The neuroendocrine sequelae of paediatric craniopharyngioma: a 40 year meta-data analysis of 185 cases from three UK centres

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<th>Journal:</th>
<th>European Journal of Endocrinology</th>
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<td>Manuscript ID</td>
<td>EJE-16-0812.R1</td>
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<td>mstype:</td>
<td>Clinical Study</td>
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<td>Date Submitted by the Author:</td>
<td>01-Dec-2016</td>
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| Keywords:              | craniopharyngioma, radiotherapy, resection, Hypothalamus, sequelae |

For Review Only
The neuroendocrine sequelae of paediatric craniopharyngioma: a 40 year meta-data analysis of 185 cases from three UK centres

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Short title: Sequelae of paediatric craniopharyngioma

Keywords
Craniopharyngioma, Radiotherapy, Resection, Hypothalamus, Sequelae

Word count
3776 (excluding title page, abstract, references, legends, tables and figures)

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ABSTRACT

Objectives

The management of paediatric craniopharyngiomas was traditionally complete resection (CR), with better reported tumour control compared to partial resection (PR) or limited surgery (LS). The subsequent shift towards hypothalamic-sparing, conservative surgery with adjuvant radiotherapy (RT) to any residual tumour, aimed at reducing neuroendocrine morbidity, has not been systematically studied. Hence, we reviewed the sequelae of differing management strategies in paediatric craniopharyngioma across three UK tertiary centres over four decades.

Methods

Meta-data was retrospectively reviewed over two time periods before [1973-2000 (Group A: n=100)] and after [1998-2011 (Group B: n=85)] the introduction of the conservative strategy at each centre.

Results

Patients either had CR (A-34%, B-19%), PR (A-48%, B-46%) or LS (A-16%, B-34%), with trends reflecting the change in surgical approach over time. Overall recurrence rates between the two periods did not change (A-38% vs. B-32%). More patients received RT in B than A, but recurrence rates were similar: for A, 28% patients received RT with 9 recurrences (32%); for B, 62% received RT with 14 recurrences (26%). However rates of diabetes insipidus (p=0.04), gonadotrophin deficiency (p<0.001) and panhypopituitarism (p=0.001) were lower in B than A. In contrast, post-operative obesity (BMI SDS>+2.0) (p=0.4), hypothalamic (p=0.1) and visual (p=0.3) morbidity rates were unchanged.

Conclusion
The shift towards more conservative surgery has reduced the prevalence of hormone deficiencies, including diabetes insipidus, which can be life threatening. However, it has not been associated with reduced hypothalamic and visual morbidities, which remain a significant challenge. More effective targeted therapies are necessary to improve outcomes.

(250/250 words)
ABBREVIATIONS

ACTH  adrenocorticotrophic hormone
AHCH  Alder Hey Children’s Hospital
ADH  anti-diuretic hormone
BMI  body mass index
BSPED  British Society for Paediatric Endocrinology and Diabetes
CR  complete resection
DI  central diabetes insipidus
GnRH  gonadotrophins
GOSH  Great Ormond Street Children’s Hospital
GH  growth hormone
GTH  gonadotrophic hormones
IGF-1  insulin like growth factor-1
IS  incomplete surgery
LS  limited surgery with or without cyst aspiration
MRI  magnetic resonance imaging
PR  partial / subtotal resection
QoL  quality of life
RT  external beam radiotherapy
RMCH  Royal Manchester Children’s Hospital
SDS  standard deviation score
TSH  thyroid stimulating hormone
UK  United Kingdom
UKCCSG  UK Children’s Cancer Study Group (now called CCLG, Children’s Cancer and Leukaemia Group)
UKMG  2005 UK Children’s Cancer Study Group Consensus Management Guidelines
INTRODUCTION

Craniopharyngiomas are rare neuroectodermal tumours that make up 5-13% of paediatric and 1-4% of adult brain tumours (1, 2). The overall incidence is estimated to be 0.13 new cases per 100,000 people/year with a bimodal age distribution, peaking at ages 5-14 years and 65-74 years (3).

Whether suprasellar and/or intrasellar, they are in close proximity to vital structures including the optic nerves and chiasm, pituitary stalk and gland, hypothalamus, third ventricle and internal carotid artery. Thus, although classed as a benign tumour that does not metastasize, craniopharyngiomas can be difficult to resect and control owing to their location as well as size, local extension, adherence and unpredictable propensity to recur regardless of initial treatment modality (1). The tumour itself as well as its treatment with surgery and radiotherapy (RT) can compromise structures in close proximity to the tumour, and their impact on survival, morbidity and quality of life can be devastating (4-9).

