Archives of Disease in Childhood 1996;75:108–114

Growth and endocrine sequelae of craniopharyngioma

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Abstract

The growth and endocrine sequelae of 75 children (33 girls and 42 boys) with craniopharyngioma, treated from 1973 to 1994, were studied by retrospective review and by follow up assessment in 66 survivors, with a mean time from initial surgery of 6.7 years (range 1.5 to 19.8 years). Although infrequently complained of, 71% of patients had symptoms to suggest an endocrinopathy at diagnosis. After surgery, multiple endocrinopathies were almost universal, such that 75% of children had panhypopituitarism at follow up. Hypoadrenal crises in association with intercurrent illness contributed significantly to morbidity and mortality, as did the metabolic consequences of concomitant antidiuretic hormone (ADH) insufficiency and absent thirst. Final height in 25 patients was significantly below genetic target height, particularly in the girls, with loss of height potential occurring during the pubertal years. The endocrine morbidity associated with craniopharyngioma and its treatment remains high but manageable with appropriate hormone replacement. However, the combination of ADH insufficiency and an impaired sense of thirst following aggressive surgery and severe hypothalamic injury remains one of the most complex management problems.

(*Arch Dis Child* 1996;75:108–114)

Keywords: craniopharyngioma, endocrinopathies, hypothalamic injury, final height.

Craniopharyngiomas account for approximately 9% of all intracranial tumours in childhood but are the commonest tumours to involve the hypothalamo-pituitary region. Multiple symptomatology is often present by the time of diagnosis but complaints of headache, nausea, and vomiting secondary to raised intracranial pressure and visual disturbance are more commonly voiced than symptoms referable to endocrine dysfunction. However, Sorva reported that in 19 out of 22 children with craniopharyngiomas, growth failure preceded the diagnosis by a mean of 4 years.[1] Other reports are quite variable (20-60%) as to the degree of growth hormone insufficiency and hypothalamo-pituitary dysfunction before treatment.[2-4] This is in contrast to the situation after treatment (which in most cases is primarily surgical), when both anterior and posterior pituitary dysfunction are almost universal, irrespective of whether or not complete tumour resection is achieved. With timely institution of hormone replacement treatment, these endocrinopathies can now be managed with relative ease. However, intractable obesity secondary to loss of satiety and diabetes insipidus with an impaired sense of thirst are complications almost exclusive to radical surgery and reflect significant hypothalamic injury. The associated morbidity may prevent normal psychosocial integration and contributes to the ongoing controversy regarding optimal management of these tumours in childhood.

We report the growth and endocrine outcome of 75 children with craniopharyngioma treated from 1973 to early 1994, with particular emphasis on current management problems and their relation to the treatment methods employed.

Methods

PATIENTS

Thirty three girls and 42 boys diagnosed as having a craniopharyngioma between the ages of 1.0 and 16.3 years (mean 6.7 years) and treated from 1973 to early 1994 were studied. At diagnosis 29 children were under 5 years of age, 33 were between 5 and 10 years, and 13 over 10 years.

NEUROSURGICAL MANAGEMENT

Primary surgical management entailed an attempt at complete tumour removal by a transcranial procedure in 58 patients (77%) and by the trans-sphenoidal approach in one other child. With the exception of two children who underwent cyst aspiration followed by conventional external beam irradiation (one case) and intracystic injection of radiolabelled yttrium (one case), subtotal tumour excision was attempted in the remaining patients. Eighteen children required second or subsequent craniotomies for tumour recurrence and 37 patients (49%) received radiotherapy, either electively following initial surgery (16 cases) or after recurrence of their tumour (21 cases). Of 40 patients presenting with hydrocephalus, 24 (60%) had some form of ventricular drainage procedure performed either pre-, per-, or postoperatively.

There were no immediate postoperative deaths, but nine children have subsequently died from their tumour or related sequelae 0.3 to 15.4 years (mean 6.4 years) after initial surgery.

