Original article

Epileptic Disord 2003; 5: 239-47

The endocrinology of hypothalamic hamartoma surgery for intractable epilepsy

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ABSTRACT – Intractable epilepsy has replaced central precocious puberty (CPP) as the main indication for surgery in patients with hypothalamic hamartoma (HH). However, concern about endocrine complications and the paucity of published endocrine data may dissuade clinicians from recommending HH surgery. We report the preoperative endocrine status and postoperative endocrine findings of patients undergoing HH surgery at our centre.

Twenty-nine patients aged 4-23 years (mean 10 years) underwent detailed clinical assessment and biochemical testing of the hypothalamic-pituitary axis before and after transcallosal resection of their HH. The perioperative evaluation included comprehensive evaluation of pubertal status, growth, weight, thyroid and adrenal function, and osmoregulation.

Forty-five percent of patients had CPP at presentation and this was not altered by HH surgery. Asymptomatic deficiencies in thyroid hormone, growth hormone and cortisol response were identified in several patients prior to surgery, and biochemical CPP was present in four, clinically prepubertal children. Free thyroxine fell after surgery in the majority, and to clinically significant levels prompting treatment in 5 patients. Low growth hormone was present in 5/8 patients who had had previous HH surgery and in 6/29 following transcallosal surgery at our centre; short stature did not result during the period of follow-up. Hypernatraemia developed in most patients postoperatively with sodium > 150 mmol/L seen in 16 (55%) patients; however, this was asymptomatic, not often associated with polyuria, and transient; no patient required ongoing antidiuretic hormone replacement. Appetite stimulation and early postoperative weight gain occurred in 45% patients, but resolved in half.

Disturbance of endocrine function may be clinically silent and should be routinely evaluated prior to HH surgery for intractable epilepsy. Following surgery, hypernatraemia, low thyroxine, low growth hormone, and weight gain are the main endocrine problems encountered. Prior, unsuccessful surgery may be a risk factor for endocrinopathy. Except for weight gain in some patients, these postoperative endocrine disturbances appear to be transient, mild or asymptomatic, and easily treated where necessary. Long term follow-up of growth and sexual development in a large series of patients is required.

KEY WORDS: hypothalamic hamartoma, central precocious puberty, epilepsy surgery, hypothalamic-pituitary axis

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Presented at the International Symposium on Hypothalamic Hamartoma and Epilepsy, Montreal Neurological Institute, Montreal, Canada, November 29th 2001.

Introduction

The association between central precocious puberty (CPP) and gelastic seizures was first described in a child who was found to have a hypothalamic tumour attached to the tuber cinereum and mammillary bodies [1]. Subsequent reports of this rare association [2, 3] adopted Le Marquand and Russell's term hypothalamic hamartoma (HH) for these developmental lesions [4]. CPP is believed to be the most frequent presenting clinical feature of HH [5], although the true incidence of HH and the relative frequencies of its clinical manifestations are not known [6]. In our large, tertiary-referral paediatric centre, less than one new case of HH per year is identified because of CPP. From a selected review of the literature undertaken by Tassinari *et al.* [7], it was estimated that only 30% of patients with HH and gelastic seizures also have CPP. As magnetic resonance imaging (MRI) has become more widely available and the nature of epilepsy in patients with HH is better appreciated, the proportion of diagnosed cases of HH with epilepsy has probably increased.

Surgical removal of HH was first attempted for the purpose of ameliorating CPP [8], but with the advent of effective medical treatment using gonadotrophin-releasing hormone analogues [9], surgery for CPP alone is now rarely performed. As recognition of the devastating nature of the refractory and often progressive epilepsy associated with HH has grown [10], surgery directed towards removing, destroying or disconnecting these lesions is being increasingly employed [11-16].

HH surgery carries a risk of endocrine complications and the potential to alter the course of any associated CPP. However, description of endocrine consequences of HH surgery has been limited and the nature of any endocrine assessments performed largely unstated [11]. Recognising this deficiency in the literature and the inherent endocrine risks associated with HH surgery, we developed a detailed perioperative protocol for endocrine evaluation and management in patients undergoing transcallosal, microsurgical resection of HH for intractable epilepsy at our centre [11]. We report the preoperative endocrine status and perioperative endocrine findings in this large series of patients, these issues being relevant to other surgical treatments for HH.