Radical excision and conservative subtotal resection are the two dominant surgical strategies.

Radical surgery with complete resection (CR) aims to achieve long term cure and was a favoured treatment for many years (10). The drawback of this aggressive strategy is injury to vital tissues which results in a high frequency of visual impairment, hypothalamic dysfunction (11), central diabetes insipidus (DI) (4) and anterior pituitary hormone deficiencies (12), without proven reduction in relapse and progression rates.

Hypothalamic sparing partial resection (PR) allows decompression and may reduce the subsequent adjuvant RT target volume. The aim is to avoid further morbidity and prevent early progression of the residual tumour (13). This has been reported to have equivalent tumour control rates as CR.

Since 2000, there has been a gradual change in surgical practice towards tailored individual risk-based interventions, more conservative surgery and early or delayed (at recurrence) RT to achieve disease control (14, 15). The United Kingdom Children’s Cancer Study Group (UKCCSG) and British Society for Paediatric Endocrinology and Diabetes (BSPED) published the first consensus
management guidelines (UKMG) (16). This has formed the basis of UK practice since 2005. However, in the absence of randomised trials for this rare disease, the optimal strategy to achieve disease control with minimal morbidity remains elusive. In this current study, we aim to review the neuroendocrine outcomes resulting from the change in primary management recommended by the 2005 UKMG (16) of newly diagnosed paediatric craniopharyngiomas from three of the UK’s largest national tertiary centres over four decades from 1973 to 2011. Management of recurrences is not within the remit of this study.

SUBJECTS AND METHODS

Patient cohorts and time periods

Six independent audits that reviewed data from 1973 to 2011 were undertaken at three tertiary centres in the UK to evaluate the management of children with craniopharyngioma (16). Since 2010, the three centres Royal Manchester Children’s Hospital (RMCH), Great Ormond Street Children’s Hospital (GOSH) and Alder Hey Children’s Hospital (AHCH) have participated in a national hypothalamic-pituitary axis tumour (HPAT) multiprofessional discussion forum to share decision making and improve care (17). Metadata from these six audits were obtained and retrospectively analyzed (Table 1). To compare outcomes before and after the change in surgical strategy at each centre, we merged the GOSH Study 1 (18) and RMCH Study 1 to form Group A (1973-2000), and GOSH Study 2, RMCH Studies 2 and 3, and the AHCH study (19) to form Group B (1998-2011).

Each study period included only children with newly diagnosed craniopharyngioma managed at the tertiary centre by a multispeciality team including paediatric endocrinologists, clinical oncologists, neurosurgeons, neuroradiologists and ophthalmologists. The median duration of follow up across the three centres was 3.7 (0.25 to 19.2) years.

Management for primary tumour
For Group A patients, the surgical strategy aimed to achieve CR where possible. For Group B patients, including those who were diagnosed before 2005, risk was assessed according to the 2005 UKMG: good risk factors included small tumour (<2-4cm), no hydrocephalus, no hypothalamic syndrome or breach of 3rd ventricle, whereas poor risk factors included larger (retrochiasmatic) tumour (>2-4cm), hydrocephalus, hypothalamic syndrome with or without breach of the 3rd ventricle based on our experience of grading hypothalamic morbidity (16, 18). CR was recommended for patients stratified into ‘good’ risk whereas conservative surgery with the addition of immediate or delayed RT (according to age cut-off at 5 years) was recommended for the ‘poor’ risk group. RT after CR was not recommended unless there was evidence of post-operative tumour recurrence. Emphasis was placed on minimising hypothalamic morbidity through a more tailored conservative approach. For tumours with a major cystic component and/or hydrocephalus, patients were re-stratified after endoscopic drainage as the procedure enabled better visualization of the floor of the third ventricle.

In the AHCH series (in Group B), the UKMG were combined with the Paris grading method for hypothalamic involvement (19). Here risk was graded as very high, high, moderate and low based on presence of hypothalamic syndrome, tumour size >2cm, hydrocephalus and breach of floor of the third ventricle. When used for initial management, fractionated external beam radiotherapy, with doses between 50Gy/30# and 54Gy/30#, was the standard of care during both study periods.

