‘Do no harm’: management of craniopharyngioma

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Abstract

Craniopharyngioma management is challenging. Although histology is benign, the tumour can be clinically aggressive with local invasion and frequent recurrences. Extensive morbidity may be present at diagnosis and furthermore, occurs as a consequence of neurosurgery and radiotherapy. Hypothalamic symptoms can have a devastating effect on quality of life and may reduce life expectancy. This case highlights both the challenge of managing hyperphagia and morbid obesity and the importance of initial treatment preserving existing hypothalamic function and the need to avoid tumour recurrence and further surgery.

A 11-year old boy presented with hydrocephalus secondary to a craniopharyngioma (he had visual failure and hypopituitarism but few hypothalamic symptoms). He underwent radical resection followed by radiotherapy. Following this treatment, he developed psychological and behavioural problems and hyperphagia. Weight gain in the first year (an increase from +1.4 to +3.7 s.d.) resulted in poor mobility and a fall which caused a slipped femoral epiphysis. In the next year, there was a 6-month period of unexpected weight loss (+4.2 to +3.8 s.d.) that culminated in emergency treatment for diabetic ketoacidosis secondary to severe insulin resistance. He developed a left hemiplegia, and a subsequent cerebral angiogram identified multiple stenoses of the Circle of Willis with a Moyamoya appearance secondary to radiotherapy. Weight gain has continued (+3.8 to +5.5 s.d.) so that bariatric surgery is a management option.

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Introduction

‘There is perhaps no other primary brain tumour that evokes passion, emotion, and as a result, controversy than does the craniopharyngioma’ (1).

Craniopharyngioma is a histological benign epithelial intracranial lesion arising from the remnants of the Rathke's pouch. Despite its benign microscopic appearance, it can be clinically aggressive with the signs of invasion and a high incidence of recurrence. Although more common in adults, when the papillary form predominates, craniopharyngioma is the commonest pituitary mass in children (2, 3) and represents 6–13% of paediatric brain tumours with a peak incidence between 5 and 10 years of age (4). The most frequent histological type in childhood is adamantinomatous, which arises from neoplastic transformation of embryonic squamous cell nests of the involuted craniopharyngeal duct that initially connects Rathke's pouch with the stomodeum (5, 6).

We report a case that highlights the significant morbidity associated with the diagnosis of craniopharyngioma,

the sequelae of treatment with neurosurgery and radiotherapy, and the challenges for the endocrinologist in deciding an optimal care.

Case history

A 11-year old boy presented after his school teacher had noticed unequal pupils; there was a 6-month history of headaches and vomiting. At the initial assessment, he had visual failure and papilloedema. Magnetic resonance imaging (MRI) scan demonstrated a suprasellar cystic lesion breaching the floor of the third ventricle with hydrocephalus suggestive of a craniopharyngioma.

Preoperative endocrine review elicited a history of fatigue but no problems with growth. His appetite was unaltered but he was drinking more than usual. On examination, his height was +0.7 s.d. and weight +1.4 s.d.; he was prepubertal. Baseline investigation showed that the prolactin level was normal and α -fetoprotein and β -human chorionic gonadotrophin levels were undetectable. Thyroid function tests were indicative of central hypothyroidism (thyroid-stimulating hormone 0.01 mIU/l; fT4 7 pmol/l). Initial endocrine management included hydrocortisone replacement with

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additional i.v. hydrocortisone cover at the induction of anaesthesia for neurosurgery. Neurosurgical management included the insertion of an external ventricular drain followed by radical resection. Histology confirmed the diagnosis of craniopharyngioma. Neurosurgery was followed by a 6-week course of external beam radiotherapy as there was post-operative evidence of residual tumour.

Diabetes insipidus (DI) occurred immediately post-operatively with increased urine output and rising sodium levels (peak serum Na 160 mmol/l). This was treated with desmopressin (DDAVP) and increased fluid input. After day 4, sodium levels began to fall and the patient had a seizure on day 6 (serum Na 130 mmol/l). The initial interpretation of the clinical picture was a syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and fluid restriction was introduced. As serum sodium levels continued to fall and there was concern about volume depletion, an alternative diagnosis of cerebral salt wasting (CSW) was considered. Management was changed to sodium and fluid replacement and optimisation of hormone replacement therapy. Serum sodium levels increased and the patient once again developed polyuria and hypernatraemia, thus signifying permanent DI.

