Chapter 11a. PITUITARY AND HYPOTHALAMIC TUMOUR SYNDROMES IN CHILDHOOD

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Abbreviations used in this chapter include; CPP-Central precocious puberty, CSW-Cerebral salt-wasting syndrome, DS-Diencephalic syndrome, LCH-Langerhans cell histiocytosis, LGG-Low-grade glioma, PNET-Primitive neuroectodermal tumour, PPD-Posterior pituitary, dysfunction, RCC-Rathke's cleft cyst, RCIP-Raised intracranial pressure, SPC-Subsequent primary cancer, SST-Standard synacthen test, TPS-Thickened pituitary stalk.

INTRODUCTION

Central nervous system (CNS) tumours are the second commonest childhood malignancy after leukaemias, accounting for 25% of cancers in children <15 years of age with an annual incidence rate of 35 cases/ million/ year(1-4). As with all childhood cancers, their incidence is gradually increasing worldwide (1, 2, 5), an effect largely attributed to improvements in diagnosis and tumour registration(6-8), and more recently campaigns such as the UK HeadSmart project aimed at increasing awareness of paediatric brain tumour symptoms (http://www.headsmart.org.uk/)(9). Concurrently, 5-year survival for CNS tumours has increased much more steeply from 57% to 65% in the last decade (~95% in low-grade gliomas), as a result of improved multimodality cancer therapies and better supportive care(10-12).

However, where survival is high, increasingly intensive treatment strategies aimed at improving cure in a small minority can conversely cause a higher toxicity burden in the larger majority, with a rapidly accruing cohort of survivors faced with reduced quality of life due to late and evolving multi-organ toxicities(13-15). Over 40% of these chronic morbidities ("late effects") are severe, disabling or life-threatening(16), and more than 80% of CNS tumour survivors develop at least one endocrinopathy, most frequently growth hormone deficiency (GHD) (17). When compared with adult CNS tumours, paediatric tumours tend to be more curable, and the early presentation of some tumours (e.g. craniopharyngiomas, primitive neuroectodermal tumours (PNET)) and their association with mutations in neural development genes blur the delineation between congenital malformations and neoplasia(18-20).

Tumour location and histology is distinctly age-dependent. 30% of tumours under the age of 14 years are infratentorial (medulloblastomas, posterior fossa juvenile pilocytic astrocytomas and ependymomas), whilst 26% and 16% of tumours diagnosed in young adulthood (15 to 24 years) are supratentorial or suprasellar respectively (non-pilocytic astrocytomas, other gliomas, pituitary adenomas and germinomas)(4, 21). Supra- and intrasellar tumours constitute 10% of all paediatric CNS tumours(21, 22) and their close proximity to the vital hypothalamo-pituitary axis (HPA) increases the risk of important endocrine dysfunction. This may occur secondary to tumour mass effect and/ or treatment, and can therefore be manifest at presentation or evolve subsequently during or after completion of oncological therapies. Dissecting the effect of tumour from treatment on endocrinopathies diagnosed after commencement of therapy is particularly complicated. We aim here to (1) outline the epidemiology, clinical features and management of common paediatric suprasellar tumours not readily addressed in other chapters, (2) examine the common clinical neuroendocrine presenting features and (3) summarise common themes in the neuroendocrine late effects observed at follow-up of these patients.

DIFFERENTIAL DIAGNOSIS OF PAEDIATRIC SUPRA- AND INTRASELLAR MASSES

The definitive diagnosis of paediatric suprasellar and intrasellar masses is crucial, as therapeutic strategies differ markedly depending on histological subtype. However, a tissue diagnosis may not always be possible due to their location, as even minor procedures such as biopsies can lead to life-threatening endocrinopathies such as diabetes insipidus (DI)(23). Biochemical measurements of serum prolactin (PRL), α-fetoprotein (AFP) and β-human chorionic gonadotrophin (β-hCG) to aid the diagnosis of prolactinomas and secreting germinomas respectively are therefore absolutely essential prior to commencement of any therapy.

Neoplastic
Craniopharyngioma
Low-grade glioma (mainly pilocytic astrocytoma)
Pituitary adenoma
Germ cell tumour (mainly germinoma)
Hamartoma
Meningeal metastases
Non-neoplastic
Pituitary hyperplasia
Pituitary stalk thickening
Langerhans cell histiocytosis*
Tuberculosis
Sarcoidosis
Rathke cleft cyst
Arachnoid cyst
Epidermoid/ dermoid cyst
Meningioma

Table 1: The differential diagnosis of paediatric suprasellar tumours and other disorders. *The classification of Langerhans cell histiocytosis as a non-neoplastic disease is debatable.

Craniopharyngiomas

Craniopharyngiomas are by far the commonest suprasellar tumour of childhood, accounting for up to 50% of masses in this region(22, 24). There is a bimodal age distribution in incidence, with the peak incidence in childhood occurring between the ages of 5-14 years at 1.4 cases/million/year(25, 26). They are benign tumours originating from the embryonal epithelium lining Rathke's pouch and are almost invariably adamantinomatous in childhood, characterised by the presence of intratumoral calcifications(27). Over-activation of the Wnt/β-catenin pathway, a pathway important in both pituitary stem cell development and carcinogenesis, has been shown to be key to their formation(18, 19). Radiologically, 65-93% of these tumours are calcified but a plain X-ray or computerised

tomography (CT) scan may be required to demonstrate this. The coexistence of solid, cystic and calcified structures on neuroimaging, as well as the characteristic cholesterol crystals seen under microscopy of the "engine fluid" aspirated surgically from cystic components are so highly suggestive of the diagnosis that histological confirmation from biopsies of solid components may be unnecessary, particularly as this may further compromise hypothalamo-pituitary function(27, 28). Anatomically, 75% of craniopharyngiomas are suprasellar with an intrasellar extension, 20% are exclusively suprasellar, and 5% are exclusively intrasellar(24, 29). Due to their location, a significant proportion of these tumours are not completely resectable, but their relative rarity, high rates of survival and benign histology have precluded them from pan-European randomised trials, resulting in the lack of agreement on the optimal treatment strategy. There is, however, an increased consensus for minimising hypothalamic and visual damage through more conservative surgical strategies (e.g. debulking or cyst aspiration with adjuvant radiotherapy as opposed to radical resection) and concentrating care in a few specialised centres, such as that outlined in the UK Best Practice Statement(30, 31). The various hypothalamic grading systems proposed may assist decision-making and surgical planning to minimise hypothalamic damage(32-34). Experience with systemic or intracystic chemotherapy, intracystic interferon and radioisotope instillation of ^{32}P or ^{90}Y have been met with conflicting success and cannot therefore be currently recommended as primary treatment approaches(35-38). Long-term survival is high (80% at 30 years(39)) but so is significant neuroendocrine morbidity, with up to 98% of survivors experiencing dysfunction in at least one hypothalamo-pituitary axis with high rates of morbid obesity(40, 41).