Methods

We assessed and operated on 29 patients with HH and intractable seizures, aged 4-23 years, at the Children's Epilepsy Program of the Royal Children's Hospital (RCH) in Melbourne, between July 1997 and July 2002. Twenty-four patients underwent surgery at monthly intervals over the last two years; 22 of these were referred from overseas. The transcallosal surgical technique and the neurological, neuropsychological and ophthalmological assessments performed before and after surgery have been previously described [11]. Previous surgical treatment of the HH had been undertaken in eight patients, including attempted subfrontal or pterional resection in seven, radiofrequency thermocoagulation in three, and stereotactic radiosurgery in one.

An endocrinologist (MZ) assessed each patient prior to surgery. Historical information sought included the age of onset and progress of pubertal development, the usual feeding and drinking behaviours of the patient, and patterns of weight increase and growth. Clinical examination included measurement of height and weight, Tanner staging of pubertal development [17], and Prader orchidometry in boys. The consultation included counselling of the patient and parents with regard to potential endocrine complications and particularly the anticipation and avoidance of postoperative weight gain where possible, by providing information about potential change in appetite and thirst in the immediate postoperative period.

Perioperative testing

A protocol of endocrine tests was developed after surgery in the first few patients at our centre, and was applied rigorously to the patients seen at monthly intervals between March 2000 and June 2002. Preoperative measurements of basal cortisol, follicle-stimulating hormone (FSH), luteinising hormone (LH), testosterone (in males), estradiol (in females), thyroid-stimulating hormone (TSH), free thyroxine (FT4), prolactin, osmolality and electrolytes were performed for each patient.

In 27/29 patients, dynamic testing of growth hormone and cortisol reserves was performed. A glucagon stimulation test [18] was used in preference to the insulin tolerance test because it poses less risk of hypoglycaemia in children [19]. Following an overnight fast, patients were administered intramuscular glucagon 0.1 mg/kg up to a maximum of 1 mg. Glucose, cortisol and growth hormone were measured at time zero and every 30 minutes for the next 3 hours. In 25/29 cases, stimulation testing of pituitary gonadotrophin production was performed using an intravenous luteinising hormone-releasing hormone (LHRH) test [20]. LHRH 100 µg was administered immediately following baseline sampling of LH and FSH; samples were repeated every 15 minutes over the next hour. The glucagon and LHRH stimulation tests were performed concurrently. Gonadotrophin analogues were continued as prescribed and not withheld prior to hypothalamic-pituitary axis testing.

TSH, FT4, GH and cortisol were measured by chemiluminescent radioimmunoassay on an Immulite® system (Bio-Mediq DPC, Doncaster, Victoria, Australia); LH, FSH and prolactin were measured using a similar technique on an ACS:180® system (Bayer Diagnostics, Scoresby, Victoria, Australia).

Postoperative management

Monitoring of fluid balance was strictly observed. A urinary catheter inserted in the operating theatre was left in postoperatively until somnolence had resolved and accurate urine measurements could be guaranteed. Hourly urine output was measured (while the catheter was in place), or calculated. Reporting levels for nursing staff were set at greater than 4 ml/kg/hr urine output over two consecutive hours. Urine and serum osmolality and plasma sodium were measured six-hourly for the first 48 hours, then 6-24 hourly depending on the clinical picture for the remainder of the first postoperative week. Hartmann's solution was administered intraoperatively, replaced on the ward with a solution of 30 mmol NaCl and 40 g glucose per litre (4% DW and 1/5 N saline), given at maintenance fluid rates (calculated by weight) until normal oral intake was re-established. Use of small doses of intranasal desmopressin (2.5-5 µg) for the treatment of hypernatremia, with or without diabetes insipidus, was at the discretion of the treating endocrinologist. Our current practice is to increase water intake rather than administer desmopressin, provided there is no persistent polyuria, the patient is asymptomatic and the sodium is not rising rapidly.

Intravenous hydrocortisone was administered with induction of anaesthesia, to five patients with demonstrated inadequate cortisol reserves on preoperative testing. Postoperatively, dexamethasone was given six-hourly for the first 24 hours to all patients, and then tapered over 4 days according to the neurosurgical protocol.

The endocrine protocol was repeated postoperatively, 2 to 3 weeks after surgery in 23/29 patients and two months to one year after surgery in six. The proximity of the postoperative testing to surgery was due to the great proportion of overseas patients in this series. Measurement of weight and height was repeated prior to patients returning home. Parents of overseas patients were encouraged to report on weight and height at regular intervals postoperatively and any investigations and clinical assessments performed after return were communicated to us, though follow-up was less than ideal. Personal follow-up of the Australian patients continued at this centre.