**Pre-operative and post-operative neuroimaging**

All patients had pre- and postoperative neuroimaging with 3-6 monthly follow-up scans depending on treatment era (CT before 1986, MRI subsequently).

Based on the surgical opinion and confirmed by post-operative neuroimaging (MRI +/- CT) extent of tumour resection was classified as CR or PR when it was total or subtotal removal respectively.
Limited surgery (LS) refers to procedures aimed at cyst drainage and treating tumour-related hydrocephalus. When comparing outcomes with CR, we have described both PR and LS as incomplete surgery (IS).

Tumour recurrence was defined as evidence on neuroimaging of solid and/or cystic tumour regrowth at any time after surgical resection and/or 3 or more months after RT (to avoid misclassification of RT induced cysts as recurrences) (18, 19).

Pre-operative and post-operative endocrine, hypothalamic and visual function

Pre- and post-op endocrine function was assessed with standard protocols at each tertiary centre. In addition to clinical features, growth and pubertal status, anterior pituitary function at diagnosis was assessed from baseline biochemical investigations, including insulin like growth factor-1 (IGF-1), prolactin, thyroid stimulating hormone (TSH) and free thyroxine, gonadotrophins, 8-9am adrenocorticotropic hormone (ACTH) and cortisol, before any dexamethasone. Dynamic tests of growth hormone (GH), cortisol reserve and gonadotrophin levels were performed before surgery when possible, and in all patients during followup. Posterior pituitary function and adequacy of anti-diuretic hormone (ADH) secretion was assessed from fluid input/output, paired early morning plasma and urine electrolytes and osmolality, and, if required, a water deprivation. Our endocrine outcomes were assessed by prevalence rates of endocrine replacement therapy and obesity defined as a BMI SDS >+2 (19, 20). For all patients, the same UK population reference standard was used to calculate BMI SDS (21).

Hypothalamic morbidity was assessed from the following parameters: the absence or presence of hyperphagia, sleep-wake disturbance, impaired temperature regulation, impaired thirst, weight gain and change in affective behaviour or memory. Visual acuity and visual fields were assessed by experienced ophthalmologists. Children unable to cooperate with assessment of visual acuity were given a score based on visual evoked potentials.
Statistical analysis

Analyses were performed with the Statistical Package for the Social Sciences version 22 (SPSS by IBM). Differences between categorical and continuous variables were analyzed by Pearson’s chi-squared test and analysis of variance.

RESULTS

Clinical characteristics of patients

Between 1973 and 2011, 185 (100 male, 85 female) patients with craniopharyngioma were recruited from GOSH (n=115), RMCH (n=50) and AHCH (n=20) [Table 1] and subdivided according to the change in treatment strategy, Group A (1973-2000, n=100) and Group B (1998-2011, n=85). The most common clinical presentations were visual problems, headaches and endocrine dysfunction.

Of the 64/115 (55%) patients who presented with hydrocephalus, 42 (66%) required CSF diversion procedures. Of the 185 patients, 13 (7%) died at median 5.9 (0.3 to 15.4) years after initial surgery from recurrence and/or hypothalamic or neurological deficits (with/without epilepsy and endocrinopathies).

Initial treatment modality and trend in tumour recurrence over time

More Group A than Group B patients underwent CR (34% vs 19%, p=0.02) [Figure 2] and thus fewer required RT (28% vs 62%, p<0.001) [Table 2]. The proportion of patients who had limited or no surgery was greater in Group B than Group A (35% vs 16%, p=0.002).

The outcomes from the three surgical modalities with RT and without RT (i.e. surveillance) are summarised in Figure 1 for our entire series and Figure 2 for Groups A and B. The overall recurrence
rate across the 4 decades was 35% (65/185) and after CR it was 24% [Table 2]. Neither tumour recurrence rates in all patients (38% vs 32%, p=0.4) nor in those who received RT (32% vs 26%, p=0.6) differed significantly between Groups A and B [Table 2].

**Anterior and posterior pituitary endocrinopathies**

Panhypopituitarism was defined as the deficiency of all anterior pituitary hormones with DI. Hormone deficiencies at diagnosis and at most recent follow-up for Group A and B are presented in Table 3. However, data for individual pituitary hormones was not available at diagnosis for Group A. Post-operative panhypopituitarism (p=0.001), gonadotrophin (GTH) deficiency (p<0.001) and DI (p=0.04) were significantly lower in Group B than in A despite similar follow up times.