Low-grade gliomas (LGGs)

LGGs account for >40% of all CNS tumours and are thus the commonest paediatric intracranial tumour(3, 8). The optic pathway, hypothalamus and suprasellar midline are the second most frequent location for LGGs (30-50%) after the cerebellum, cerebral hemispheres and brainstem(12, 42). Even in the suprasellar region they are the second commonest paediatric tumour after craniopharyngiomas, and are similarly regarded as benign (grade I or II), the vast majority being juvenile pilocytic astrocytomas(43). The genetic tumour predisposition syndrome neurofibromatosis type 1 (NF-1) is present in 10-16% of cases, whilst 15% of asymptomatic NF-1 children will have LGGs on neuroimaging. NF-1-associated tumours more often originate from the optic nerves (70%) than from the hypothalamochiasmatic area (27-40%) and tend to a more indolent course (11, 12, 42, 44-47). Mutations involving *KIAA1549, BRAF* and *Ras* proto-oncogenes are associated with pilocytic astrocytomas and disruptors targeted at these pathways form the basis of current clinical therapeutic trials(48, 49). Complete tumour resection has been shown to be a favourable risk factor for survival(12, 42), but suprasellar and/or optic pathway tumours cannot be completely resected without causing major visual and neuroendocrine morbidity. Treatment trials have thus focussed on medical strategies, with radiotherapy being delayed in favour of chemotherapy in young children due to concerns of cognitive dysfunction(50), subsequent primary cancers (SPCs)(51, 52) and radiation-induced vasculopathies(53), despite showing superior 5-year progression-free survival rates (65% vs. 47%)(11). However, to date none of the previous international treatment trials – LGG1 (1997-2004) or LGG2 (2005-2010) – were randomised, these being purely observational studies aimed at improving visual outcomes but with little reported success(11, 12, 54). At the time of writing, the first randomised interventional study of chemotherapeutic strategies (LGG3) is being designed with careful long-term prospective measurements of visual and neuroendocrine outcomes. Both hypothalamic tumour location and radiotherapy exposure are important independent risk factors for long-term anterior hypothalamo-pituitary deficits, however only surgical resection has been shown to be independently associated with posterior pituitary dysfunction and life-threatening salt and water imbalances(23, 42). Similar to craniopharyngiomas, overall survival is high (85% at 25 years), but ~80% of survivors experience at least one endocrinopathy(23).

Pituitary adenomas

Pituitary adenomas are rare in childhood, accounting for just 3% of all supratentorial tumours with an estimated annual incidence of 0.1 cases/ million/ year in children(55). The vast majority are functioning, with prolactinomas alone accounting for 50% of adenomas and 2% of all paediatric and adolescent intracranial tumours. Therefore, the measurement of plasma prolactin (PRL) may be diagnostic and is absolutely mandatory prior to planning surgery for any pituitary mass, as medical treatment alone may be entirely curative(56, 57). ACTH- and GH-secreting adenomas are the next commonest, whilst TSH-secreting, gonadotrophin-secreting and non-functioning adenomas are vanishingly rare(57-59). A child with a pituitary adenoma may be the index case for a genetic tumour predisposition syndrome, particularly given their rarity, and therefore careful documentation of their family history and testing for **multiple endocrine neoplasia type 1 (*MEN1*) and aryl-hydrocarbon interacting protein (*AIP*) gene mutations** are therefore paramount in all cases(60). Prolactinomas in particular are classified into microadenomas (<1 cm), macroadenomas (>1 cm) and giant prolactinomas (>4 cm) with plasma PRL levels generally, but not exclusively, increasing with tumour size. Hyperprolactinaemia may also result from stalk compression by tumour mass (interrupting hypothalamic dopaminergic inhibition of PRL secretion) and antipsychotic medication but PRL concentrations are usually <2000 mU/l and patients rarely symptomatic(61). Laboratories should always screen for artefactual hyperprolactinaemia due to macroprolactin, but levels >5000 mU/l are usually diagnostic and symptomatic. Occasionally, falsely low results can be due to interference by extreme hyperprolactinaemia on antibody-antigen sandwich complex formation, a phenomenon known as the hook effect. Samples should therefore be diluted 100-fold and repeated for confirmation(62). Clinical presentation varies according to the size of tumour, gender and pubertal status, with girls usually experiencing galactorrhoea, pubertal delay or amenorrhoea and boys presenting later with larger more aggressive tumours with raised intracranial pressure(56).

Given the paucity of good quality outcome data in children, treatment guidelines follow those for adults(57, 63), recommending dopamine agonists (DAs) as first line, ideally cabergoline due to its high efficacy and tolerability(61). Starting doses, dose escalation and duration of therapy in children remain undefined and are critical questions given the potential for more aggressive disease and cardiac valve abnormalities with long-term cumulative exposure(64). Surgery should be reserved for those cases resistant to DAs or for neurosurgical emergencies (e.g. neuro-ophthalmic deficits, pituitary apoplexy) and both trans-sphenoidal and transcranial approaches should be considered by an experienced paediatric neurosurgeon. Radiotherapy has usually been reserved for treatment failures in view of the presumed risk of post-treatment endocrine morbidity and second primary cancers. However, the former may have been overestimated in view of the high incidence of endocrinopathies already present at diagnosis(65), and therefore this treatment modality should be considered earlier and prior to other more experimental treatments such as temozolamide chemotherapy(61). As with other hypothalamo-pituitary tumours, long-term neuroendocrine and secondary cardiovascular morbidity is significant(66).

Germinomas

In contrast to craniopharyngiomas and LGGs, germinomas account for just 3-4% of all primary paediatric and young adult CNS tumours <24 years(21, 67). There is a clear peak in incidence in adolescence and young adulthood, with age-adjusted incidence rates rising from 0.9 cases/million/year in patients <10 years to 1.3-2.1 cases/million/year in patients aged 15-24 years(21, 67). Boys are affected nearly three times as often as girls, and this sex distribution is magnified in adolescence (male: female ratio of >8:1)(21). Germinomas are also the commonest CNS tumour in the Klinefelter and Down syndromes(68). DI and central precocious puberty (CPP) are common findings at diagnosis and present in 30-50% and 11-12% of patients respectively. However, germinomas grow indolently (if at all), meaning that both clinical and radiological features can often be subtle at onset, and delays in diagnosis up to 21 years have been reported(69-72). Histologically, intracranial germinomas are of germ cell origin (accounting for 34% of all such tumours(73)) and resemble their gonadal counterparts (ovarian teratoma or testicular seminoma) in secreting AFP and β-hCG. They have a particular predilection for the pineal gland (37-66%) and suprasellar region (23-35%), such that synchronous pineal and suprasellar tumours are pathognomonic. Their propensity for metastases throughout

the cerebrospinal fluid(24, 68, 74) coupled with their radiosensitivity has meant that whole neuraxial irradiation has been standard therapy for decades, with overall and progression-free survival rates approaching 100%(69). Chemotherapy alone has been shown to result in inferior survival(75), and more recent attempts to reduce the irradiation field with adjuvant chemotherapy in an effort to preserve cognitive function have shown little reduction in overall survival(68, 76, 77). As for other suprasellar tumours, the rate of post-treatment endocrine morbidity is significant, with 50-60% of patients having at least one endocrinopathy(69).

