible to re-test all patients who have declared themselves to have acute pituitary lesions, by reason of acute ACTH deficiency or diabetes insipidus. Likewise, although the incidence of hypopituitarism seems to be lower after TBI in children (110), it is worth considering testing, or at least monitoring the progression of growth and puberty, in this population.

**When to test?** Prospective studies (44, 50, 60) show that the secretory capacity of the pituitary gland is dynamic after TBI. Some acute deficiencies improve in the 3–6 months after TBI, whereas new deficits can appear in the same period. New deficiencies rarely develop after six months of TBI – we have never seen a case – so we recommend six months as the ideal time to screen patients for new hypopituitarism and to re-evaluate those with acute deficits, to check whether there has been recovery. There are occasional reports of delayed recovery (44) – we have seen this occur up to five years after TBI (111) – so clinicians should be prepared to re-evaluate at a later date if clinical indices suggest recovery.

**How to test?** Although the thyrotrophin and gonadotrophin axes can be reliably interpreted by basal testing, interrogation of the corticotrophic and somatotropic axes requires dynamic testing, and this should be done according to local expertise and experience, with locally derived cutoffs for normality. The insulin tolerance test is the gold standard for testing the corticotrophic and somatotropic axes. The risk of seizures in TBI and SAH may stimulate reluctance to use insulin hypoglycaemia, though the Danish data form has shown that this test is safe if high-risk groups are avoided (51). In cases of clinical doubt, the glucagon stimulation test (GST) or GH+arginine tests can be used to assess GH reserve. If glucagon is used to assess ACTH/cortisol reserve, the 8% false-positive rate should be considered (101) and cases of suspected ACTH deficiency confirmed by Synacthen testing.
The diagnosis of secondary hypothyroidism may be rendered difficult by the suppression of TSH by high-dose glucocorticoids, and the possibility of sick euthyroid syndrome in critical illness should be taken into account when interpreting thyroid function tests.

Confirmation of DI requires a water deprivation test typically carried out 8 weeks after pituitary insult.

**Subarachnoid haemorrhage**

**Acute hypopituitarism**

The commonest abnormality in the early phase after SAH is hyponatraemia. Although hyponatraemia does not seem to increase mortality in SAH (38, 112), a recent paper has published data showing that sodium fluctuation predicts worse neurological outcome (112). As 10% of all cases of hyponatraemia after SAH are due to acute ACTH/cortisol deficiency (71), we routinely check random plasma cortisol in hyponatraemic patients, diagnosing and treating ACTH deficiency as per the recommendations above following TBI. Acute diabetes insipidus is less common, but particularly after clipping of anterior communicating aneurysms, may be complicated by adipsia (78, 113). Hypernatraemia should always prompt consideration of the diagnosis of adipsic DI.

**Chronic hypopituitarism**

Routine screening for chronic hypopituitarism is not justified in SAH patients. Many studies have evaluated potential clinical predictors of hypopituitarism in SAH. In the systematic review by Schneider, there was no association between clinical state (Hunt and Hess Score), the amount of blood on initial CT (Fisher CT Score) or any other clinical parameter known to be associated with poor outcome after SAH and risk of hypopituitarism (20). This is in contrast to TBI, where severity of TBI, in some studies, is a predictor of hypopituitarism. All patients with symptoms suggestive of hypopituitarism and those with a low screening plasma cortisol value should undergo formal pituitary testing at three months. Patients should be re-tested at 12 months if clinical or biochemical parameters raise the possibility of delayed recovery (20).

**Intracranial tumours (non-pituitary) and cranial radiotherapy**

There is insufficient evidence to support routine endocrine testing in patients with non-pituitary intracranial tumours, and therefore, testing should be based on clinical suspicion. Testing for hypopituitarism should begin one year after cranial radiotherapy (Fig. 1). Testing for GH deficiency is only indicated if GH therapy is considered safe in the context of management of the underlying malignancy.

Pituitary dysfunction after radiotherapy may reflect hypothalamic, rather than pituitary damage. There may therefore be discordant responses to mechanistically different provocative tests. For instance, as GHRH directly stimulates the pituitary, the GHRH+arginine test...
can give a falsely normal GH response in patients who develop GHD of hypothalamic origin (114), and it is therefore unreliable in early years after cranial radiation. Although the ITT is considered the gold standard for diagnosis of GHD in most clinical scenarios, in adults after radiotherapy, a failed response to the ITT in isolation may not necessarily reflect GHD but rather failure to further stimulate an already maximally stimulated axis (96). In contrast, a failed response to the GHRH + arginine test almost always indicates GHD (115). Therefore, in the absence of multiple anterior pituitary hormonal deficits after cranial radiotherapy, many advocate for the need for two mechanistically different tests before confirming the diagnosis of isolated GHD.