During the early post-operative period, he was noted to be 'eating well, rather too well' and 'more aggressive'. Anterior pituitary function testing confirmed panhypopituitarism. Ophthalmology review revealed a marked afferent papillary defect with optic neuropathy and a nasal visual field loss. Visual acuity was $<1/60$ in his right eye and an intact visual field with reduced visual acuity of 6/24 was observed in the left eye. This improved after 24 months.

Psychological, behavioural and social problems were complicating factors in management. Even in the immediate post-operative period, he began refusing medication and blood tests. An aggressive outburst, 8 weeks post-operatively, required acute admission in order to provide respite for his single parent father. During that admission, he expressed concerns that 'he was fat' and 'he wanted to kill himself'.

During the first post-operative year, his weight increased from 46 kg (+1.4 s.d.) to 98 kg (+3.7 s.d.; Fig. 1). Excessive weight was beginning to cause mobility problems and a fall resulted in a slipped right upper femoral epiphysis; the epiphyses were pinned bilaterally. Testosterone and growth hormone (GH) replacement were started. Needle phobia led to poor compliance with GH treatment; even so, growth was unaffected with no reduction in height s.d. (last recorded height +1.6 s.d.). During the second year, his weight continued to increase reaching 120 kg (+4.2 s.d.). However, over a period of 6 months, his weight reduced to 104 kg (+3.8 s.d.; Fig. 1). The patient refused blood tests until he became unwell and required further admission to hospital. Investigations revealed significant dehydration with hyperglycaemia (plasma

Figure 1 Patient's weight chart indicating two time points – occurrence of fall and slipped femoral epiphysis, and period of sustained weight loss prior to the diagnosis of DKA secondary to severe insulin resistance.

glucose 22 mmol/l), ketonuria and acidosis (pH 7.2; plasma bicarbonate 7 mmol/l). Diabetic ketoacidosis (DKA), secondary to severe insulin resistance, was diagnosed and he was treated accordingly. He was obese and had a family history of type 2 diabetes mellitus, and acanthosis nigricans, insulin autoantibodies (IAA) and glutamic acid decarboxylase (GAD) antibodies were negative and insulin levels were high. He responded well initially to metformin and subsequently was also started on a thiazolidinedione and an incretin mimetic.

During his admission with DKA, the patient developed a left hemiplegia and a subsequent cerebral angiogram demonstrated widespread stenoses around the Circle of Willis with a Moyamoya type appearance (Fig. 2). He made a good recovery but subsequently had two transient ischaemic attacks and was started on aspirin and dipyridamole. Following the diagnosis of

Figure 2 Cerebral angiogram demonstrating widespread stenoses of the arteries around the Circle of Willis and a moderate Moyamoya appearance.

type 2 diabetes, his weight continued to increase over the following year from 104 kg (+3.8 s.d.) to 172 kg (+5.5 s.d.; Fig. 1). The options for weight management are currently being considered.

Discussion

This case demonstrates the significant morbidity that is present at diagnosis and that can occur following treatment with neurosurgery and radiotherapy. At presentation, the patient had visual failure and hypopituitarism, but hypothalamic function was essentially intact. Following radical resection of a craniopharyngioma breaching the floor of the third ventricle, hypothalamic morbidity occurred. Psychological and behavioural problems complicated management. Hyperphagia resulted in uncontrolled obesity that led to the sequelae of a slipped femoral epiphysis and severe insulin resistance presenting as DKA. In addition, there was the occurrence of a rarely reported late effect of radiotherapy, cerebral artery stenoses which, in the setting of dehydration with DKA, caused neurological deficits. Morbid obesity, type 2 diabetes mellitus and a high risk of stroke have a significant impact on his quality of life and life expectancy.

The following discussion addresses the importance of individualising initial treatment for the patient with a craniopharyngioma and considers potential strategies for managing hypothalamic obesity. Morbidity is significant even at initial diagnosis in patients with a craniopharyngioma (7–9). This may include symptoms and signs related to raised intracranial pressure (present in >50%), encroachment of the tumour on the optic nerves resulting in visual failure (30–60%), hypothalamic involvement (up to 30%), endocrine manifestations such as anterior hypopituitarism (20–30%) and DI (9–17%), and in some cases, chemical meningitis following cyst rupture.