Results

Pubertal status and gonadotrophins

Thirteen patients (45%) had a history of precocious pubertal development. Onset of CPP occurred between 4 months and 8 years of age (mean 3.5 years), and was the first diagnosis made in seven patients. These children had infantile onset of CPP (less than 10 months), but in retrospect had been having gelastic seizures since the neonatal period, most often misdiagnosed as infantile colic.

Eight patients had prior medical treatment for CPP and, at the time of preoperative assessment, four were receiving monthly intramuscular depot injections of leuprolide acetate and one was taking cyproterone acetate daily. Of those patients receiving leuprolide, only one had advanced pubertal hair and breast development for their age, and none had a biochemical pubertal response to LHRH stimulation. Of those with a history of CPP who were either untreated or receiving only cyproterone acetate at the time of assessment, four (45%) were clinically pubertal. In addition, four patients aged 4.5-6 years with no past history or clinical signs of CPP, had pubertal gonadotrophin responses to LHRH stimulation at preoperative testing, indicating biochemical CPP.

Two patients with CPP who were untreated at the time of surgery began treatment shortly after, as there was no biochemical evidence of resolution following surgery. One patient early in our series developed clinical signs of CPP in the months following surgery, but had insufficient testing to exclude biochemical CPP before surgery. In two young patients with biochemical CPP that was not clinically apparent, pubertal FSH and LH responses to LHRH reverted to normal following surgery *(figure 1B)*. Overall, it appeared that the course of CPP and pituitary gonadotrophin production was not affected by surgery in this series.

Thyroid function, growth hormone, cortisol and prolactin

Two patients had subnormal FT4 levels with normal TSH concentrations prior to surgery, neither of whom had had previous HH surgery. Another patient had undergone two previous HH resection attempts and was receiving supplemental thyroxine sodium at the time of referral. At the initial postoperative evaluation, FT4 levels had fallen from the preoperative value in most cases *(figure 1C)*. Falls to subnormal levels occurred in eight patients. In four, the postoperative FT4 was between 8.9 and 10 pmol/L and was interpreted in the early postoperative period as consistent with a 'sick euthyroid' state. The other four patients had levels below 8 pmol/L and were either started on supplemental thyroxine sodium at that time (two patients), or after subsequent testing remained abnormal (two patients). One other patient was given thyroxine after repeat testing some months after surgery showed persistently low FT4. Thus, six patients are currently receiving thyroxine (five following transcallosal surgery), although the long-term requirement for supplementation in these patients is unknown at this stage.

Nine patients had subnormal peak GH responses to glucagon stimulation prior to surgery; five peak levels were in the partially deficient range (10-19 mU/L), while four were severely deficient (< 10 mU/L) *(figure 1D)*. Five of these nine patients had previous HH surgery ($P = 0.04$, one-tailed Fisher's exact test). None were short in stature, however eight were obese (body mass index greater than