Hypothalamic hamartomas

Hypothalamic hamartomas are extremely rare congenital (rather than neoplastic) malformations consisting of grey matter heterotopia in the tuber cinereum and inferior hypothalamus(22, 24, 78). Their true prevalence is unknown but is estimated to occur in between 1 in 50 000 – 1 million individuals(79-81). Symptom onset occurs in infancy to early childhood, with the mean age of first seizures occurring between 6 weeks – 4.5 years(81-84). The triad of epilepsy (usually gelastic seizures), central precocious puberty and developmental delay is classic with the seizure semiology eventually evolving into multiple, more severe seizure types(78). Rarely, they are associated with Pallister-Hall syndrome, an autosomal dominant disorder characterised by polydactyly and other midline defects (imperforate anus, bifid epiglottis, panhypopituitarism and dysmorphic facies)(80, 85). The intrinsic epileptogenicity of these lesions(86, 87), the trend towards evolving seizure semiology, the worsening of behavioural and psychiatric co-morbidities and the general failure of anti-epileptic drug therapy has led clinicians to explore the options of surgical or stereotactic radiosurgical resection despite their deep-seated location, with variably reported success in the remission of seizure activity and behavioural disturbances, but more modest improvements in cognitive function(78, 79, 88-90). Li *et al.*'s(91) case series reported successful remission of CPP and little, if any, late-onset endocrinopathy; but a larger cohort study by Freeman *et al.*(92) suggested that clinically silent endocrine dysfunction (particularly GH and TSH deficiency) is common both at diagnosis and postoperatively. Transient posterior pituitary dysfunction leading to DI and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has also been described(92, 93). One adult cohort study corroborates these findings, showing that >1/3 of these patients had endocrine dysfunction and approximately 2/3 experienced excessive weight gain postoperatively(94).

Langerhans cell histiocytosis (LCH)

LCH (previously "histiocytosis X") is one of the three major histiocyte disorders, and involves clonal proliferation of bone marrow-derived dendritic antigen-presenting ("Langerhans") cells which accumulate in various organs(95). It is a rare disease with an incidence of 2.6-8.9 cases/million/year, the majority presenting in infancy (median age at diagnosis 2-3.8 years, incidence at age <1 year 9.0-15.3 cases/ million/year vs. age >5 years 0.7-4.5 cases/million/year) with no sex predilection(96-99). The variability in organ involvement causes a spectrum of clinical features ranging from a single self-healing cutaneous lesion to fatal multiorgan disease, particularly if the liver, spleen, lungs and haemopoietic system (the "risk" organs) are involved(95). Multisystem involvement is present in 27-56% of cases, of which 28-80% have "risk" organ involvement(96-98, 100, 101). LCH can thus be considered a primary haematological disorder which, in a proportion of cases, infiltrates the CNS, although its aetiology, whether neoplastic or reactive, remain poorly understood(100). In the CNS, the hypothalamo-pituitary region is involved in up to 25% of cases, which almost invariably leads to DI (previously known as Hand-Schuller-Christian disease if associated with orbital and bony lesions)(96, 97, 99, 102, 103). Commonly associated radiological findings include thickening of the pituitary stalk with progression to space-occupying tumours and an absence of the posterior pituitary bright spot(104). Indeed, LCH is the commonest underlying diagnosis in patients with central DI and an intracranial mass, occurring in 70% of this cohort(105). The presence of multisystem involvement, particularly if involving "risk" organs, craniofacial bones, gastrointestinal tract, skin or genitalia) is a particular risk factor for DI(103, 106). Treatment is dependent on the number of organs involved and may range from biopsy/ curettage, intralesional steroids and radiotherapy/ UV phototherapy for single bone and cutaneous lesions to systemic chemotherapy with steroids and vinblastine for multisystem disease(100). Notably, no treatment protocol has been

shown to reverse existing or prevent future DI(103), though current therapeutic recommendations are aimed at preventing disease progression and limiting endocrinopathy with prolonged, low-dose systemic chemotherapy(100, 104, 107). Overall 5-year survival remains relatively high at 71-95%, but 3-25% of patients experience at least one endocrinopathy (particularly GH deficiency), with no current chemotherapeutic regimens showing superior overall- or endocrine event-free survival (96, 101, 102, 106).

Pituitary stalk thickening

A thickened pituitary stalk (TPS) may be discovered either as part of the evaluation of a patient presenting with central DI, visual impairment or other endocrine dysfunction or incidentally on neuroimaging performed for other purposes. It is discussed here as it is an important differential for germinomas and LCH, resulting frequently in diagnostic and management dilemmas, due to a number of reasons:

1. There is no clear consensus as to what constitutes abnormality for children; previous adult studies have shown that the 95th centile for the transverse dimensions of the infundibulum at the optic chiasm and pituitary insertion are 4.21-4.35 mm and 2.69-2.89 mm respectively (upper limit 4.21-4.58 mm and 2.93-3.04 mm)(108, 109). Raybaud and Barkovich suggest using a paediatric threshold thickness of 3.8 mm at the optic chiasm and 2.7 mm at the pituitary insertion for investigating further pathology, particularly if there are interruptions in the normal smooth tapering of the infundibulum from median eminence to pituitary insertion(110).
2. The radiological appearances of a TPS, LCH and germinomas cannot be easily differentiated and there is substantial overlap (Table 2). The normal infundibulum lacks a blood-brain barrier and therefore always enhances with contrast, obscuring neoplastic processes. TPS is the commonest initial radiological finding in both LCH and germinomas, and concurrent absence of the posterior pituitary bright spot is inconsistent(70, 111, 112). Similarly, the two commonest causes of TPS in the paediatric age group are LCH and germinomas, accounting for 7-75% and 9-71% of TPS cases respectively(112-115). Other common causes of TPS in adults such as lymphocytic hypophysitis and neurosarcoidosis are rare in children(112).
3. Biopsies of the TPS to obtain a definitive histological diagnosis can be inconclusive and lead to further substantial endocrine morbidity, including panhypopituitarism with DI and are thus generally avoided(114).
4. The interval from the time of initial symptoms to diagnostic MRI can be prolonged, particularly for germinomas (up to 21 years), occasionally with initially normal neuroimaging(70-72, 116). An initially normal MRI does not therefore preclude an occult germinoma or other pathological process in the presence of idiopathic central DI, leading some authors to recommend serial 3-6 monthly scans and follow-up, although the duration of serial scanning is unclear(110). Additionally, there have been cases of occult germinomas masquerading as radiologically or even histologically diagnosed lymphocytic hypophysitis in children(117, 118).

In an attempt to define which patients with isolated TPS are at risk of neoplasia and therefore require more intensive follow-up or biopsy, Robison *et al.* suggest risk factors such as the presence of DI (strongest risk factor), the coexistence of DI with anterior pituitary dysfunction or a progressive increase in infundibular size of >15% from baseline(114). Apart from size, no other particular MRI appearances have been found to be specific for paediatric-related tumour processes(119). Various proposed diagnostic pathways have been proposed for the management of TPS and idiopathic DI(114, 119, 120).