Management of hypopituitarism

Acute hypopituitarism

Corticosteroids

A random cortisol value of <300 nmol/L, or a measurement between 300 and 500 nmol/L with clinical parameters suggestive of ACTH deficiency, are grounds for empirical glucocorticoid therapy. If the patient is unwell, parenteral glucocorticoids (e.g. hydrocortisone 200 mg daily in divided doses or by continuous infusion) is justifiable, pending laboratory analyses. If the patient is not acutely unwell stress doses of oral hydrocortisone, 20 mg three times daily, can be given; patients can be discharged on a maintenance dose of 10 mg twice-daily until formal assessment as an outpatient. Long-term glucocorticoid therapy is continued only in patients who fail dynamic testing.

Thyroxine

Due to the relatively long half-life of T4 (one week), treatment of central hypothyroidism is not necessary in the immediate setting and should not precede glucocorticoid replacement.

Diabetes insipidus

DI usually occurs within two days of pituitary insult and is characterised by thirst and hypotonic polyuria. If the patient is unconscious or cognitively impaired, hyponatraemia ensues quickly. Most cases resolve by the third post-operative day, but a minority may progress to permanent DI. Prompt replacement of water deficit and administration of desmopressin are required once a diagnosis of DI is confirmed. We recommend administering a single parenteral dose of desmopressin (s.c. or i.m.), which is active for 6–12 h (41). Further doses are administered only if polyuria persists. Rarely, a triphasic response can occur in which initial DI is followed by a transient period of hyponatraemia and antidiuresis with a return to permanent DI up to two weeks postoperatively. For this reason and due to the fact that DI is in most cases transient, regular desmopressin is prescribed only if polyuria persists beyond 48 h. It is important to continue to monitor the plasma sodium concentration after starting desmopressin treatment and to advise patients and caregivers about the potential risk of triphasic response and the need for urgent blood draw for plasma sodium should they develop symptoms suggestive of hyponatraemia. Withdrawal of desmopressin before discharge from hospital is useful in identifying those who have spontaneous return of endogenous vasopressin secretion. Hypokalaemia should be corrected as it can cause renal resistance to desmopressin therapy.

The dose of desmopressin required is proportional to the degree of vasopressin deficiency. In those with partial DI, a nocturnal oral dose of 0.2 mg may suffice, whereas those with more severe disease may require up to 0.2 mg two to three times per day. It is our practice to advise patients to hold one dose per week to allow an aquaresis to occur and prevent the development of dilutional hyponatraemia (41).

Chronic hypopituitarism

Growth hormone

GHD is associated with reduced lean body mass (116), decreased exercise capacity (117), impaired cardiac function (118) and reduction in bone mineral density (116). GHD adults also score lower on quality of life assessments. These effects have the potential to impair recovery and rehabilitation of neurosurgical patients. The beneficial effects of GH replacement have been well documented (119), and although data specifically in neurosurgical patients is scarce, there are no grounds to believe replacement GH in patients with severe deficiency will be less effective than in other situations of GHD.

Gonadotrophins

Replacement of sex steroids should be considered in the post-acute phase with benefits on bone (120, 121), muscle...
and sexual health; the choice of replacement will be determined by the desire for fertility, cost, convenience and patient preference.

**Neurosurgical hyponatraemia**

**Clinical context**

Hyponatraemia is the commonest electrolyte abnormality and is associated with increased mortality (123, 124) and longer hospital stay (123). It is common in neurosurgical units, with the highest incidence seen after SAH followed by intracranial tumours, TBI and pituitary surgery (38) (Table 2). Neurosurgical patients are vulnerable to developing symptomatic hyponatraemia, due to co-existence of other factors that cause cerebral irritation such as the underlying cerebral pathology, elevated intracranial pressure, acidosis, hypoxia or hypercapnia (39). Hyponatraemic seizures may occur at higher plasma sodium concentrations than might be expected in other settings (81). The pathophysiology of hyponatraemia in neurosurgical patients can be multifactorial and assessment could be made difficult by the use of high volumes of intravenous fluids to prevent cerebral vasoconstriction and mannitol to reduce intracerebral pressure.