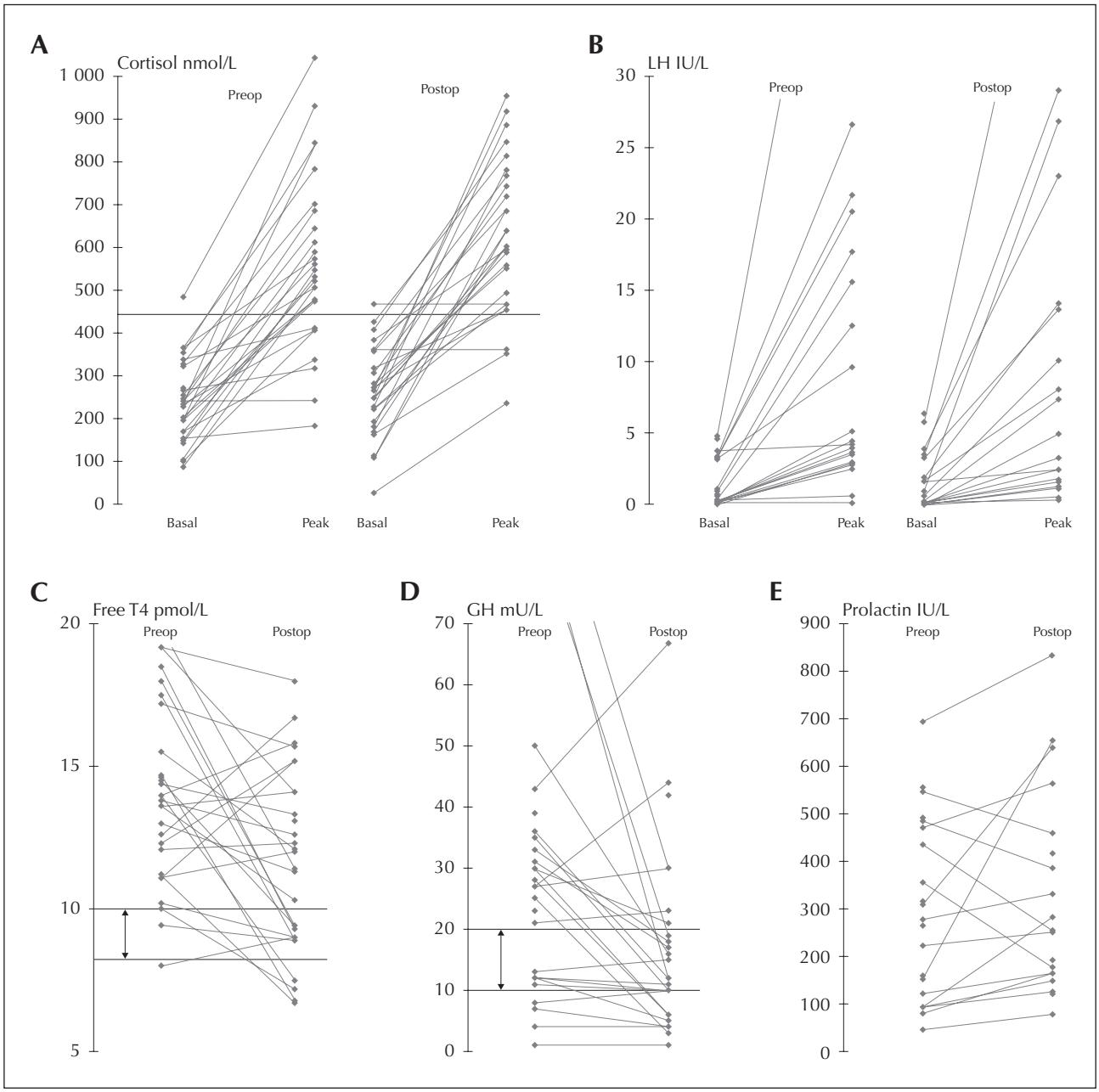

Figure 1. Preoperative and postoperative assessment of anterior pituitary function. (A) Results of glucagon stimulation testing of cortisol production, with basal and peak (stimulated) cortisol shown for each patient (points connected by a straight line). Normal peak cortisol levels are twice basal, or greater than 450 mmol/L (horizontal rule). Five patients had an inadequate cortisol rise above basal level before surgery, but no patient developed any new cortisol deficiency. **(B)** Results of luteinising hormone-releasing hormone (LHRH) stimulation testing of luteinising hormone (LH) production, with basal and peak (stimulated) LH shown for each patient (points connected by a straight line). Any increase from basal levels is consistent with pubertal pituitary function. Two children below 6 years of age with precocious pubertal LH responses before surgery, showed normalization of this test after surgery, but overall, pubertal status was not affected by surgery. **(C)** Free thyroxine (T4) levels fell to subnormal levels (less than 10 pmol/L) in eight patients following surgery, four to within a range consistent with a 'sick euthyroid' state of convalescence from surgery (double-headed arrow between horizontal rules). Four patients with levels below this range, plus one with a normal initial postoperative free T4 required thyroxine sodium supplementation. **(D)** Peak growth hormone levels in response to glucagon stimulation shown before and after surgery (points connected by a straight line). Prior to surgery, five patients fell within the partially deficient range (double-headed arrow between horizontal rules) and four were severely deficient. Postoperatively, six patients developed deficient peak GH levels. Short stature was not observed in this cohort prior to surgery and growth hormone supplementation has not been required since. **(E)** Prolactin levels rose above preoperative levels in a few patients, but significant hyperprolactinaemia did not occur.

the 98th percentile for age) and seven had a history of precocious puberty, both of which result in taller than expected stature for age and mid-parental height expectation. Postoperatively, six patients developed deficient peak GH levels where these had been normal before surgery. Growth in these children continues to be monitored and thus far none have required GH supplementation (follow-up of 4-22 months).

Five patients had inadequate increases of cortisol above basal levels in response to glucagon stimulation prior to surgery *(figure 1A)*, three of whom had previous HH surgery ($P = 0.11$, one-tailed Fisher's exact test). Two of these three patients had similarly inadequate responses after the transcallosal surgery, but no patient developed new cortisol deficiency in our series. There was a tendency for prolactin levels to increase following surgery *(figure 1E)*, but significant hyperprolactinaemia was not seen. Levels of 450-1000 IU/L are commonly seen when hypothalamic lesions are present.