**Hypothalamic morbidity**

Hypothalamic morbidity rates did not differ significantly before and after surgery between Group A and B post-operatively (p=0.2 & 0.1) [Table 4]. BMI SDS at diagnosis and at last follow up for Group A and B is shown in Figure 3 (data for GOSH Study 1 not available). Between Group A and B, BMI SDS at last follow-up (p=0.1) [Table 4] and change in BMI SDS from presentation to last follow-up (p=0.2) did not differ. There was also no significant difference between the two groups in the proportion of patients with a BMI SDS >+2.0 at presentation (14% vs 26%, p=0.3) and at last follow up (36% vs 46%, p=0.4) [Table 4], and who experienced a BMI SDS increase of ≥+1.0 after surgery (38% vs 47%, p=0.5). In contrast to Group A, in Group B there was a significant increase from presentation to last follow-up in the proportion of patients with hypothalamic symptoms (49% vs 80%, p=0.04) and with BMI >+2SDS (26% vs 46%, p=0.01) [Table 4, Figure 3].
Visual morbidity

Data for visual morbidity was available for all patients in Group A but only 36 in Group B. For all cohorts, there were no significant differences in visual morbidity before and after surgery \([90/135 (67\%) \text{ vs } 96/136 (71\%), p=0.5]\). Similarly, no significant differences were noted before and after surgery in Group A \([60/100 (60\%) \text{ vs } 68/100 (68\%), p=0.2]\) and B \([30/35 (86\%) \text{ vs } 28/36 (78\%), p=0.4]\). Post-operative visual morbidity rates between Group A and B \([68/100 (68\%) \text{ vs } 28/36 (78\%), p=0.3]\) did not differ significantly.

DISCUSSION

Management strategy, disease stabilisation and risk of tumour recurrence

Our study comprises 185 children with craniopharyngioma managed at three tertiary centres from 1973 to 2011. Over these four decades, the management strategy shifted from a preference for radical surgery and avoiding RT in the earlier period (1973-2000) to more conservative surgery and adjuvant RT later on (1998-2011). This was associated with no major change in tumour recurrence (A-38\% to B-32\%). In the absence of RT, tumour recurrence rates varied with the extent of surgery and time period, and were highest after PR in Group A (69\%). Deaths have also decreased possibly owing to more intensive management of comorbidities.

Change in surgical management over time in our series compared to other major centres

The most compelling trends in management are evident between 1975 to 2011 from Toronto Hospital for Sick Children (20) and between 1966 to 2012 from three large consecutive multinational studies undertaken by German researchers (22, 23). At the Hospital for Sick Children, the proportion of children who had CR in the periods 1975-1989 \(n=50\), 1990-2001 \(n=43\) and 2001-2011 \(n=33\) was 90\%, 86\% and 12\% respectively (20). In the three European nations’ studies, 38\% children had CR
in the period 2001-2007 (n=120) and only 18% in 2007-2012 (n=106) (22, 23). Before 2000, the transcranial approach was used more widely across our centres to achieve CR where radical tumour removal was the goal. Over time and since the 2005 UKMG, there has been greater use of the trans-sphenoidal approach and limited surgery (for patients with poor risk factors, i.e. younger children aged <5y with large tumours >2-4cm and hypothalamic syndrome or hydrocephalus at diagnosis) (16). Thus the general decline in the rates of CR in our experience are in keeping with the UKMG and other studies, (16, 24).

Recurrence rates in our series compared to other published studies

Numerous publications have reported experiences, outcomes and risk-benefit profiles of primary management modalities for craniopharyngioma in children and adolescents. Among these are the multinational studies mentioned above (20, 22-23). Other publications are observational reports from single centres with relatively small numbers of paediatric patients and some also include adult patients owing to the rarity of the condition. In the absence of randomised trials and meta-analysis, these studies do provide valuable insight which has been summarised in a number of reviews (1, 9, 14, 25-28).

The 24% rate of recurrence in our study after CR across 4 decades compares favourably to the 35% reported by Clarke et al in a systematic review of 109 publications from 1977 to 2012 with data on recurrence available for 377 of 531 paediatric patients (25). For partially resected tumours treated with RT, the recurrence risk of 50% was considerably higher than the 32% in our patients. However, the number of patients in each study included in this review were small (median 11, range 1-29). Mortini et al (1) reviewed 26 studies published between 1990 to 2012. These studies were not restricted to the paediatric population and recurrence rates varied widely: up to 50% after CR and 25-100% after PR.