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Accepted 23 April 1996

Table 1 Presenting symptoms attributable to hypothalamo-pituitary dysfunction in 75 patients with craniopharyngioma; values are number or number (%)

Symptoms	Presenting complaint	Present on direct inquiry	Total
Growth failure/short stature	10	15	25(33)
Increased thirst/polyuria/enuresis	1	20	21(28)
Anorexia/poor weight gain	6	17	23(31)
Rapid weight gain	1	10	11(15)
Temperature intolerance	0	4	4(5)
Frequent infections with lethargy	0	4	4(5)
Delayed puberty	3	1	4(5)
Precocious puberty	0	0	0(0)

RETROSPECTIVE REVIEW AND FOLLOW UP ASSESSMENT

Information was obtained from the clinical records either retrospectively (65 cases) or prospectively in 10 cases diagnosed after October 1992. After this date, clinical and magnetic resonance imaging (MRI) follow up assessments have been undertaken in the 66 survivors, with a mean follow up time of 6.7 years (range 1.5 to 19.8 years) from initial surgery. Endocrine evaluation comprised a review of current pituitary hormone replacement therapy and fluid balance status, as well as anthropometric and pubertal assessment.

PREOPERATIVE ENDOCRINE EVALUATION

Whenever possible—depending on clinical status, and providing patients were not already on high dose steroids—a 9 am plasma cortisol measurement was taken before surgery, together with serum prolactin, total thyroxine, and thyroid stimulating hormone; and measurement of early morning paired plasma and urine electrolytes and osmolalities.

POSTOPERATIVE ENDOCRINE EVALUATION

All patients had a pharmacological assessment of anterior pituitary function within two months of surgery, unless radiotherapy followed immediately after operation, when assessment was delayed until after its completion. Provocative tests of pituitary secretion, using either intramuscular glucagon (0.1 mg/kg, to a maximum of 1 mg) or intravenous insulin (0.05 U/kg), together with administration of intravenous luteinising hormone releasing hormone (LH-RH) (25 $\mu g/m^2$) and intravenous thyrotrophin releasing hormone (TRH) (7 $\mu g/kg$, to a maximum of 200 μg) were performed by standard techniques.

REPLACEMENT THERAPY

Replacement therapy with thyroxine (100 $\mu g/m^2$/day), hydrocortisone (15 mg/m^2/day), and intranasal desmopressin were given in maintenance doses as appropriate. Biosynthetic human growth hormone was used in a 'physiological' dose regimen of 15 to 20 IU/m^2/week by daily subcutaneous injection in those patients treated after 1985. Cadaveric pituitary derived human growth hormone (GH) given three times weekly by intramuscular injection was used in patients treated before this date and thereafter changed to a daily replacement dose of the biosynthetic preparation. Ethinyl oestradiol was used to induce puberty in the girls, usually in a starting dose of 2 μg daily (orally) and either human chorionic gonadotrophin (hCG) (three cases) or testosterone (initially 50 mg depot testosterone esters intramuscularly once a month) were used for pubertal induction in the boys.

AUXOLOGY

Anthropometric assessment was performed at diagnosis and six monthly thereafter by standard auxological techniques.[5] Parental heights were measured as above and data from both parents were available in 68 cases (three children were adopted and four had no contact with one biological parent). Bone age was assessed annually using the revised Tanner-Whitehouse method.[6] Pubertal status was assessed according to the method of Marshall and Tanner[7 8] and testicular volumes were measured using the Prader orchidometer.[9] Final height was considered to have been achieved if the epiphyses were fused and growth velocity was less than 2 cm per year.

STATISTICAL ANALYSIS

Measurements of height, sitting height, and subischial leg length were expressed as standard deviation scores[5] (SDS) for age and sex (SD), using normative data from Tanner and Whitehouse.[10] Final height data were analysed in relation to corrected midparental height SDS. Statistical methods were by paired or unpaired t test.

Body mass index (BMI = w/h^2; w = weight in kg, h = height in m) which was used as a measure of obesity was similarly expressed in terms of SDS.[11] Non-parametric methods were used to compare changes in BMI SDS between patient groups according to growth status after surgery (Kruskal-Wallis one way analysis of variance).

The study was approved by the local standing committee on ethical practice and written parental or patient consent obtained in all cases.

Results

HYPOTHALAMO-PITUITARY FUNCTION AT PRESENTATION

Symptoms

Symptoms at presentation referable to hypothalamo-pituitary dysfunction are shown in table 1. Although endocrine symptoms were infrequent as a presenting complaint, there was a history of poor growth in one third of the patients preceding the diagnosis by a mean of 2.9 years (range 0.5 to 5.0 years). Of the 10 patients with growth failure as the presenting complaint, eight were aged 10 years or over at diagnosis. All four children with a history of lethargy and frequent, prolonged infections were adrenocorticotrophic hormone (ACTH) deficient on preoperative testing. Two children, aged 2.2 and 2.7 years, with evidence of hypopituitarism at diagnosis had a history of prolonged seizures, resistant to anticonvulsants, in association with intercurrent illness.