The location and the aggressive nature of the tumour pose challenges in deciding what initial treatment is optimal. The main modalities include neurosurgery and external beam radiotherapy. There are no randomised control studies to inform practice. Most evidence has come from cancer registries. Mortality rates are affected by initial treatment. For example, for patients treated between 1966 and 1992, the 5-year progression-free survival was 89% for patients treated with radiotherapy and conservative surgery compared with 81% after complete excision and 53% after partial excision (10). The comparable figures at 10 years were 77%, 69% and 37% respectively. Mortality figures are improving; for instance, patients diagnosed before 1980 had a 50% survival at 5 and 10 years, whereas this rose to almost 100% when the diagnosis occurred after 1990 (11).

Neurosurgical treatment can range from an aggressive approach when the aim is complete excision attempted in all patients to a conservative approach

comprising biopsy, drainage of the cyst, chiasm decompression and no intervention that would affect the infundibulum or hypothalamus (6). The case for an aggressive approach rests with the only chance of cure and the possibility of avoiding the need for radiotherapy. Complete excision is likely when tumours are less than 2 cm in diameter, but not so if greater than 4 cm (12, 13). Nearly half of craniopharyngiomas are greater than 3 cm in diameter at diagnosis (12, 14). In patients with larger tumours, who have hydrocephalus or hypothalamic involvement and undergo radical resection, there is a high likelihood of hypothalamic morbidity (>50%), operative mortality (2.5–10%) and late mortality (11–28%) (15, 16). Of relevance to the subject of this case presentation, hypothalamic obesity is associated with the extent of the neurosurgical procedure. MRI studies indicate that when the anatomy was left undisturbed, body mass index (BMI) increased by +1.1 s.d.; whereas when there was a breach of the tuber cinereum, BMI increased by +2.5 s.d.; complete deficiency of the floor of the third ventricle was associated with a 5.5 s.d. increase in BMI (17). Neurosurgical management is now increasingly influenced by symptoms and signs at presentation and MRI findings.

There is no consensus on the use of adjuvant radiotherapy and its timing after neurosurgery. The case for limited resection and adjuvant radiotherapy is supported by evidence of adequate long-term control in 70–80% of patients. This treatment modality reduced recurrence rates from 75–100% to 16–25%, with no detriment in long-term morbidity or mortality (13). This approach often avoids repeat surgery that is associated with the high level of hypothalamic morbidity and mortality (12, 13). However, there is concern about the late effects of radiotherapy, which include neurocognitive and neuroendocrine disturbance, optic neuropathy and the risk of secondary malignant neoplasms (18). The incidence of these adverse events depends on the age of the patient, volume of normal brain irradiated, and dose and type of radiation. In the present case, radiation-induced vasculopathy caused the Moyamoya appearance on cerebral angiogram (Fig. 2). This is potentially a serious complication of whole brain radiotherapy in children with brain tumours (19). However, this risk is probably insignificant when compared with the morbidity and mortality associated with the tumour itself, radical resection or repeat surgery.

Careful management of salt and water balance is essential during the immediate post-operative period. Ninety per cent of patients develop DI post-operatively which will remain permanent in 60–80% (8, 14). The diagnosis of DI is relatively straightforward and management involves a combination of judicious fluid balance and DDAVP administration. By contrast, establishing the cause of hyponatraemia can be challenging, as illustrated in the present case.

Possibilities include high urinary salt loss from severe polyuria with DI, SIADH component of the triphasic response, considered to be the secondary to vasopressin neuronal necrosis that occurs 1–14 days following neurosurgery or CSW. CSW may be a response to plasma volume expansion as a result of DDAVP treatment, or to SIADH itself. Alternatively, CSW may be a primary response to over-secretion of atrial natriuretic peptide or brain natriuretic peptide. SIADH and CSW differ in certain characteristics. Thus, there is evidence of volume depletion and suppressed plasma aldosterone levels in CSW but not in SIADH. Levels of uric acid are low in SIADH but not in CSW. Nevertheless, the clinical diagnosis between SIADH and CSW is often not straightforward. Management involves fluid restriction in the former, whereas salt and fluid replacement and in some cases, administration of fludrocortisone, are required for CSW.