Miscellaneous non-neoplastic hypothalamo-pituitary masses

Other hypothalamo-pituitary malformations can mimic neoplastic processes in the suprasellar region, and should therefore be considered in the differential diagnosis particularly before commencing oncological therapies:

- Pituitary hyperplasia – Hypothalamic releasing hormones are trophic on the pituitary gland, hence hypersecretion of these hormones can cause anterior pituitary enlargement and mimic a true mass. The commonest physiological cause of pituitary hyperplasia is puberty, where the maximal height of the gland can be 10 mm in girls and 7 mm in boys(121, 122). Pituitary hyperplasia can also occur pathologically, for instance in chronic primary hypothyroidism leading to thyrotroph hyperplasia due to a lack of negative feedback(22, 121).
- Rathke's cleft cysts (RCCs) – RCCs are congenital cystic epithelial remnants of Rathke's pouch which fail to involute during pituitary development, hence arising in the pars intermedia but often extending superiorly(22). Although often incidental and asymptomatic (occurring in 11% of autopsy cases(123)), cystic growth can lead to visual deficits and endocrinopathies, requiring surgical marsupialisation (resection exacerbates endocrine dysfunction)(124). Unlike craniopharyngiomas (the other common cystic suprasellar lesion), RCCs do not calcify.
- Rare entities – In contrast to adults where autoimmune lymphocytic hypophysitis is the commonest cause of isolated TPS, this is exceptionally rare in children, but should be considered in the differential together with other granulomatous diseases (neurosarcoidosis, tuberculosis) and arachnoid, dermoid and epidermoid cysts(22, 125).

Tumour	Primary location	T1 intensity§	T2 intensity§	Contrast enhancement	Other features
Craniopharyngioma	Supra>intrasellar	Variable, heterogenous	High	Yes (cystic rims)	Cysts, heterogenous, calcification
LGG	Suprasellar, optic pathways	Low	High	Yes	Generally homogenous
Pituitary adenoma	Intrasellar (intrapituitary)	Low	Low	No	Sella turcica expansion
Germinoma*	Suprasellar, pituitary stalk	Isointense – low	Isointense – low	Yes	Loss of posterior pituitary bright spot, coexistent pineal tumour
Hamartoma	Suprasellar (tuber cinereum)	Isointense	Isointense – high	No	-
LCH*	Suprasellar, pituitary stalk	Isointense	Isointense	Yes	Loss of posterior pituitary bright

					spot, coexistent osseous lesions
Lymphocytic hypophysitis*	Suprasellar, pituitary stalk, intrasellar	Isointense	Isointense	Yes	Loss of posterior pituitary bright spot
Pituitary hyperplasia	Intrasellar	Isointense	Isointense	Yes	Homogenous
RCC	Intrasellar	Isointense – high	Isointense – low	No	Round & smooth walled
Granuloma (sarcoidosis, TB)	Suprasellar, pituitary stalk	Isointense – low	Low – isointense	Yes	Coexistent parenchymal and leptomeningeal lesions
Arachnoid cyst	Suprasellar	Very low (isointense with CSF)	High (isointense with CSF)	No	-

Table 2: The differential diagnosis of paediatric suprasellar masses by radiological features. LGG, low-grade glioma; LCH, Langerhans cell histiocytosis; RCC, Rathke's cleft cyst. [§]MRI signal intensity in comparison to that of gray matter. *Note that germinomas, LCH and lymphocytic hypophysitis cannot be differentiated on radiological features alone(22, 24, 110, 126).

NEUROENDOCRINE DYSFUNCTION AT DIAGNOSIS OF HYPOTHALAMO-PITUITARY TUMOURS

Neurological syndromes

The proximity of hypothalamo-pituitary tumours to the floor of the third ventricle and optic chiasm accounts for the high frequency of RICP and visual symptoms at presentation.

- Raised intracranial pressure (RICP) – RICP symptoms (headache, vomiting, and/ or papilloedema) are the commonest presenting feature of any paediatric brain tumour (30-60%)(127, 128); but occur with even greater frequency in suprasellar lesions such as craniopharyngiomas (78%) and LGGs (86%)(39, 44). Children may therefore present to acute neurosurgical units as a neurosurgical emergency or subacutely with a chronic course that may initially be misdiagnosed as tension/ migrainous headaches or infective gastroenteritis with unrecognised concurrent visual disturbances. Current UK recommendations are to scan all children with headaches occurring <4 years of age, in association with confusion, disorientation, or nocturnal waking, and headaches and/ or vomiting persisting >4 weeks and >2 weeks respectively(9). Persistent vomiting in the absence of other features suggestive of gastroenteritis (diarrhoea, pyrexia) should

also prompt consideration of an intracranial lesion. It is important to note that due to the delayed fusion of cranial sutures, children <4 years of age with hydrocephalus more often (41%) present with a rapidly increasing head circumference than classical RICP symptoms(128).

- Visual deterioration – Visual field loss and/ or worsening visual acuity are the second commonest presenting feature, particularly in LGGs, where up to 100% of cases may have visual impairment due to direct involvement of the optic pathway(129). Other suprasellar tumours affect visual function by mass effect on the optic chiasm, occurring in up to 50-70% of craniopharyngiomas and 15% of pituitary adenomas(29, 66, 130). Contrastingly, visual symptoms are rare (~5-7%) in children with other CNS tumours(128). Other common ophthalmological symptoms that warrant urgent neuroimaging include new onset nystagmus, incomitant (paralytic) squints, optic atrophy and proptosis, particularly given the difficulties in assessing visual function in young children and the danger of passing off a squint as being "normal" in childhood without detailed examination(9, 128, 131). Parinaud's syndrome, a combination of upward gaze palsy, convergence-retraction nystagmus and pupillary dilatation with light-near dissociation is a rare particular presentation of bifocal suprasellar/ pineal germinomas due to pressure of the pineal tumour on the tectal plate(71, 132). Although the aim of oncological therapy in many of these low-grade tumours is to preserve vision, this has not been generally successful, likely due to nerve fibre dropout and optic atrophy(54), therefore early diagnosis and treatment is essential.
- Seizures – Seizures are an uncommon presenting clinical feature of paediatric hypothalamo-pituitary tumours, occurring in <10% of craniopharyngiomas, LGGs and germinomas(33, 71, 133-135), and are more often the result of reversible metabolic causes such as hypoglycaemia (from cortisol and/ or GH insufficiency), hypernatraemia (from DI) or hyponatraemia (from SIADH). Gelastic or dacrystic (laughing or crying, from the Greek *gelos* and *dakryon* respectively) seizures are notoriously difficult to diagnose but are characteristic of hypothalamic hamartomas (80-90%) due to the intrinsic epileptogenicity of these lesions that are essentially disorders of neuronal migration(82, 86, 94).
- Other neurological and cognitive symptoms – Hemiparesis and ataxia are less common but significant presenting features of intracranial tumours, as are cognitive impairment, delayed development, behavioural changes and psychiatric symptoms, all of which mandate detailed neuro-ophthalmological examination in such cases, particularly in the presence of the neurocutaneous stigmata of tumour-predisposing syndromes such as neurofibromatosis and tuberous sclerosis.