Endocrinopathies
The missing information about individual pituitary hormone status at diagnosis for Group A precludes comparing whether there was a change from diagnosis to last follow up in Group A and also individual hormone deficiencies at diagnosis between the two groups. However, we would not anticipate the latter to be significantly different and this is further supported by the proportion of patients with panhypopituitarism being similar (Group A 50% vs Group B 48%). At latest follow-up, from the earlier Group A (1973-2000) to the more recent Group B study (1998-2011), we found a significant reduction in the occurrence of DI (80% to 65%), GTH deficiency (95% to 59%) and panhypopituitarism (68% to 43%). The move towards a more conservative approach with adjuvant RT as well as the increased use of the trans-sphenoidal route was likely to have contributed to preserving the pituitary stalk and the hypothalamic-pituitary integrity. This has benefits for survival and reproductive capacity. Cohen et al (20) from Toronto observed similar trends from 1975 to 2011 for DI (93% to 55%) and panhypopituitarism (86% to 58%). Although they reported an increased frequency of GH (20% to 85%) and GTH deficiency (30% to 61%) across their cohorts, the prevalence of these endocrinopathies in their most recent cohort was similar to our Group B (93% GH and 59% GTH deficiency). Better diagnostic awareness over the years may explain these findings.

Hypothalamic morbidity

Affective behaviour and memory were not evaluated with standardised assessments for all patients routinely across all the centres. Thus, our findings for hypothalamic morbidity are limited to clinical manifestations and BMI data. Hypothalamic morbidity remained prevalent at diagnosis and post-operatively with 58% and 61% patients respectively affected across our 6 cohorts from 1973-2011. The lack of differences in rates of post-operative hypothalamic dysfunction and obesity between the two time periods suggests that hypothalamic morbidity continues to be a challenging burden. Moreover, despite a greater preference for hypothalamic sparing strategies in Group B, post-operative hypothalamic morbidity worsened significantly from diagnosis. Thus as previously reported
by Müller et al (29), obesity appears to be inherent to the disease itself rather than the treatment imposed. Despite a similar BMI change from diagnosis to the post-operative period between Group A and B (median BMI SDS 0.80 vs 0.88), there was a higher prevalence of obesity at baseline in Group B (A: 14% vs B: 26%, median BMI SDS - A: 0.80 vs B: 1.20). This may reflect more recent secular trends of higher rates of obesity (boys and girls <20 years old: 4.7-7.4% and 5.7-8.1% from 1980-2013 respectively) seen in the paediatric population in the UK over the last 4 decades (30). The significant increase in rates of hypothalamic morbidity from presentation to last follow-up in Group B but not in Group A might be explained by greater awareness and documentation of this complication in recent times.

Müller and co-workers have highlighted the prevalence, prognostic indicators and sequelae of hypothalamic involvement from their landmark studies (31). This includes long-term results from the largest cohort of survivors from the multi-centre HIT-Endo registry (32). Progression free survival at 20 years was 58% and was not influenced by hypothalamic involvement or extent of resection. Those with hypothalamic involvement (compared to those without) had lower overall survival at 20 years (84% vs 95%) and impaired quality of life from obesity, physical fatigue, dyspnoea, lack of motivation and impaired psychosocial development.

Visual Morbidity

The lack of any significant differences in visual morbidity pre- and post-operatively (67% vs 71%) and between the two study periods (68% vs 78%) demonstrates that this remains another major burden of craniopharyngioma. It is well established that over 50% of children with these tumours will have a myriad of visual field and acuity deficits at diagnosis and at follow-up (25, 33). While surgical decompression has an important role in preserving vision, operative trauma to the visual apparatus can worsen visual field defects (19). RT given in close proximity to the optic nerves also increases the risk of visual impairment (34).
Tailored management based on evaluating individual risk and prognostic factors

Our practice enshrined in the UKMG is in keeping with a worldwide shift towards a more tailored approach and preference for conservative surgery along with RT for long-term disease control (14, 35). The emphasis is also to minimise morbidity rather than ambitious attempts to completely excise this heterogenous tumour. While the complications from pituitary damage can be managed relatively easily with hormone replacement, the risk of premature mortality and loss of reproductive function cannot be eliminated. Additionally, no effective treatment is available for the debilitating morbidity arising from injury to the hypothalamus (31) and visual apparatus. There is thus an increased focus on identifying individual risk and tailoring treatment accordingly. To enable risk stratification, a variety of classifications have been proposed based on the patient’s age, clinical cues for morbidity, tumour size, location, extension, relationship with vital structures and markers of hypothalamic involvement on MRI such as involvement of third ventricle, mamillary body and obstructive hydrocephalus (1, 15, 36-39). Based on their findings of lower progression free survival in those with tumours ≥4.5cm, Yosef et al (40) have also appealed for a worldwide consensus on classification by size of tumour.