Fluid balance and sodium

Preoperative plasma sodium values were normal in 28/29 patients *(figure 2)*. One patient who had previously undergone a partial resection of the HH via a pterional approach, and two stereotactic radiosurgical procedures had a preoperative sodium of 150mmol/L.

Postoperatively, only three patients had sodium concentrations within the normal range (135-145 mmol/L) in every postoperative sample taken; two of these patients had only a few samples taken. Sodium rise was seen within 24 hours in most cases and stabilized at a mean level of 145 mmol/L, 3 mmol/L higher than the preoperative mean *(figure 2)*. Peak values above 150 mmol/L were recorded in 16 patients (55%), and values above 160 mmol/L were seen in three. The two patients with the highest peak sodium concentrations recorded (165 mmol/L), both had previous HH surgery complicated by subcortical infarction and included the patient with the high preoperative level. However, no significant association was found between a history of previous surgery and the level of hypernatremia. No patient appeared symptomatic of their hypernatraemia, though somnolence and seizures were seen in the early postoperative period in many patients. At the end of the first postoperative week, 17 patients (58%) had normal sodium (less than or equal to 145 mmol/L), 10 patients (35%) had values between 146 mmol/L and 150 mmol/L, and 2 (7%) had levels above 150 mmol/L. At last follow-up, these proportions had not changed, however we have records of sodium concentration beyond the first postoperative month in only six patients.

Postoperative polyuria in association with hypernatraemia was present in only 12 patients. In most cases, owing to the short duration of the polyuria, it was not possible to distinguish between a normal postoperative diuresis resulting from liberal intraoperative intravenous fluid administration, and true diabetes insipidus. Desmopressin was given to 19 patients; up to three doses were given in 13 cases, and two patients required six and seven doses respectively. Three patients required desmopressin for hypernatremia (without polyuria) beyond the first postoperative week; these patients received supplementation for

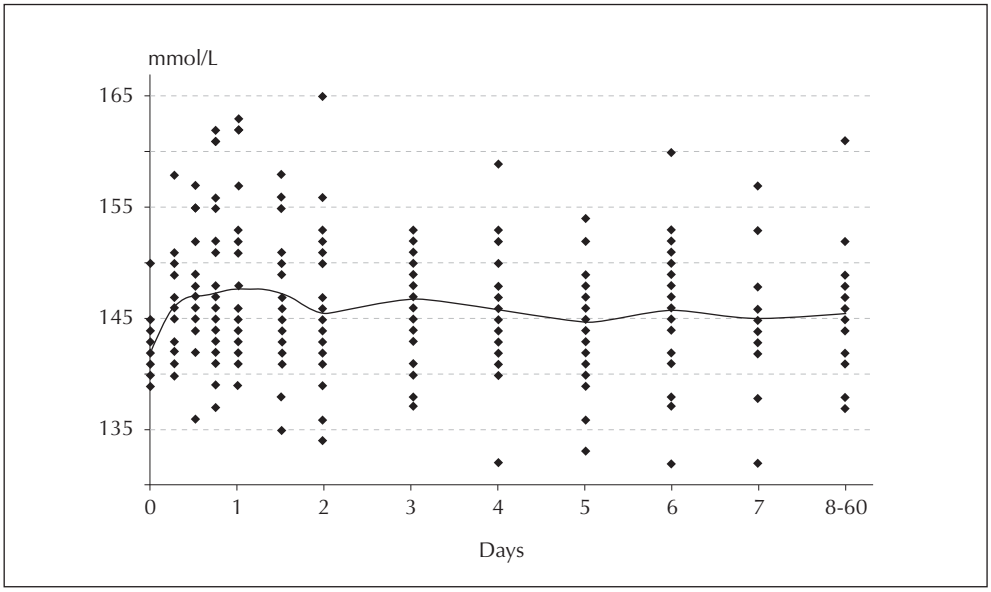

Figure 2. *Modified scatterplot of plasma sodium against time, preoperatively (0 days) and following resection of hypothalamic hamartoma in 29 patients. One sodium measurement per time category was included for each patient, and points for patients with the same value overlap. The last sodium measurements were performed between 8 and 60 (mean 23) days after surgery in 23 patients. The curved line shows the mean sodium for the group at each time interval.*

between 3 and 11 months, but none has an ongoing requirement, 15-16 months following cessation of supplementation in each case.