Table 2 Documented endocrine deficits preoperatively, after postoperative stimulation tests (PSTs) and at follow up assessment. T_4 = serum total thyroxine; LH = luteinising hormone; FSH = follicle stimulating hormone

Endocrine dysfunction	*Preoperative (n/total)*	*Postoperative PSTs (n/total)*	*At assessment** (n/total)*
Growth hormone			
Deficient (peak < 7 mU/l on stimulation test)	10/15	69/75	72/75
Insufficient (peak 7 to < 20 mU/l on stimulation test)	3/15	4/75	2/75
Adrenocorticotrophic hormone			
Deficient (peak cortisol < 150 nmol/l on stimulation test)	13/50*	51/75	64/75
Insufficient (peak cortisol < 450 nmol/l on stimulation test)	3/50	11/75	2/75
Thyroid stimulating hormone			
Deficient (T_4 < 70 nmol/l + abnormal TSH response to TRH)	20/62†	61/75	70/75
Insufficient (T_4 ≥ 70 nmol/l + abnormal TSH response to TRH)		3/75	1/75
Gonadotrophin			
Probable deficiency (peak LH and FSH < 1 mU/l)	3/6‡	53/67	69/73
Prolactin			
Raised basal serum prolactin (≥ 500 mU/l)	12/37	16/50	7/46
Antidiuretic hormone			
Clinical and/or biochemical deficiency§	22/75	70/75	60/75

* Inclusive of those patients with a 9 am plasma cortisol < 100 nmol/l.
† Inclusive of those patients with abnormal thyroid function on single 9 am serum sample.
‡ Inclusive only of adolescent patients having LH-RH stimulation tests prior to surgery.
§ As assessed by water intake/urine output; paired measurements of plasma and urine osmolality and clinical response to intranasal desmopressin.
** Including last known pituitary hormone status of those children who have died.

Endocrinopathies

Documented preoperative endocrine deficits are shown in table 2. Of 22 patients with clinical or biochemical evidence of diabetes insipidus at presentation, eight children had concomitant ACTH deficiency or insufficiency (as defined in table 2), such that symptoms were completely masked in one case and only became manifest on introduction of dexamethasone before surgery. In the remaining seven cases, mild symptoms were present on direct questioning before starting dexamethasone but became more overt with introduction of steroids; six of these patients required treatment with intranasal desmopressin preoperatively.

Anthropometry

At presentation, mean height SDS (SD) for chronological age for all 75 patients was -1.0 (1.5); 16 children (21%) had a height SDS below -2.0. Mean corrected mid-parental height SDS was + 0.1 (0.9). Of 54 patients (age range 1.4 to 16.3 years) who had body segment measurements at diagnosis, there was no significant difference in segmental proportions. The median BMI SDS at diagnosis for all 75 patients was -0.1 (range -4.6 to + 4.2); eight patients had a BMI below -2 SDS and for the 11 patients with a history of rapid weight gain before diagnosis, median BMI SDS was + 2.9 (range -0.2 to + 4.2).

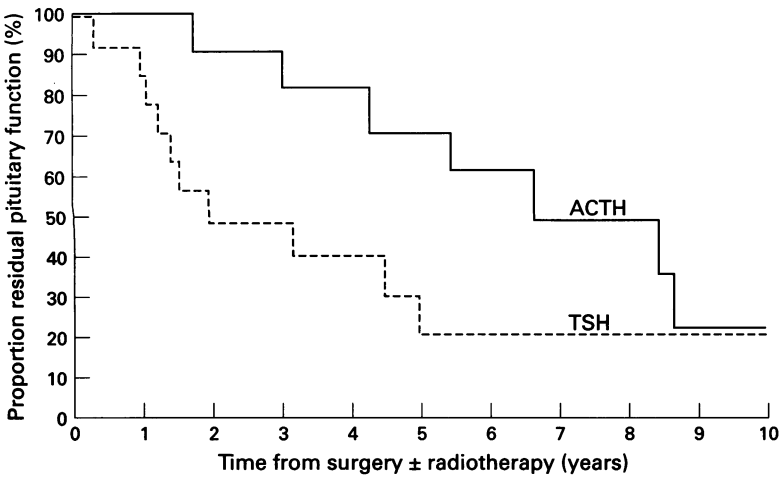

Figure 1 Proportion of patients who did not require hydrocortisone (n = 14) or thyroxine (n = 14) replacement after postoperative pituitary stimulation tests who developed ACTH and TSH deficiency as a function of time (in years) from initial surgery. As not all patients received cranial irradiation (including those developing ACTH and/or TSH deficiencies), time to an 'event' was defined as the time from surgery to start of replacement therapy.