Long-term endocrine follow-up includes assessment of hypothalamic pituitary function and optimisation of hormone replacement to maintain water balance, and normal growth and pubertal development. Hypothalamic symptoms can complicate management and may involve disturbance of mood, temperature control and sleep. For the endocrinologist, disturbances of thirst and appetite are the most challenging aspects of management (7, 13, 14). Hypodipsia or adipsia complicates the management of DI and hyperphagia results in increasing levels of obesity from damage to the ventromedial nucleus in the hypothalamus. There are two hypotheses as to the mechanism of obesity. One relates to disruption of central appetite centres resulting in hyperphagia, followed by obesity and hyperinsulinaemia. The other postulates disinhibition of the efferent output of the vagus nerve affecting the pancreatic β -cell thereby causing insulin hypersecretion. This promotes partitioning of energy into adipose tissue and hence obesity.

The management of hypothalamic obesity is challenging. There is little evidence of benefit from changes in lifestyle. There is some evidence that pharmacotherapy is beneficial and recent case reports suggest that bariatric surgery may also be a therapeutic option. On the basis that higher levels of insulin drive obesity, the somatostatin analogue, octreotide, has been studied as a potential agent to combat hypothalamic obesity. Positive results were obtained in an initial study of eight patients who lost 5 kg of weight and reduced their BMI by 2 kg/m² after 6 months of therapy with octreotide (20). A follow-up RCT in 18 subjects demonstrated that patients receiving octreotide showed no change in BMI, but weight increased by less than 2 kg when compared with a BMI increase of 2 kg/m² in a 9 kg increase in weight in patients on placebo (21). Octreotide appears to be effective at maintaining but not significantly reducing weight. The use of octreotide in patients with hypothalamic obesity remains experimental and the benefit of weight maintenance has to be considered in the context of frequent injections and side effects.

Sibutramine is an appetite suppressant and has been shown to be effective in simple obesity. A 20-week double-blind RCT of sibutramine in 50 children, 22 with hypothalamic obesity and 28 with simple obesity, reported significant weight loss (22). However, the reduction of BMI s.d. in children with hypothalamic obesity was modest (0.3–0.4 s.d.) when compared with children with simple obesity (0.9–1.0 s.d.).

Bariatric surgery is considered as the first-line treatment for adults in the UK with simple obesity and a BMI of greater than 50 kg/m². It is also the second-line treatment for BMI greater than 40 kg/m² or 35 kg/m² with a comorbidity. There has been reluctance to consider bariatric surgery for patients with hypothalamic obesity in view of its specific pathophysiology and that ongoing hyperphagia in a patient with restricted gastric capacity could result in a greater risk for the patient. The effect of gastric banding was studied in four children with hypothalamic obesity whose mean BMI s.d. at the time of surgery was +10.7 (2.7) s.d.; mean follow-up was 2.9 (1.3) years and mean weight loss per year was –0.7 (0.3) s.d. (23). In a single case report of the effect of gastric bypass surgery in an adolescent with hypothalamic obesity, the BMI had fallen from > 60 kg/m² to 50 kg/m² within 2.5 years of surgery (24). Furthermore, insulin levels decreased before and after meals; a similar effect occurred in ghrelin levels pre-prandially. Both these publications reported an improvement in eating behaviour. Bariatric surgery may offer hope to patients with hyperphagia and hypothalamic obesity.

In summary, the goal of treatment in craniopharyngioma is to relieve the raised ICP and optic nerve compression, preserve existing hypothalamic function and vision, provide long-term tumour control, avoid repeat surgery and minimise neurotoxic effects from surgery and radiotherapy. Initial treatment should be tailored according to low- or high-risk factors as listed in Table 1. Ongoing registration of patients in cancer registries is required to collate long-term outcome in order to better inform future management strategies in craniopharyngioma. It is self-evident that management is undertaken by a multi-disciplinary team, with the endocrinologist playing a key role.

Table 1 Recommended management pathway for a paediatric patient with a craniopharyngioma⁴

Risk factors	
Good	Poor
Small tumour (≤ 2 –4 cm)	Large (retrochiasmatic) tumour (> 2–4 cm)
No hydrocephalus	Hydrocephalus
No hypothalamic symptoms	Hypothalamic symptoms
No breach third ventricle floor	Breach third ventricle floor
Consider radical resection with radiotherapy if necessary	Consider limited resection with adjuvant radiotherapy
Recommended management	

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