Appetite and weight

Thirteen patients were overweight at the time of preoperative assessment *(figure 3)*, with both weight and body-mass index (BMI) greater than the 95th percentile for age. Five overweight patients had a history of other surgical treatment of the HH and nine had a history of CPP. Four overweight patients with a history of CPP were receiving medical treatment with either leuprolide acetate or cyproterone acetate. Not surprisingly, the association between overweight and a history of CPP was significant ($P = 0.027$, two-tailed Fisher's exact test).

Appetite stimulation with a tendency to hyperphagia was seen in the early postoperative period in 13 patients. In many cases this was amenable to disciplined regulation of food intake with parental cooperation and dietary advice. In children with associated autistic spectrum disorders, postoperative memory disturbance, or both, appetite stimulation was difficult to manage using behavioural techniques alone. Two patients were prescribed dexamphetamine 5 mg twice daily as a short-term measure to suppress appetite and this was suggested for one other patient after their return home. Clinically significant weight gain (BMI increase > 2.5 kg/m^2) was observed in 10 of 22 patients (45%) for whom weight measurements performed 3-18 months after surgery are available. Five of these patients showed subsequent arrest of weight gain or some weight loss, with a return towards previous percentiles *(figure 3)*. The weight gain continues to be a concern for five patients, 3-40 months (mean 24) after surgery. There was no association between postoperative weight gain and previous HH surgery, preoperative weight or pubertal status.

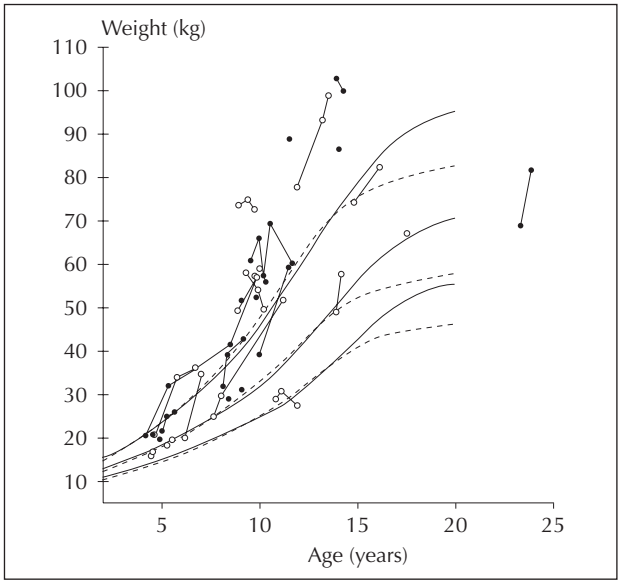

Figure 3. Weight-for-age in children undergoing hypothalamic hamartoma resection. *Preoperative (first point) and postoperative (subsequent points) weights are shown as connected points (open circles for girls, solid circles for boys). The curved lines are the 5th (bottom), 50th (middle) and 95th (top) percentiles of weight-for-age for both girls (dashed lines) and boys (solid lines), according to the National Center for Health Statistics 2000 CDC clinical growth charts: USA (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm). Thirteen patients were overweight at the time of preoperative assessment. Ten patients experienced clinically significant early weight gain following surgery; five showed subsequent return towards preoperative percentiles and five have ongoing overweight concerns.*

Discussion

Hypothalamic control of endocrine function

The neurendocrine hypothalamus can be divided into magnocellular and parvicellular neurosecretory systems. The large cells of the supraoptic and paraventricular nuclei define the supraoptic region of the hypothalamus and constitute the magnocellular secretory system [21]. They project their axons to the posterior lobe of the pituitary via the infundibulum, where they release stored antidiuretic hormone (ADH) and oxytocin directly into the peripheral circulation. ADH is released in response to a rise in serum osmolality (detected by osmoreceptors in the preoptic area), in response to low circulating plasma volume (detected by left atrial stretch receptors), and in response to low blood pressure (detected by baroreceptors in the aorta and carotid arteries) [22]. Disturbances of ADH secretion, thirst mechanisms, or both can result from disruption of osmoreceptors in the preoptic and supraoptic region, whereas damage to the supraoptic and paraventricular nuclei or pituitary stalk will impair ADH secretion but not thirst. Hypernatraemia will develop if the resultant increase in dilute urine output is not met by increased water intake [23].

As reviewed by Page [24], the small peptidergic neurones of the parvicellular secretory system are found in the infundibular and dorsal paraventricular nuclei, and also in a 3-4 mm thin zone of periventricular cells extending along the anteroposterior length of the hypothalamus. The infundibular nucleus (arcuate nucleus of the rat) occupies the floor of the third ventricle and is continuous with the periventricular zone in the lateral walls. The exact location of many of the various peptides in these nuclei has not been determined in humans, but they include LHRH, somatostatin, growth hormone-releasing hormone, thyrotropin hormone-releasing hormone, corticotropin-releasing hormone and dopamine-secreting cells [24]. The axons of these nuclei project to the median eminence in the floor of the third ventricle and the releasing factors then travel by a portal venous system to the anterior lobe of the pituitary where they act to stimulate (or in the case of

somatostatin and dopamine, inhibit) pituitary hormone release [25].