POSTOPERATIVE HYPOTHALAMO-PITUITARY FUNCTION

Anterior pituitary function

The numbers of patients with individual pituitary hormone deficiencies on postoperative endocrine evaluation and at follow up assessment are shown in table 2. Following surgery for complete tumour resection, two children had normal anterior pituitary function, one of whom still has no endocrine deficit 9.4 years from operation. In 13 other cases (12 of whom had subtotal tumour resections), there was residual anterior pituitary function with one or more hormones achieving normal values after provocative testing. ACTH was the most commonly preserved (13 cases in total) with normal thyroid function in a total of 11 cases. Ten out of 14 cases showing some thyroid stimulating hormone (TSH) reserve after surgery eventually became TSH deficient, with a mean time to starting thyroxine of 2.1 years (range 0.35 to 5.0 years). Similarly, of 14 patients whose initial ACTH was sufficient, and who did not require hydrocortisone replacement, seven subsequently became ACTH deficient (fig 1) with a mean time of 5.5 years (range 1.9 to 8.8 years) until start of hydrocortisone treatment. Nine of those developing TSH deficiency and six of those developing ACTH deficiency received cranial irradiation after initial surgery.

Adrenal crises with hypoglycaemia

Thirteen children (age range 1.4 to 16.2 years) required admission to hospital with symptomatic hypoglycaemia precipitated by intercurrent infection (12 cases), in particular gastroenteritis (seven cases) and alcohol consumption (one case). Four patients had recurrent episodes and two children sustained severe neurological sequelae as a result of pro-

longed hypoglycaemia (one of whom has been reported separately).[12]

Of the nine children who subsequently died, two (aged 2.3 and 2.5 years) died suddenly and unexpectedly at home after acute intercurrent illnesses, 1.2 and 0.3 years from surgery, respectively. Inadequate cortisol replacement and absorption with associated hypoglycaemia at the time of infection were thought to be direct contributors to their deaths.

Posterior pituitary function

After surgery, 93% of patients developed diabetes insipidus and this was permanent in 80% of cases (table 2). At follow up assessment, 14 of the 66 survivors were not taking intranasal desmopressin, although three patients had symptoms and biochemistry to suggest mild diabetes insipidus and two others were taking carbamazepine for epilepsy which coincidentally may have 'treated' partial ADH deficiency. MRI showed normal calibre pituitary stalks in two, and thinned but visible stalks in four out of 63 patients at follow up assessment; of these only three retained normal function.

After attempted radical surgery, 10 children developed diabetes insipidus with an absent or impaired sense of thirst. All had other evidence of significant hypothalamic dysfunction. Maintenance of osmotic balance was precarious with recurrent episodes of hypernatraemia and hyponatraemia; two patients had major thrombotic events requiring full anticoagulation. Mean length of stay in hospital after surgery for these patients was 17 weeks (range 4.0 to 46.0 weeks). Six children subsequently died from 0.4 to 15.4 years (mean 7.8 years) after initial surgery and in one other of the total of nine deaths, there was evidence of extrapontine myelinolysis at necropsy.