Endocrine dysfunction

Although neuro-ophthalmological symptoms are the commonest presenting feature of hypothalamo-pituitary lesions, they are often preceded by symptoms associated with undiagnosed endocrinopathies in as many as two-thirds of patients(136). This may be due to hormone excess (e.g. secreting pituitary adenomas, central precocious puberty) or hormone deficiency from pituitary invasion or compression by tumour mass, disrupting the various hypothalamo-pituitary endocrine pathways. The incidence of dysfunction in each of the hypothalamo-pituitary axes is partly dependent on the lesion (Table 3) though the reasons for this are largely unknown.

GH deficiency (GHD) and gonadotrophin dysfunction (either *central precocious puberty (CPP)* or *gonadotrophin deficiency (GnD, i.e. pubertal delay/ arrest)*) are often the initial and commonest endocrinopathies at presentation of both craniopharyngiomas (GHD – up to 100%; GnD – up to 85%, CPP – up to 3%) and LGGs (CPP – up to 56%; GHD – up to 27%; GnD – up to 12%)(39, 44, 137-139). CPP is particularly prevalent in LGGs as it can occur in the context of NF-1 even in the absence of a hypothalamo-pituitary lesion(140). It is also one of key components of the hypothalamic hamartoma clinical triad, present in up to 45% of patients at diagnosis(79, 92). In both these cases it is presumed to result from premature activation of hypothalamic GnRH, unlike its occurrence in up to 35% of germinomas, where gonadotrophin-independent CPP can occur due to secretion of β-hCG which shares a common alpha subunit with LH and FSH and thus stimulates the same receptors(71, 74).

Other anterior pituitary deficits evolve only with extensive disease, and are usually only seen at presentation with craniopharyngiomas, although more subtle deficits may have previously been under-recognised with other tumours. *ACTH deficiency* (secondary hypoadrenalism) is particularly important to diagnose and treat pre-operatively, and is present at diagnosis in up to 71% of craniopharyngiomas, 19% of germinomas, 10% of hamartomas and 3% of LGGs (71, 92, 137, 141). Similarly, *TSH/TRH deficiency* (secondary/ central hypothyroidism) is present in up to 32% of craniopharyngiomas, 19% of germinomas and 10% of LGGs and hamartomas(41, 71, 92, 142). *Mild to moderate hyperprolactinaemia* (<2000 mU/l) is common in all non-prolactinoma hypothalamo-pituitary lesions, needs to be distinguished from true prolactinomas (>5000 mU/l) and does not usually lead to clinically significant galactorrhoea.

Posterior pituitary dysfunction, particularly central ("cranial") DI, is the hallmark endocrinopathy of germinomas and LCH, being present in up to 90% and 40% of patients respectively at diagnosis (70, 102). However, DI can also occur as a presenting clinical feature for other suprasellar lesions which may be missed if symptoms of polyuria and polydipsia are not elucidated.

Tumour	**Commonest endocrinopathy at presentation**
Craniopharyngioma	GH deficiency, pubertal delay/ arrest
Optic pathway LGG	Central precocious puberty
Pituitary adenoma	Hyperprolactinaemia (prolactinomas)
Suprasellar germinoma	Diabetes insipidus, central precocious puberty (hCG-secreting)
Hypothalamic hamartoma	Central precocious puberty
Langerhans cell histiocytosis	Diabetes insipidus

Table 3: Common endocrinopathies at presentation of various hypothalamo-pituitary lesions. GH, growth hormone; LGG, low-grade glioma; hCG, human chorionic gonadotrophin.

Endocrine dysfunction is under-recognised at presentation, as demonstrated by the discrepancies between spontaneous reports of growth retardation, weight loss/ gain, polyuria and polydipsia compared to their true incidence based on direct enquiry or assessment(41). Longitudinal retrospective studies have shown that growth failure and weight gain can occur up to 3 years before the diagnosis of a craniopharyngioma, especially in the presence of hypothalamic infiltration(143). Since the diagnosis of GH deficiency requires dynamic endocrine testing, and idiopathic CPP can be a normal variant in young girls, a significant underlying lesion may be missed without mandatory neuroimaging, despite studies showing that 14-45% of female patients with CPP have a hypothalamo-pituitary mass(144-146). DI may remain occult in the ACTH-deficient patient, or unrecognised until the patient is water-deprived or rendered effectively adipsic by general anaesthesia, coma or further hypothalamic damage sustained during surgery, with potentially fatal consequences. Lethargy, recurrent infections, somnolence and cold intolerance may be subtle symptoms of ACTH and/ or TSH deficiencies, whilst hypothalamic dysfunction (discussed below) manifesting as hyperphagia, escalating obesity, sleep-wake cycle disturbance and temperature dysregulation may be mistaken for psychosocial dysfunction.

Pre-operative endocrine assessment and management of hypothalamo-pituitary tumours

Due to their relative rarity and a general lack of data on optimum treatment strategies, all paediatric hypothalamo-pituitary tumours should be discussed in a multidisciplinary forum which comprises, at minimum, a neuro-oncologist, neuroradiologist, paediatric endocrinologist and pituitary surgeon. Careful endocrine assessment with appropriate neuroimaging are vital before definitive therapy (Table 4). Early morning cortisol/ ACTH measurements should ideally be performed before any dexamethasone is given for cerebral oedema, alongside paired urine and plasma osmolalities & electrolytes as these will influence perioperative fluid management. Plasma tumour markers (PRL, β-hCG, AFP) should be obtained prior to any surgical intervention regardless of radiological appearances, as both prolactinomas and germinomas can be treated medically without requiring a biopsy. In some cases cerebrospinal fluid β-hCG and AFP may be required to aid diagnosis. Early access to a paediatric endocrinologist enhances diagnostic decision-making and ensures appropriate peri-operative fluid management particularly in the presence of life-threatening salt/ water and hypocortisolaemic crises. If dexamethasone has not been commenced for peritumoral oedema and where a patient's hypothalamo-pituitary-adrenal status is unknown, parenteral hydrocortisone (1-2 mg/kg) should be given at anaesthetic induction and 6-8 hourly thereafter for 48-72 hours, weaning to maintenance doses over 5-10 days according to clinical status until this axis can be formally assessed with a synacthen test. Clinicians should be aware of cortisol's permissive effects on the renal tubule for free water clearance; thus its replacement will unmask occult DI. In this situation, precise fluid balance measurements and the judicious use of desmopressin (0.1-0.2 µg IM/ SC) by an experienced endocrinologist are required. GH, thyroxine and oestradiol/ testosterone supplementation may also be necessary.