Central nervous system control of appetite, food intake and weight is complex. It has long been known that bilateral destruction of the medial hypothalamus in the tuberal region produces both hyperphagia and weight gain, whereas destruction of the lateral hypothalamus bilaterally produces anorexia [26]. This led to designation of the ventromedial nucleus of the hypothalamus as the 'satiety centre', and the lateral hypothalamic area as the 'hunger centre'. More recently, a number of neuropeptides active in the stimulation (orexigenic) or suppression (anorexigenic) of food intake have been identified, and these are differentially expressed in tuberal region nuclei of rodents. As summarized by Schwartz *et al.*, the arcuate nucleus in these animals has an important role in transduction of leptin-mediated adiposity signals into neuropeptide transmission, and this may in turn influence activity of the ventromedial nucleus and lateral hypothalamic area [27].

Endocrine dysfunction and hypothalamic hamartoma

The association between HH and CPP is well established. Postulated mechanisms of CPP in HH include autonomous LHRH secretion within the hamartoma [28], and induction of hypothalamic pubertal neurendocrine function by HH secretion of transforming growth factor alpha [29]. Pulsatile increase in serum LH and FSH followed a gelastic seizure in one 13-year-old girl with HH and normal pubertal development [30], but the significance of this observation in relation to CPP in HH is unknown. Obesity is common in children with CPP, but girls with HH have a higher BMI before medical treatment than do those with idiopathic CPP [31].

Hypothalamic hamartoma may be associated with Pallister-Hall syndrome, a rare entity that also features polydactyly, anogenital and laryngeal anomalies [32]. The original description of the syndrome emphasised its neonatal lethality associated with panhypopituitarism and hypoadrenalism [33]. Less severely affected individuals have been reported with CPP [34], growth hormone deficiency [35], or both [36].

Growth failure, diabetes insipidus and hypogonadism have not been described in patients with isolated HH, in contrast to the frequent occurrence of these at presentation of other hypothalamic pathologies (astrocytoma, glioma, and craniopharyngioma). The absence of clinically significant hypopituitarism in patients with HH may relate to the developmental nature of the lesion, its tendency to displace rather than replace or infiltrate normal structures in development, and its lack of postnatal growth potential. However, in this series, we found asymptomatic deficiencies of hypothalamic-pituitary axis function on detailed preoperative endocrine evaluation of several patients who had not undergone surgery, including low FT4 in two, GH deficiency in four, and inadequate cortisol response in two. While the clinical significance of these findings is questionable and their cause uncertain, without comprehensive preoperative investigation these deficiencies may have been erroneously attributed to surgical morbidity if discovered postoperatively. Also, the use of hydrocortisone with anaesthesia is necessary for patients with inadequate preoperative cortisol reserves.

Endocrine dysfunction following hypothalamic surgery

Lesions involving the hypothalamus for which resective surgery may be indicated include craniopharyngiomas, some optic pathway gliomas and HH. Endocrine morbidity is a well-recognized complication of surgery for craniopharyngioma, with permanent diabetes insipidus reported in 80 to 93% of children after radical resection, major hormone replacement (two or more) necessary in 85 to 95% of patients, and obesity seen in up to 52% of patients [37]. Panhypopituitarism is said to occur in 75% of children after large or complete craniopharyngioma resection, whereas only 5% are left endocrinologically intact [38]. Given the proximity of some HH to the pituitary stalk, the attachment to the tuberal region in many cases and the intrahypothalamic nature of HH associated with epilepsy [39], some endocrine dysfunction following effective HH surgery might be expected to occur. Fear of endocrine morbidity such as is seen after craniopharyngioma surgery could deter the neurosurgeon from attempting to resect a lesion that is both nonproliferative in nature and benign in histological appearance [40], despite the refractory and severe epilepsy and devastating neurobehavioural consequences that occur in many children with HH [10].