Radiotherapy in the primary treatment of craniopharyngioma

The rationale for RT in the primary treatment of craniopharyngioma is to stabilise residual disease after PR, and avoid the unfavourable morbidity and mortality following CR (41). Our findings are in agreement with observations that the combination of conservative surgery and RT achieves tumour control that is similar to CR alone (29, 31-32).

Strengths and Limitations of the study

In this study, we have the advantage of evaluating tumour control and associated sequelae in a large cohort of patients managed with a range of surgical strategies, with or without adjuvant RT, and with
data that spans four decades. All were managed at large tertiary centres recognised to have the relevant paediatric neuro-oncology, neuroendocrinology and neurosurgical expertise.

A major limitation was that meta-data available from the six independent studies were analysed retrospectively and missing information could not be obtained. The follow-up duration for individual studies may be not sufficiently long to fully ascertain the outcomes of treatment on morbidity and survival rates. When examining the impact of various surgical modalities on tumour recurrences, we were not able to control for confounding variables such as the age of the patient, duration of history before diagnosis (42), modern surgical technology and neuroimaging. Selection bias in the choice of treatment especially in patients with particular baseline clinical characteristics is a limitation beyond our control. Data on other pertinent outcomes, such as quality of life (33) and neurocognitive function (43), were not available.

CONCLUSION

Although subject to the limitations of incomplete meta-data, our results offer a clear timeline message that limited surgery/sub-total resection combined with adjuvant RT achieved similar rates of tumour control as planned CR. Importantly, the less radical surgical approaches employed and the greater use of adjuvant RT over time were associated with reduced endocrine morbidity. However, reducing the burden of hypothalamic and visual morbidity remains a challenge and more effective targeted therapies are necessary to improve outcomes.

Declaration of interest: The authors have no conflicts of interest.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.
Author Contributions: JSG, SE, MS, ECI, HS, MD, JB and BP provided details about the original studies from the respective centres. TSET collected the metadata, analysed it and prepared the paper under supervision of LP and PEC. RH, KA, CM and IK managed patients surgically and provided input on neurosurgical practices at the three respective centres. NT, MNG and BP provided input on radiotherapy practice for treatment of paediatric craniopharyngioma in UK centres. All authors contributed to finalising the paper.

Acknowledgements: We thank Catherine De Vile, David B Grant, Brian E Kendall, Brian G R Neville, Richard Stanhope, Kate E Watkins from GOSH, Connor Mallucci, Arun Doss, Swathi Upadrasta, William Newman, Shivaram Avula and Benedetta Petterini from AHCH for their contribution towards conducting and disseminating results of the craniopharyngioma audits/studies at their respective centres.

REFERENCES


manuscript submitted for review to European Journal of Endocrinology

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FIGURE LEGENDS

Figure 1. Extent of surgical resection, radiotherapy (RT) and recurrence for all patients across the 3 centres from 1973-2011

Extent of tumour resection was classified as complete resection or partial resection when it was total or subtotal removal respectively. Limited surgery refers to procedures such as ventriculostomy, Ommaya reservoir and ventriculo-peritoneal shunt with or without cyst aspiration.

* Post-operative neuroimaging data for two patients was not available and extent of surgery could not be ascertained. They underwent surveillance and had no recurrence. 1 patient underwent a watch and wait strategy without any radiotherapy. No tumour recurrence was reported for this patient.

Figure 2. Extent of surgical resection, radiotherapy (RT) and recurrence for patients (a) Study Group A (1973-2000) and (b) Study Group B (1998-2011)

(a)

* Post-op neuroimaging data for two patients was not available and extent of surgery could not be ascertained. They underwent surveillance and had no recurrence.

(b)

* 1 patient underwent a watch and wait strategy without any radiotherapy. No tumour recurrence was reported for this patient.