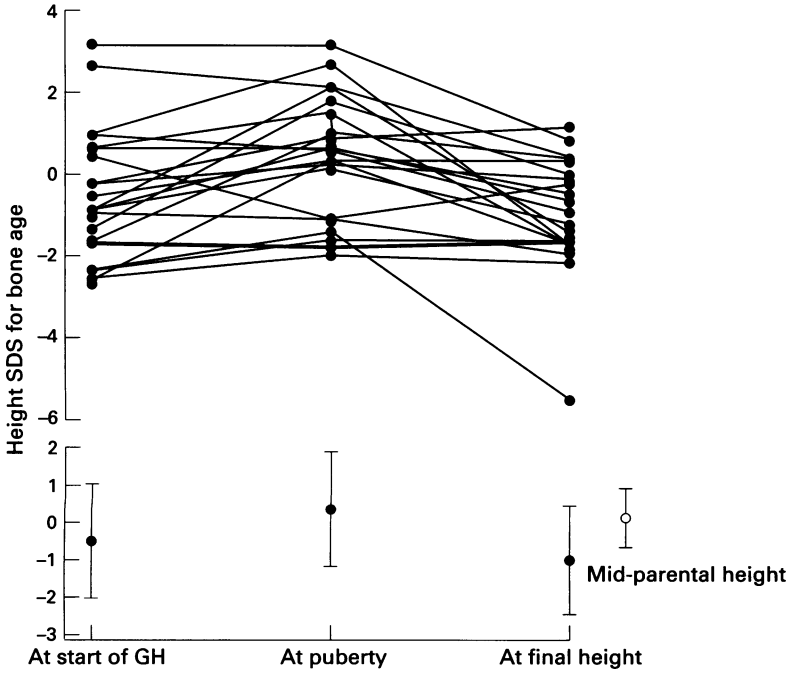

Figure 2 Height SDS for bone age at start of GH, at onset or induction of puberty and at final height for 22 out of 25 patients attaining final height and who were treated with GH. Upper: trajectories of individual subjects. Lower: mean (SD) are shown by the horizontal bars with corrected mid-parental heights for comparison.

Growth and growth hormone replacement

Of the 73 children with GH insufficiency on postoperative stimulation tests (table 2), 32 had normal (16 cases) or 'catch-up' growth (16 cases) for 0.25 to 6.4 years (mean 2.0 years) after surgery without GH treatment. Median change in BMI SDS over the first year from surgery was + 1.6 SD in those patients with subnormal growth following operation compared with + 3.2 SD in patients with normal growth and + 5.0 SD in those showing catch up growth (Kruskal-Wallis, $p < 0.00001$).

At the time of follow up assessment, 60 patients had received or were receiving GH treatment. Thirty one patients (41%) had one or more tumour recurrences from 0.2 to 9.4 years (mean 1.9 years) from initial surgery; 25 recurrences occurred within the first three years from operation. The mean time from surgery to start of GH treatment for the 60 patients treated with GH was 2.0 years (range 0.2 to 9.5 years) with a total time elapsed of 117 patient years before start of treatment. Mean duration of GH treatment was 4.9 years per patient (range 0.2 to 14.7 years) with a total of 292 treatment years. Of the 31 recurrences, 23 patients had either never received GH treatment (six cases) or tumour recurred before start of GH treatment (17 cases) compared with eight patients with recurrence while on GH (Fisher's exact test, $p < 0.0005$). There was no difference in the mean time on or off GH between 35 patients treated with GH and not having a recurrence and the eight patients with tumour recurrence while taking GH.

Puberty

At follow up assessment a total of 48 patients had either entered or completed puberty. In 42 out of 45 children who were prepubertal before diagnosis, onset of puberty was induced at a mean chronological age of 13.3 years (range 10.5 to 18.2 years) in 17 girls and a mean chronological age of 13.5 years (range 11.2 to 17.2 years) in 25 boys.

Three boys had spontaneous onset of puberty after surgery: one had attained adult secondary sexual characteristics, one had stage 4 genitalia and 12 ml testicular volumes, and the third was in early puberty (5 ml testicular volumes) at follow up assessment. Two out of the three were GH deficient/insufficient, one of whom was also TSH deficient.

Of nine girls achieving final height in whom puberty was induced, only one attained full adult sexual maturation, pubic hair development remaining at stage 3 or less in seven cases and axillary hair development remaining at stage 1 in six cases. Of 15 boys reaching final height in whom puberty was induced, 11 achieved stage 5 genitalia, nine stage 5 pubic hair, and nine stage 3 axillary hair. Testicular volumes increased marginally to 3 ml (two cases) and to 4 ml (one case) with testosterone esters alone.