Endocrine dysfunction is sparsely reported in the literature following HH surgery. In our review of 46 cases, four patients were reported with transient diabetes insipidus and one with transient appetite stimulation [11]. In a recent series of 13 cases, Palmini *et al.* reported one patient with a transient syndrome of inappropriate ADH secretion, and one patient with persistent hyperphagia [12]. In contrast, of the eight patients assessed at our centre who had had previous HH surgery, three had isolated GH deficiency, one had isolated cortisol deficiency, one had both GH and cortisol deficiency, and one had both of these in combination with hypernatraemia (150 mmol/L). This last patient is case #9 in the report of Palmini *et al.* (not reported with postoperative endocrinopathy), and highlights the need for detailed and long-term endocrine follow-up.

The incidence of endocrinopathy and weight gain after transcallosal HH resection in our series of 29 patients contrasts with endocrine deficits and obesity seen after other surgical interventions for different hypothalamic tumours (as above). The mild and mostly transient nature of the endocrine dysfunction observed in our patients may relate firstly to the anatomical relationship of the HH to the

neurendocrine hypothalamic nuclei, pituitary stalk and gland, and secondly, to the surgical approach and technique. Hypothalamic hamartomas are quite unlike expansive, infiltrative craniopharyngiomas; in trying to effect total resection of a craniopharyngioma, the surgeon is mindful of the risk of tumour recurrence and is accordingly more aggressive in dissecting adjacent involved structures [41]. Transcallosal, interforniceal resection of HH on the other hand, proceeds from within the lesion in the third ventricle, and there is no requirement to dissect or retract normal hypothalamic tissue in order to gain access. Structures below the pial floor of the third ventricle, such as the pituitary stalk and gland, are not encountered. Also, unilateral or predominantly unilateral attachment of the HH to the hypothalamus proper assists in preservation of hypothalamic nuclei and endocrine function.

The ventromedial and infundibular nuclei are at risk of operative damage with any surgical treatment of HH, as the lesion is usually attached to the floor of the third ventricle and to one or both lateral walls in the tuberal and mammillary regions. In our series, postoperative appetite stimulation was seen in 13 patients, early weight gain in 10 and persistent overweight in five patients. Although leptin-mediated metabolic changes are the likely explanation in the latter group, factors contributing to appetite stimulation in the early postoperative period may include the use of dexamethasone, anxiety, disorientation, short-term memory disturbance, altered thirst, lowered FT4, developmental disorders including autism, and parental nurturing instincts. In our experience, immediate postoperative management of parent-child interaction to minimise postoperative weight gain in the first two weeks, plays a major part in reducing long-term weight issues. Where persistent appetite stimulation is a problem, pharmacological suppression of appetite may be indicated.

Postoperative increase in sodium levels was almost universal; however, diabetes insipidus was uncommon, symptomatic hypernatremia did not occur and permanent salt-water imbalance was not seen. In the early postoperative management of hypernatraemia, the use of desmopressin should probably be limited to patients with definite diabetes insipidus, symptomatic hypernatraemia or rapidly rising sodium. In other patients, increased water intake and sodium monitoring should be sufficient, as hypernatremia alone may merely reflect transient impairment or resetting of the osmostatic mechanism which can be expected to resolve spontaneously. Although to our knowledge none of our patients has persistent disturbance of salt-water balance, it is possible that some may have subclinical impairment of ADH secretion or thirst that would only manifest under extreme conditions such as water deprivation or excessive losses.

Low GH response to stimulation and low FT4 seen in several patients who had undergone surgery previously and in our series, may reflect early postoperative changes that resolve with time. This is suggested by the normal growth and lack of supplementation requirement in those few children with postoperative GH deficiency. Longer follow-up of growth, and biochemical testing will provide valuable information in this respect.

Despite valid concerns, the risk of significant endocrine dysfunction following transcallosal HH surgery for intractable epilepsy appears low. Accordingly, surgical decisions should be based on other criteria, such as the likelihood of seizure control, risk of memory impairment and stroke. Comprehensive clinical and biochemical assessment of endocrine function before surgical treatment of HH should be performed routinely, as endocrinopathy other than CPP may be occult, but significant in the context of surgery. Preoperative consultation with an experienced endocrinologist is essential in the counselling of patients and their families, and in the anticipation of postoperative appetite stimulation and weight gain. Postoperative follow-up should include ongoing clinical and biochemical assessment. Long-term data are needed in relation to pubertal development and growth of children, and sexual function in adulthood.

Acknowledgements

We wish to thank the medical and nursing staff of the Endocrinology and Neurosurgery departments, Royal Children's Hospital, for their assistance in the perioperative management of our patients; Elizabeth Grimmer, RN, for coordinating the investigation of each patient; staff of the Day Medical Unit, Royal Children's Hospital, and the endocrine laboratories of the Women's and Children's Health Care Network for conducting the biochemical investigations. □

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