**Assessment**

Establishing the underlying cause of hyponatraemia requires accurate assessment of volume status to determine whether the patient is hypovolemic, euvolemic or hypervolemic (Table 3). Clinical markers such as low central venous pressure (CVP), tachycardia, hypotension and elevated plasma urea may be helpful in identifying hypovolemia, whereas an elevated CVP, signs of fluid overload and a positive fluid balance indicate hypervolemia.

The diagnosis of SIADH is based on well-defined parameters (Table 4) (125). Glucocorticoid deficiency should always be excluded. Cerebral salt wasting (CSW) is rare, and its presence is suggested by hyponatraemia accompanied by volume depletion, natriuresis and a response to intravenous saline (Table 5) (126).

**Treatment**

The key to management is the accurate assessment of the underlying cause and chronicity of hyponatraemia. When hyponatraemia develops over several days, cerebral adaptation prevents cerebral oedema. Symptoms are far more likely if the drop in plasma sodium is rapid. In this setting, the ability of the brain to adapt is exceeded, water is shifted into brain cells and cerebral oedema ensues (127). This can lead to raised ICP, seizures, cerebral herniation, hypoxia and even death, if hyponatraemia is not corrected promptly and effectively (39).

Most neurosurgical hyponatraemia is acute, and some present as a medical emergency. Recent expert panel recommendations emphasise the importance of rapid initial correction of 3–5 mmol/L over 2–4 h, to reduce cerebral oedema (128). For severe symptoms, 100 mL of

<table>
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<th>Table 3</th>
<th>Differential diagnosis of neurosurgical hyponatraemia.</th>
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<tr>
<td></td>
<td>Hypovolemic</td>
</tr>
<tr>
<td>Urine sodium &lt;20 mmol/L</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Urine sodium &gt;40 mmol/L</td>
<td>CSW</td>
</tr>
<tr>
<td></td>
<td>Diuretics, Addisons disease</td>
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<td></td>
<td>Salt losing nephropathy</td>
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(122)

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<tr>
<th>Table 4</th>
<th>Diagnostic criteria for SIADH (125).</th>
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<tbody>
<tr>
<td>1. Hypo-osmolality: Plasma osmolality &lt;275 mosmol/kg</td>
<td></td>
</tr>
<tr>
<td>2. Inappropriate urine concentration: Urine osmolality &gt;100 mosmol/kg</td>
<td></td>
</tr>
<tr>
<td>3. Elevated urine sodium &gt;40 mmol/L with normal salt and water intake</td>
<td></td>
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<tr>
<td>4. Euvolemia</td>
<td></td>
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<tr>
<td>5. Exclusion of glucocorticoid and thyroid hormone deficiency</td>
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</table>

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<th>Table 5</th>
<th>Distinguishing features between SIADH and cerebral salt wasting.</th>
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<tbody>
<tr>
<td>SIADH</td>
<td>Cerebral salt wasting</td>
</tr>
<tr>
<td>Blood volume status</td>
<td>Euvolemic</td>
</tr>
<tr>
<td>Urinary Na (mmol/L)</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Plasma osmolality</td>
<td>Low</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>High</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>Decreased</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>No change</td>
</tr>
<tr>
<td>Treatment</td>
<td>Fluid restriction</td>
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3% saline given as a bolus over 10 min is used, repeated three times until clinical improvement. The remainder of the target rise in plasma sodium can occur over the rest of the 24 h. For mild-to-moderate neurological symptoms, 3% saline infusion at a rate of 0.5–2 mL/kg/h can be administered. Plasma sodium rise should be aimed at <8 mmol/L/24 h and should not exceed 12 mmol/L/24 h to reduce the risk of osmotic demyelination. The target is lower where the risk of osmotic demyelination is higher (129).

Most patients with neurosurgical hyponatraemia have complete reversals of biochemical abnormalities by the time of discharge from hospital. Chronic hyponatraemia is therefore unusual, and if it does occur, can be managed according to standard recommendations (128).

**Conclusion**

Pituitary dysfunction is commonly encountered in neurosurgical patients and can lead to adverse outcome both in the acute and chronic setting. It is likely that the future role of the endocrinologist in the identification and follow-up of these patients will increase. Collegiate engagement between the neurosurgeon and neuroendocrinologist is imperative to ensure that hypopituitarism and disorders of salt and water balance are identified and managed in a prompt and safe manner to improve patient outcomes, reduce hospital stay and facilitate recovery and rehabilitation.

**Declaration of interest**

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