Figure 3. BMI SDS at diagnosis and at last follow-up for Groups A (1973-2000) and B (1998-2011)
Solid diagonal line denotes BMI SDS increase of $\geq +1.0$ from diagnosis to follow-up.
Table 1. Patient characteristics from 6 studies undertaken at 3 UK tertiary centres from 1973-2011, subdivided into two study groups: Group A including 2 studies from 2 centres over 1973-2000 and Group B including 4 studies from 3 centres over 1998-2011.

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<td>-0.70 (-3.70 to +1.40)</td>
</tr>
<tr>
<td>Mean Height SDS at follow-up (range)</td>
<td>Mean Height SDS at follow-up (range)</td>
</tr>
<tr>
<td>NA</td>
<td>-0.48 (-3.90 to +1.50)</td>
</tr>
<tr>
<td>Mean BMI SDS at diagnosis (range)</td>
<td>Mean BMI SDS at diagnosis (range)</td>
</tr>
<tr>
<td>NA</td>
<td>+0.86 (-2 to +2.5)</td>
</tr>
<tr>
<td>Mean BMI SDS at follow-up (range)</td>
<td>Mean BMI SDS at follow-up (range)</td>
</tr>
<tr>
<td>NA</td>
<td>+1.39 (-2.15 to +4.3)</td>
</tr>
</tbody>
</table>

NA= Not available, AHCH = Alder Hey Childrens’ Hospital, GOSH = Great Ormond Street Hospital, RMCH = Royal Manchester Childrens’ Hospital
Table 2. Treatment modalities and tumour recurrence rates for Groups A (1973-2000) and B (1998-2011), as defined in Figure 1 (N=185). The extent of tumour resection was classified as complete resection (CR) or partial resection (PR) when it was total or subtotal removal respectively. Limited surgery (LS) includes procedures such as ventriculostomy, Ommaya reservoir and ventriculo-peritoneal shunt with or without cyst aspiration. Incomplete surgery (IS) refers to PR and LS.

<table>
<thead>
<tr>
<th>No. of patients (%)</th>
<th>Total (Group A and B)</th>
<th>Group A, n=100</th>
<th>Group B, n=85</th>
<th>P (Chi-square, A vs B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour recurrence</td>
<td>65/185 (35)</td>
<td>38/100 (38)</td>
<td>27/85 (32)</td>
<td>0.4</td>
</tr>
<tr>
<td>Complete resection (CR)</td>
<td>50/185 (27)</td>
<td>34/100 (34)</td>
<td>16/85 (19)</td>
<td>0.02</td>
</tr>
<tr>
<td>Recurrence after CR without radiotherapy (RT)</td>
<td>11/45 (24)</td>
<td>6/31 (19)</td>
<td>5/14 (36)</td>
<td>0.2</td>
</tr>
<tr>
<td>Incomplete surgery (IS) and RT</td>
<td>76/185 (41)</td>
<td>25/100 (25)</td>
<td>51/85 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence after IS and RT</td>
<td>22/76 (29)</td>
<td>9/25 (36)</td>
<td>13/51 (25)</td>
<td>0.3</td>
</tr>
<tr>
<td>Surveillance after any type of surgical approach</td>
<td>104/185 (56)</td>
<td>72/100 (72)</td>
<td>32/85 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence after surveillance</td>
<td>42/104 (40)</td>
<td>29/72 (40)</td>
<td>13/32 (41)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjuvant RT</td>
<td>81/185 (44)</td>
<td>28/100 (28)</td>
<td>53/85 (62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence after RT</td>
<td>23/81 (28)</td>
<td>9/28 (32)</td>
<td>14/53 (26)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
### Table 3. Pituitary hormone deficiencies across the 3 centres for Groups A (1973-2000) and B (1998-2011). Data are presented as the number of patients with a hormone deficiency/number of patients tested (%).