Final height

At follow up assessment 25 patients (nine females, 16 males) had attained final height

Table 3 Mean sitting height (SH) and subischial leg length (SLL) SDS at induction of puberty and at final height for 18 (11 boys, 7 girls) of the 25 patients attaining final stature with mean SDS for SH minus SDS for SLL calculated as an index of segmental disproportin. Values indicating significant disproportion are highlighted in bold

	Boys (n=11)		Girls (n=7)	
	Induction of puberty	*Final height*	*Induction of puberty*	*Final height*
Mean sitting height (SH) SDS (SD)	- 1.43 (1.56)	- 0.77 (1.61)	- 3.18 (0.89)	- 2.18 (0.46)
Mean subischial leg length (SLL) SDS (SD)	- 0.82 (0.60)	0.06 (0.61)	- 1.85 (0.93)	- 0.73 (0.55)
Mean difference in segmental proportions (SH - SLL/SDS) (SEM)	- 0.61 (0.40)	- 0.83 (0.45)	- 1.33 (0.45)*	- 1.44 (0.24)†

* p = 0.02; † p = 0.001.

with a mean height SDS (-0.8 (1.5)) significantly lower than their corrected mid-parental height SDS (+ 0.1 (0.8)) (p = 0.003). Figure 2 shows that despite a history of growth failure preceding the diagnosis by a mean of 2.4 years in 11 of these patients and all but two requiring GH replacement after surgery, the predominant loss in height potential in relation to genetic target height occurred during the pubertal years. Four of the nine girls and 11 of the 16 boys achieved final heights within the 95% confidence limits of their mid-parental heights. All but two girls were below the 10th centile for the normal population whereas half of the boys were at or above the 50th centile at final height. The differences between the girls and boys are further demonstrated in fig 3. Although the pattern of growth from diagnosis to onset or induction of puberty and to final height was similar for both boys and girls, the girls were shorter at all stages than the boys and final height was significantly less (p = 0.002) than their corrected mid-parental height (mean difference (SEM) of 1.26 SD (0.27) between final height and mid-parental height). Mean chronological age for the girls was 8.9 years at diagnosis, 11.7 years at start of GH treatment, and 14.6 years at onset or induction of puberty, as compared with 6.5, 8.8, and 13.6 years for the boys, respectively.

Mean body segment measurements are shown for 18 patients (seven girls and 11 boys) at induction of puberty and at final height in table 3. Chronological age at induction of puberty was from 11.4 to 17.9 years (mean 14.4 years) for the girls and from 11.2 to 17.2 years (mean 13.5 years) for the boys. There was disproportion with a short upper segment relative to leg length in both boys and girls at onset of puberty but the discrepancy between sitting height and subischial leg length was only significant in the girls (p = 0.02). In both sexes, the difference in segmental proportions present at induction of puberty did not alter significantly at final height, that is, there was no catch-up growth in the upper segment during puberty (table 3).