Clinical assessment
Height
Weight
Sitting height
BMI
Tanner pubertal stage
Bone age
Endocrine biochemistry
IGF-1/ IGF-BP3
LH, FSH, oestradiol/ testosterone
TSH, free T_4 ± free T_3
Early morning cortisol & ACTH
Early morning paired urine & plasma osmolalities & electrolytes
Tumour markers
PRL
AFP
β-hCG

Table 4: Recommended minimum pre-treatment endocrine assessment for hypothalamo-pituitary tumours. BMI, body mass index; IGF-1, insulin-like growth factor 1; IGF-BP3, insulin-like growth factor binding protein 3; LH,

luteinising hormone; FSH, follicle-stimulating hormone; TSH, thyroid stimulating hormone; T, thyroxine; T_3, triiodothyronine; ACTH, adrenocorticotrophic hormone; PRL, prolactin; AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotrophin.

Rare emaciation/ failure to thrive syndromes

- *Diencephalic syndrome (DS)* – DS is a rare syndrome of severe emaciation first described over 60 years ago typically seen in infants <2 years of age in the presence of a hypothalamic tumour(147). The original description incorporated four "major" criteria – profound emaciation (often leading to a multitude of misdirected investigations for failure to thrive), preserved (or accelerated) linear growth, hyperactivity and euphoria – and three "minor" features: pallor without anaemia, hypoglycaemia and hypotension. There is marked loss of subcutaneous fat despite increased caloric intake. Other associated features result from either tumour location (nystagmus, papilloedema, optic atrophy, vomiting, ataxia) or increased sympathetic tone (sweatiness, tremor). Classically, DS occurs in <10% of hypothalamic LGGs(11, 136), but has also been described in suprasellar high grade gliomas(148, 149), germinomas(150, 151), teratomas(152), ependymomas(153), craniopharyngiomas(154), epidermoid cysts(155) and rarely with non-suprasellar lesions such as brainstem gliomas(156). Since Russell's original description, however, the definition for DS has now too loosely broadened to include all cancer-related cachexia(157), with <4% of patients with DS having onset of symptoms at >2 years of age(150, 158), and some publications reporting adult-onset DS where growth velocity is irrelevant(154, 159), such that it is difficult to determine whether the patients described in these cases truly have DS or not. Its pathophysiology remains poorly understood, although the most consistent biochemical finding is of high random plasma GH concentrations that is neither suppressed by an oral glucose tolerance test, nor further stimulated by insulin-induced hypoglycaemia, with low or normal IGF-1 concentrations, indicative of a GH-resistant state(148, 160, 161). Studies showing increased resting energy expenditure(162, 163) support the theory of a dysregulated metabolism rather than abnormal caloric intake. At the time of writing, the next LGG trial is being designed to incorporate an international study of this rare entity, which is an independent risk factor for death, progression(11) and severe endocrine morbidity(23).
- *Anorexia & eating disorders* – Anorexia nervosa is an over-represented symptom in multiple published case reports of patients with hypothalamic lesions (particularly slow-growing germ cell tumours), with an average delay in diagnosis of nearly 3 years(164), though symptoms tend to resolve with appropriate therapy. Given the ventromedial and lateral hypothalamic location of the hunger and satiety centres, it is reasonable to postulate the effect of a suprasellar lesion on appetite. However, current understanding of the orexigenic and anorexigenic neuroendocrine regulators of tumour-related anorexia is still incomplete, and reports of non-suprasellar CNS tumours presenting with anorexia(157, 165, 166) suggest dysregulation beyond the hypothalamus, whilst the effect of inflammatory cytokines present in disseminated disease (tumour necrosis factor-α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ (IFN- γ)), may also play a role(157). An intracranial lesion needs to be differentiated from true anorexia nervosa, which should fulfil DSM-V or ICD-10 criteria(167, 168)), in all patients presenting with anorexia and weight loss. A full auxological, pubertal and endocrine biochemical assessment should be performed to exclude neuroendocrine disease, particularly in boys where the lower prevalence of anorexia nervosa requires mandatory pituitary neuroimaging. Anorexia nervosa presenting with amenorrhoea may be due to a suprasellar tumour causing hypogonadotrophic hypogonadism(169), and initially normal imaging may not exclude an eventual diagnosis of a tumour, particularly for germinomas(165). Severe weight loss at diagnosis may be a predictor for future hypothalamic obesity(170).

NEUROENDOCRINE DYSFUNCTION AFTER DIAGNOSIS AND/OR TREATMENT

The evolution of endocrinopathy and its association with treatment

Whilst the initial endocrinopathies present at diagnosis are fairly typical for particular tumour subtypes, the pattern of post-treatment endocrine dysfunction in survivors of these lesions is interestingly very similar in frequency and timing. It has long been recognised that there is an evolution in the incidence of dysfunction in each of the hypothalamo-pituitary axes over time, closely mimicking that seen in congenital neurodevelopmental disorders such as septo-optic dysplasia (171). Although the various axes are differentially sensitive to irradiation, with the GH axis being the most susceptible (even at doses as low as 20 Gy), and the ACTH axis being the most robust (130, 172, 173), the similar evolutionary pattern of endocrine dysfunction seen in patients with a wide range of hypothalamo-pituitary lesions even in the absence of therapeutic irradiation suggests that the pattern of deficits is related most strongly to the position of the tumour (and thus recurrent disease) rather than treatment. GH deficiency is thus commonest, followed by gonadotrophin dysfunction (either CPP or hypogonadotrophic hypogonadism), ACTH and TSH deficiency and least commonly posterior pituitary dysfunction, usually presenting as central DI (which is never seen after similar pituitary irradiation doses administered to non-suprasellar tumours)(23, 39, 41, 92, 102, 174-177). Hence, lifelong endocrine follow-up of these survivors with regular clinical and biochemical assessments is vital as all patients with such tumours remain at high-risk for the development of these deficits. An example of a suggested post-treatment risk-based surveillance strategy for follow-up of paediatric craniopharyngiomas is illustrated in Table 5.

Interval from treatment	**Complete Resection**	**Incomplete resection + radiotherapy**	**Incomplete resection + surveillance**
Immediate post-operative period			
Radiology	MRI at 24-72 hours ± CT then MRI at 3 months		
Neurosurgery	For perioperative neurosurgical complications (shunt infections etc.)		
Endocrine	For perioperative fluid balance management (diabetes insipidus, SIADH, salt-wasting)		
Years 1-2			
Radiology	6-monthly MRI	12-monthly MRI	4-monthly MRI
Neurosurgery	3-monthly		2-monthly
Clinical Oncology	-	3-monthly	-
Endocrine	3-6 monthly		
Ophthalmology	3-6 monthly	6-12 monthly	3-4 monthly

Psychology	At 2 years		
Years 3-5			
Radiology	12-monthly MRI		6-monthly MRI
Neurosurgery	6-12 monthly		4-6 monthly
Clinical Oncology	-	6-12 monthly	-
Endocrine	6-monthly		
Ophthalmology	6-12 monthly		6-monthly
Psychology	At 5 years		
After 5 years			
Radiology	At clinician's discretion		12-monthly MRI
Neurosurgery	-		At clinician's discretion
Clinical Oncology	-	12-monthly	-
Endocrine	6-monthly until final adult height 12-monthly until transition 12-24-monthly thereafter		
Ophthalmology	-	12-24 monthly	-
Psychology	At 18 years (career guidance)		