<table>
<thead>
<tr>
<th></th>
<th>TSH</th>
<th>ACTH</th>
<th>GH</th>
<th>Gonadotrophins†</th>
<th>Diabetes Insipidus</th>
<th>Panhypopituitarism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50/100 (50)</td>
</tr>
<tr>
<td>Latest follow up</td>
<td>70/75 (93)</td>
<td>64/75 (85)</td>
<td>72/75 (96)</td>
<td>71/75 (95)</td>
<td>60/75 (80)</td>
<td>68/100 (68)</td>
</tr>
<tr>
<td>after surgery ± RT§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Diagnosis</td>
<td>22/84 (26),</td>
<td>21/84 (25),</td>
<td>26/64 (41),</td>
<td>15/75 (20),</td>
<td>6/85 (7)</td>
<td>21/44 (48),</td>
</tr>
<tr>
<td>Latest follow up</td>
<td>70/81 (86),</td>
<td>63/81* (78),</td>
<td>75/81 (93),</td>
<td>47/79** (59),</td>
<td>55/84 (65),</td>
<td>35/81 (43),</td>
</tr>
<tr>
<td>after surgery ± RT</td>
<td>4 NA</td>
<td>4 NA</td>
<td>4 NA</td>
<td>6 NA</td>
<td>1 NA</td>
<td>4 NA</td>
</tr>
<tr>
<td><strong>Pearson’s χ² Group A vs. B</strong></td>
<td>p=0.2</td>
<td>p=0.2</td>
<td>p=0.4</td>
<td>p&lt;0.001</td>
<td>p=0.04</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

NA = Data not available

† Gonadotrophin deficiency was defined based on biochemical findings of low LH and FSH levels on GnRH stimulation and patients requiring sex steroid replacement.

§ Data on individual pituitary axes not available for 25 patients

* 1 patient did not have biochemical evidence of ACTH deficiency (hence not included) but had clinical features of glucocorticoid deficiency.

** 1 patient did not have biochemical evidence of gonadotrophin deficiency, but instead she experienced precocious puberty.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p (Chi square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion (%) of patients with hypothalamic symptoms</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>At presentation</td>
<td>62/100 (62%)</td>
<td>19/39 (49%), 46 NA</td>
<td></td>
</tr>
<tr>
<td>At last follow-up</td>
<td>58/100 (58%)</td>
<td>12/15 (80%), 70 NA</td>
<td>0.1</td>
</tr>
<tr>
<td>p-value for within group difference between presentation and last follow-up</td>
<td>0.6</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Median (range) BMI SDS</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>At presentation</td>
<td>0.80 (-2.00; 2.50)</td>
<td>1.20 (-2.92; 4.52)</td>
<td></td>
</tr>
<tr>
<td>At last follow-up</td>
<td>1.33 (-2.15; 4.30)</td>
<td>1.94 (-0.71; 4.50)</td>
<td>0.1</td>
</tr>
<tr>
<td>Change from presentation to post-op</td>
<td>0.80 (-2.70; 3.25)</td>
<td>0.88 (-2.54; 5.31)</td>
<td>0.2</td>
</tr>
<tr>
<td>Median (range) postoperative BMI SDS by surgical treatment</td>
<td>Complete resection 2.52 (0.23; 3.92)</td>
<td>Incomplete resection 2.00 (-0.71; 4.50)</td>
<td></td>
</tr>
<tr>
<td>Proportion (%) of patients with BMI &gt;2SDS*</td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>At presentation</td>
<td>3/21 (14)</td>
<td>19/73 (26)</td>
<td></td>
</tr>
<tr>
<td>Post-op at last follow-up</td>
<td>8/22 (36)</td>
<td>32/69 (46)</td>
<td>0.4</td>
</tr>
<tr>
<td>p-value for within group difference between presentation and last follow-up</td>
<td>0.1</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Median (range) BMI SDS for all obese patients</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>At presentation</td>
<td>2.40 (2.30; 2.50)</td>
<td>2.45 (2.02; 4.52)</td>
<td></td>
</tr>
<tr>
<td>Post-op at last follow-up</td>
<td>2.93 (2.15; 4.30)</td>
<td>2.91 (2.07; 4.50)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Obesity, BMI > 2SDS; severe obesity, BMI > 4SDS [20]; NA = Data not available.* No. of patients with BMI >4SDS were at presentation 0 and 1/73(1%) patient in Groups A and B respectively, Post-op at last follow-up 1/22(5%) and 2/69(3%) patients in Groups A and B respectively.
Figure 1. Extent of surgical resection, radiotherapy (RT) and recurrence for all patients across the 3 centres from 1973-2011

62x26mm (150 x 150 DPI)
Figure 2a. Extent of surgical resection, radiotherapy (RT) and recurrence for patients Study Group A (1973-2000)

74x37mm (150 x 150 DPI)
Figure 2b. Extent of surgical resection, radiotherapy (RT) and recurrence for patients Study Group B (1998-2011)
Figure 3. BMI SDS at diagnosis and at last follow-up for Groups A (1973-2000) and B (1998-2011)