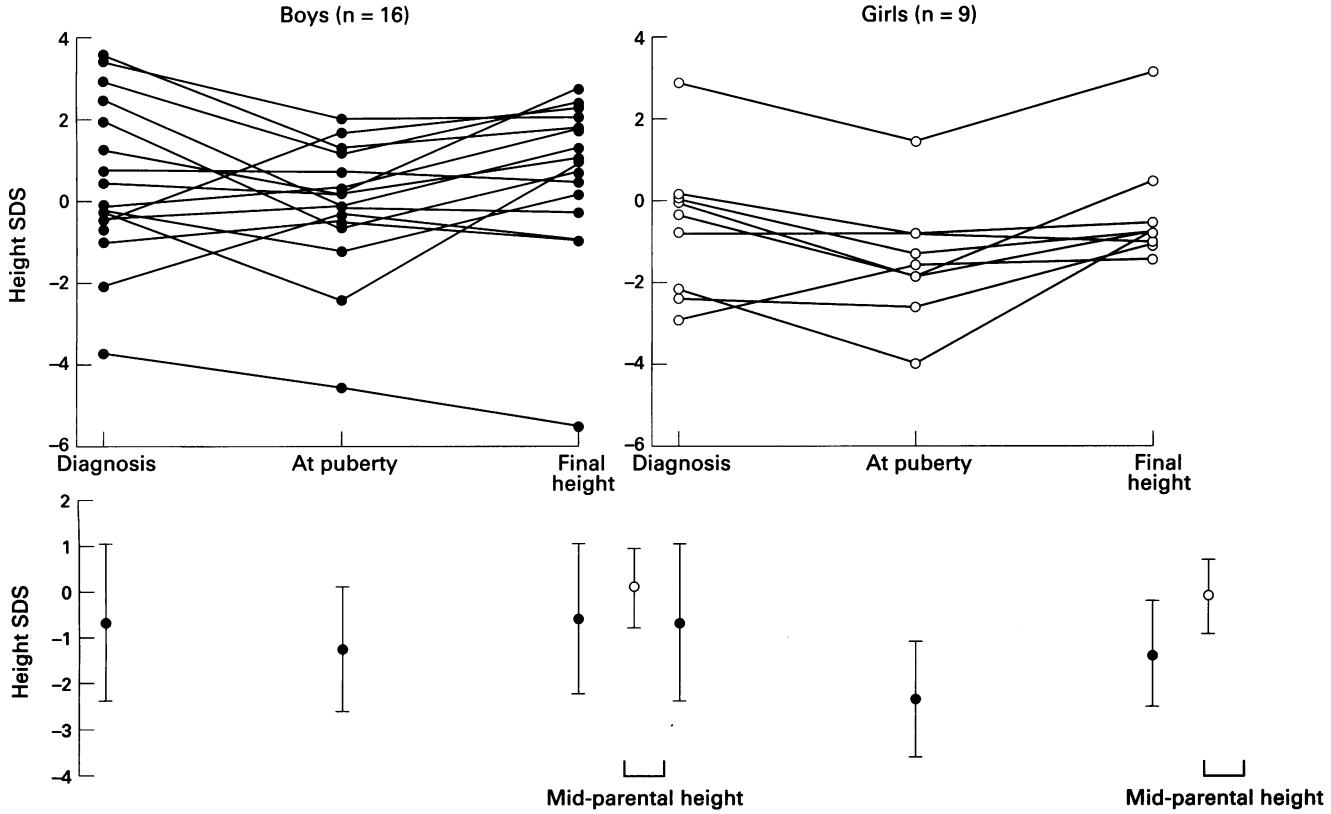

Figure 3 Height SDS for chronological age in 16 boys and nine girls at diagnosis of craniopharyngioma, at onset or induction of puberty and at final height. Upper: trajectories of individual subjects. Lower: mean (SD) are shown by the horizontal bars with corrected mid-parental heights for comparison.

Discussion

With current pituitary hormone replacement treatment and unlimited supplies of biosynthetic human GH, the endocrine management of children with craniopharyngioma should be straightforward. It is well recognised, and our results reconfirm, that multiple endocrinopathies are almost universal following treatment,[3 13 14] irrespective of the extent of initial surgical resection achieved. Thus although there may be some pituitary reserve after subtotal tumour removal the delayed effects of cranial irradiation, likely to be given to these patients to prevent tumour recurrence, ensure that 75% of children have panhypopituitarism by a mean of seven years from initial surgery. Apart from the rare finding of precocious puberty after craniopharyngioma surgery,[13 15] the occurrence of spontaneous onset and progression of normal puberty, as seen in three of the boys in our series, is extremely uncommon. Hypoadrenalism and associated hypoglycaemia continue to contribute to morbidity and mortality, as does the child with diabetes insipidus and an aberrant sense of thirst; the latter remaining one of the most complex management problems following aggressive surgery for this disease.

As in other studies,[1-3] although symptoms attributable to endocrine dysfunction were uncommon as the presenting complaint, the majority of our patients (71%) had symptoms (either volunteered or directly asked for) to suggest an endocrinopathy at diagnosis. Most patients did not have provocative tests of GH secretion before surgery and those who did may have been 'preselected', accounting for the 87% incidence of GH insufficiency in these patients. However, the available data for preoperative endocrine status in children with craniopharyngioma, although limited, suggest that hypothalamo-pituitary dysfunction is present in 80-90% of subjects and GH insufficiency occurs in approximately 75% of patients tested.[16] The incidence of other pituitary hormone deficits before surgery has been summarised from published reports as 40% for gonadotrophin insufficiency, 25% for TSH and ACTH insufficiency, 9-17% for ADH insufficiency, and 20% for a raised serum prolactin, although numbers reported are small.[16] Our figures are comparable, although higher, particularly with regard to ADH insufficiency, where we have included those with concomitant ACTH insufficiency in whom symptoms of diabetes insipidus were completely or incompletely masked until the start of glucocorticoid replacement.[17]

Two children presented with prolonged convulsions (probably due to hypoglycaemia secondary to hypopituitarism) and 13 patients had episodes of symptomatic hypoglycaemia after surgery, all but one in association with intercurrent infection. Although all those after surgery were on standard doses of hydrocortisone replacement and most were on GH treatment, it is of note that in only four cases was the steroid dose increased at the time of illness despite advice given routinely to parents to double or triple the dose of hydrocortisone during periods of infection and the necessity for parenteral hydrocortisone with any vomiting illness, particularly gastroenteritis. The need for continued parent and patient education and repeated re-emphasis of these instructions is therefore imperative. In our patients no age was immune, and the importance of warning adolescents and parents about the potent hypoglycaemic effects of alcohol should be stressed.