Table 5: A suggested post-treatment surveillance strategy for survivors of paediatric craniopharyngiomas(30)

GH deficiency

GH deficiency affects virtually all survivors of paediatric hypothalamo-pituitary lesions at some stage. If not already present at diagnosis, it is virtually guaranteed to occur after pituitary-directed therapy such as radiotherapy or surgery(41, 178). Diagnosis of GH deficiency requires dynamic endocrine testing with the gold standard being the insulin tolerance test, although this is contraindicated in patients with a history of seizures. Serum IGF-1 and its binding protein IGF-BP3 are less accurate markers of GH deficiency, although they may be useful in severe growth failure in the context of a hypothalamo-pituitary tumour where GH testing is considered too hazardous(179, 180). Paradoxical normal growth may continue despite GH deficiency either due to precocious or accelerated puberty, or the syndrome of "growth without growth hormone", where secondary hyperinsulinaemia occurs due to the rapid weight gain observed post-treatment(181). Both situations deserve prompt investigation and GH substitution which, in replacement doses, does not increase tumour recurrence(182, 183), but promotes anabolism and lean body mass. This should therefore not be delayed beyond 3-6 months after definitive therapy, particularly in patients who have irreversible loss of height from spinal irradiation (e.g. for germinomas)(184).

Gonadotrophin dysfunction

Gonadotrophin dysfunction may manifest in three ways. Firstly, CPP (defined as a testicular volume of ≥4 ml in a boy <9 years or breast budding in a girl <8 years) which, if not already present at diagnosis (e.g. hamartomas, LGGs, germinomas) is increased particularly by radiotherapy(173). There is no evidence that surgical resection of hypothalamic hamartomas, the commonest lesion associated with CPP, improves these symptoms, despite ameliorating the seizures(92). As mentioned above, coexistence of an early puberty with GH deficiency may mask the latter as height velocity may initially appear to be maintained or even accelerated, but not when corrected for bone age. Any child in puberty should therefore concurrently have an urgent assessment of GH secretion and consideration of replacement to restore height in combination with GnRH analogues to delay skeletal maturation if it is felt psychosocially appropriate. It is worth noting that prior CPP does not preclude later pubertal delay or arrest(23).

Pubertal delay or arrest may either be due to hypogonadotrophic hypogonadism from tumour- or treatment-related injury to the hypothalamus (causing GnRH and/ or LH/FSH deficiency) or to primary gonadal failure from systemic chemotherapy (hypergonadotrophic hypogonadism). Patients may fail to enter puberty altogether by the expected age (14 years in boys, 13 years in girls), enter puberty normally and subsequently fail to progress, or demonstrate secondary amenorrhoea (girls) or sexual dysfunction (boys). In this situation concurrent GH deficiency can be corrected simultaneously or 6 months prior to commencing sex steroid replacement to initiate an appropriately-timed pubertal growth spurt. There is no advantage to adult height in delaying sex steroid replacement any further, particularly in light of the benefits on bone mineral accretion(185).

Most chemotherapeutic drugs used in CNS tumour regimens (e.g. carboplatin, vincristine, etoposide) are not considered gonadotoxic, but other high-risk agents such as cyclophosphamide, temozolomide and cisplatin are occasionally used, with their effects being modulated by age at exposure and gender(186). Since it is possible to protect future fertility in boys even as young as 12 years with some masculinisation (Tanner stage 3+ and/ or testicular volume of 8+ mls) by sperm cryopreservation, this should be considered before definitive therapy, even in those not receiving chemotherapy(187). Contrastingly, girls who have achieved regular spontaneous menses should be warned of the reduced window of reproductive capacity and a premature menopause due to a reduced ovarian follicular reserve(188). Notably, patients with hypothalamo-pituitary tumours who have received chemotherapy can potentially have concurrent hypogonadotrophic hypogonadism and primary gonadal failure, compounding the future risk of subfertility.

ACTH deficiency

The hypothalamo-pituitary-adrenal (HPA) axis is fortunately relatively robust to irradiation and chemotherapeutic damage. However, in the context of a hypothalamo-pituitary tumour, the most important diagnostic challenge is to accurately determine adrenal reserve and differentiate reversible dexamethasone-induced ACTH suppression (after treatment for cerebral oedema) from true, permanent ACTH deficiency. Given the lifelong implications of the latter, it is our opinion that the diagnosis should be carefully made ideally with the gold standard insulin tolerance test (ITT) and repeatedly reviewed with time. This may additionally necessitate regular plasma morning cortisol and ACTH measurements and 24-hour cortisol day curves. Although the standard synacthen test (SST) is often used to test adrenal integrity in adults, this supraphysiological stimulus does not test the entire pathway and the integrity of the hypothalamus or pituitary. There is evidence to suggest that in CNS tumour survivors the SST may be less sensitive than the ITT or low dose synacthen stimulation in detecting more subtle degrees of deficiency(189-191). In patients who have received peri-operative dexamethasone for peritumoral oedema, formal testing of the HPA axis may be best left until 2-3 months after substitution with maintenance hydrocortisone as doses can be more safely omitted whilst testing is performed. Testing should be performed in a tertiary paediatric endocrinology unit used to managing patients with multiple endocrinopathies, with routine glucose rescue at 25-30 minutes and hydrocortisone at the end of low-dose (0.1 units/kg) insulin-induced hypoglycaemia or glucagon stimulation. Treatment of adrenal

insufficiency with glucocorticoids may unmask occult DI, and the coexistence of ACTH deficiency, DI and adipsia due to hypothalamic damage can be fatal and should be avoided where possible.

TRH/ TSH deficiency

The thyroid, like the hypothalamo-pituitary-gonadal axis, can be rendered underactive by either central TRH/ TSH deficiency (inappropriately normal/low TSH for a low free T_4 or T_3) due to the tumour itself or surgery, or primary hypothyroidism (high TSH with a normal (compensated/ subclinical) or low (frank) free T_4) from spinal irradiation and/or chemotherapy, with the potential for the two states coexisting in some patients. There is little evidence for the role of irradiation in the former. In the adult cohort studied by Littley *et al.*, no patients treated with low-dose radiotherapy alone experienced TSH deficiency(172). Similarly, Gan *et al.* found that the only independent risk factor for TSH deficiency in LGGs was hypothalamic involvement of the tumour(23). TRH stimulation tests may not differentiate hypothalamic (tertiary) from pituitary (secondary) damage, and serial thyroid function tests or an absent TSH nocturnal surge may be more specific(192).

Primary hypothyroidism can present many years after the initial irradiation or chemotherapeutic insult. Annual thyroid function tests in at-risk children are important for early detection of subclinical hypothyroidism and institution of early treatment, particularly in light of the known effects on the developing brain. Given the known risk of radiation-associated second primary thyroid cancers, the carcinogenicity of nuclear fallouts and the long-term cardiovascular mortality risk of subclinical hypothyroidism, few clinicians would leave a persistently raised TSH in such a patient cohort untreated(193).

Hyperprolactinaemia

The importance of serum prolactin (PRL) measurements in the diagnosis of prolactinomas has already been discussed. Similarly, a rise in PRL levels can occur post-treatment in two situations. In the presence of a prolactinoma, this can indicate tumour “escape” from dopamine agonist (cabergoline/bromocriptine) control requiring further therapy. The more common situation arises where hyperprolactinaemia is due to stalk compression by a progressive sellar or suprasellar tumour or hypothalamic damage. In this situation PRL concentrations are usually <2000 mU/l(194) and patients are unlikely to be symptomatic, with galactorrhoea being unusual(23). Chronic severe primary hypothyroidism will also lead to hyperprolactinaemia due to the stimulatory effects of a raised TRH on the lactotroph.

Posterior pituitary dysfunction (PPD)

Posterior pituitary dysfunction can present itself in three ways – DI, SIADH, or cerebral salt-wasting syndrome (CSW), the latter attributed to hypersecretion of cerebral atrial natriuretic (ANP) and brain natriuretic peptides (BNP) in response to plasma volume expansion by ADH. The latter two syndromes are rare outside the context of an acute cerebral insult and are usually transient, whilst DI may be a presenting feature and/or a permanent post-operative deficit. DI does not develop after cranial irradiation in the absence of a hypothalamo-pituitary tumour or surgery to the area(23, 62). Whilst PPD is the least common form of endocrinopathy, the rapid shifts from hyper- to hyponatraemia in the acute setting can prove life-threatening, as evidenced by a recent retrospective cohort study of optic pathway LGGs with high survival showing showed that nearly 50% of the deaths that occurred were associated with uncontrolled PPD(23). This risk is further increased by coexistent ACTH deficiency, hypothalamic adipsia and treatment with anti-epileptic medications, which have SIADH-like effects.

After hypothalamo-pituitary surgery, PPD presents as a well-described triphasic response in ADH secretion: firstly, immediate but transient DI up to day 2; secondly, SIADH from day 1-14; and finally a second phase of DI, which is usually permanent if it persists beyond 21 days, the preceding SIADH is prolonged or severe, or if extensive surgery

has been performed(195, 196). This triphasic response is thought to result from necrosis of hypothalamic ADH-secreting magnocellular neurons and is seen more often in children than adults (23% vs. 14% in one craniopharyngioma study)(197). The three phases may also occur independently, and CSW may coexist and complicate diagnosis and management. Dramatic changes in sodium concentrations can therefore occur with the inherent risk of seizures, cerebral oedema and death; such patients require high intensity care with precise fluid management supervised by an experienced paediatric endocrinologist. Detailed management of these disorders is beyond the scope of this chapter, but can be summarised in the algorithm seen in Figure 1.

IMMEDIATE POST OPERATIVE MANAG

- **Assess volume status -** Cardiovascular observations, perfusion, oed
  U&E's, glucose and osmolalities, urine SG and urine output. If volume dep
  (NaCl 0.9%). Fluid restrict if oedematous.
- **Fluids -** IV 0.45% NaCl & 5% Dextrose or oral fluids if tolerated.

  Insensible losses - 300mls/m^2/24hrs

  Maintenance fluid - 4ml/kg/hr - first 10kg, 2ml/kg/hr - second 10
  subsequent kg.
- Maintain neutral fluid balance **plus** insensible losses **(i.e. Input = Outp**

EUVOLAEMIC STATE :
Plasma Na^+ 132 - 150mmol/L

HYPERNATRAEMIC STATE:
Plasma Na^+ >150mmol/l
Plasma osmolality > 300

Stable biochemistry and urine output
AND
Neutral fluid balance

CONCENTRATED OLIGURIA
Urine output <1ml/kg/hr
Urine/plasma osmo ratio >1.5
Urine SG >1.010

DILUTE POLYURIA
Urine output > 5ml/kg/hr for 2 consecutive hours
AND
Urine/plasma ratio <1
Urine SG < 1.010

Increase fluid input by continuing maintenance and insensible losses

Figure 1: Algorithm for the management of post-operative salt-water balance disorders(30).

The hypothalamic syndrome

The hypothalamic "syndrome" is loosely defined and usually refers to a constellation of features attributed to hypothalamic dysfunction. Central to it is hypothalamic obesity, a morbid, inexorably escalating obesity (BMI usually >+3 SDS) first described over a century ago(198). It occurs in up to 77% of craniopharyngiomas, 53% of optic pathway LGGs, 40% of pituitary adenomas, 40% of germinomas and 23% of hamartomas(42, 66, 92, 199, 200). Despite this, its pathophysiology is still poorly understood, although it is becoming increasingly evident that both hyperphagia and a dysregulation of anorexigenic and orexigenic hormones contribute(199). Young age at diagnosis, hypothalamic injury by tumour, high dose irradiation or surgery (including biopsies), and multiple endocrinopathies are all risk factors(195, 201). Unlike common obesity, the weight gain is largely resistant to caloric restriction, lifestyle interventions, medical and surgical therapies(202-207).

Other hypothalamic symptoms include sleep-wake cycle disturbances, adipsia, temperature dysregulation, cognitive (particularly memory loss) and behavioural (particularly autistic) disorders. These disorders are even more difficult to treat than replacement of the endocrine deficits. Where endocrine deficits, particularly ACTH deficiency and DI coexist, hypothalamic adipsia is potentially fatal particularly during intercurrent illness and surgery, requiring careful day-to-day fluid management with obligate daily fluid intake and desmopressin dose adjustments. The difficulties in managing patients with panhypopituitarism with concurrent hypothalamic dysfunction should not be underestimated, therefore avoiding these complications must be an important aim of initial therapy.

Conclusion

Paediatric hypothalamo-pituitary tumours are uncommon, and may present with occult or unusual clinical features posing diagnostic dilemmas that incur treatment delays or necessitate prolonged MRI surveillance. Notwithstanding their generally high survival rates, tumour- or treatment-related neuroendocrine morbidity is very significant and not always simply reversible by hormone replacement therapy. Consequently, treatment decision-making should aim to preserve not only visual, but also hypothalamo-pituitary function. Paediatric endocrinologists and pituitary surgeons should be part of the decision-making multidisciplinary team, with radiological, visual and biochemical assessments together aiding management planning. A detailed baseline endocrine assessment is paramount to both diagnosis and treatment and will ultimately improve long-term outcome monitoring, the clarification of tumour- and treatment-related consequences and management of lifelong morbidity. Given the potentially significant reduction in health-related quality of survival, lifelong, age-appropriate follow-up and management within a dedicated multidisciplinary neuroendocrine unit familiar with the complexity of patients' needs is recommended. To achieve this, rehabilitation, reproductive, neuropsychological and vocational services need developing further in parallel with appropriate transition processes to adult services if we are to better manage and improve outcomes for this high-risk group of young patients.

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