Posterior pituitary function has been shown to be more frequently preserved with less extensive surgery; Sanford reporting a 6% incidence of diabetes insipidus following limited surgery (< 25% tumour resection) and irradiation[18] as compared with an incidence of 70-93% in series pursuing a more radical surgical policy,[19-21] with which our results of permanent diabetes insipidus in 80% of patients are comparable. Ninety per cent of children in Yasargil's series had permanent diabetes insipidus despite macroscopic preservation of the pituitary stalk in 28% of cases.[21] The chronically hyperosmolar child with an impaired sense of thirst is a complication exclusive to radical surgery, contributing significantly to the disabling hypothalamic damage found in up to 57% of cases in various reported series[22] and thus to overall morbidity and mortality. The latter is poignantly illustrated by Katz's follow up data[23] of Matson's series of patients,[24] whereby a policy of attempted radical tumour resection in all patients resulted in nine out of 14 (64%) non-operative deaths being directly attributable to the metabolic consequences of hypothalamic damage. Despite management of our patients with a fixed daily fluid intake and small, regular (twice or three times daily) doses of desmopressin, fluid balance remained unstable, as reflected by the prolonged hospital stays after surgery of up to 10-11 months in some cases and the high proportion of eventual deaths in these children.

The well recognised but incompletely understood phenomenon of 'growth without growth hormone'[25-27] is known to be closely associated with, but not exclusive to,[2] patients manifesting excessive weight gain after surgical intervention, obesity being reported in up to 60% of children following radical surgery for craniopharyngioma.[1 20] Our data suggest that those patients showing catch-up growth are those with the most pronounced weight gain after surgery. However, Schoenle *et al* recently found no correlation between growth velocity and BMI or skinfold thickness (although numbers of patients were small).[28]

Although 15-68% of patients have been shown to grow at a normal or accelerated height velocity despite GH deficiency after surgery,[14] the majority of children eventually require substitution GH treatment. The question as to whether the mitogenic effects of GH influence tumour recurrence rate therefore remains important to establish with continued long term surveillance. Our data concur with the evidence so far that GH treatment does not increase the risk of craniopharyngioma recurrence.[29 30]

Although in terms of final height attainment, our patients have done better than previously reported by Burns *et al*,[31] with 60% of subjects achieving final heights above the lower limits to be expected from their parental heights, this was seen predominantly in the boys, the girls falling significantly short of their genetic height potential. Their relatively older age at diagnosis when they were already shorter than the boys and the then later onset of GH treatment may have partly accounted for this, although our data suggest that height potential was lost for both sexes during the pubertal years rather than in prepuberty. We have no explanation for the latter but this may be related to GH dose, as both sex steroids and GH are required for optimal growth during puberty but little is known of the correct replacement doses of GH to use.[32] In addition, some patients were initially treated with the now obsolescent dose regimens used with cadaver derived pituitary GH. Body segment disproportion was also greater in the girls and in both sexes there was inadequate upper segment growth during puberty such that the degree of disproportion present at induction of puberty was not improved by final height. This may reflect the same phenomenon seen in boys and girls with constitutional delayed puberty,[33] particularly as many of the patients reaching final height had puberty induced at a later age than we would now routinely advocate. It remains to be seen whether normal growth and pubertal development are possible in the majority of patients with optimal institution of GH and sex steroid replacement. Certainly, an increase in upper segment growth to equal that of the lower would permit final height to be appropriate for genetic potential.

In conclusion, the endocrine morbidity in association with craniopharyngioma and its treatment remains high but in most cases should be manageable with appropriate hormonal replacement and continued patient and parent education. However, the extreme metabolic consequences of irreversible hypothalamic damage due to aggressive surgery, particularly combined ADH insufficiency and absent thirst, should prompt neurosurgeons to preserve hypothalamic function at all costs, especially as other treatment options, such as radiotherapy, may offer excellent long term tumour control.

We are grateful to the Child Growth Foundation for their financial help with this study and to Serono Laboratories (UK) Ltd, for funding for secretarial assistance.

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