Rev Esp Endocrinol Pediatr 2025; Volumen 16 (Suppl 2)
10.3266/RevEspEndocrinolPediatr.pre2025.May.976

TUMORES DEL SISTEMA NERVIOSO CENTRAL

Therapeutic management of craniopharyngiomas

Manejo terapéutico de los craneofaringiomas

Manuela Cerbone[1,2], Hoong-Wei Gan[1,2]

[1] *Department of Endocrinology. Great Ormond Street Hospital for Children. NHS Foundation Trust. Great Ormond Street. London. UK*
[2] *Genetics and Genomic Medicine Research and Teaching Department. UCL Great Ormond Street Institute of Child Health. University College London. London. UK*

Abstract

The management of craniopharyngiomas in children and young people under 19 years of age (CYP) is challenging, not only because of their rarity, but also because of their diverse presentation to adult and paediatric, endocrine, and oncological, medical and surgical specialists.

Although rare, craniopharyngiomas account for 80% of tumours in the hypothalamic-pituitary region in childhood. Despite being benign rather than malignant, the proximity of these tumours to the visual pathways, hypothalamus, and pituitary gland means that both treatment of the tumour and the tumour itself can cause pronounced long-term neuroendocrine morbidity in a context of high overall survival.

Since children with tumours will live for an average of another 68 years, their health-related quality of survival is arguably paramount. Managing CYP with craniopharyngiomas is further complicated by a lack of high quality, randomised evidence for treatment recommendations. The optimal management strategy for these tumours is as yet undefined. This creates unacceptable inconsistencies and inequalities in care across units and specialties.

Age-specific and tumour-specific multidisciplinary teams (MDTs) treating both CYP and adults should be involved in a coordinated discussion in order to achieve high quality care which will improve survival and reduce any secondary, long term, health-related morbidity in this young cohort. This would also improve and expedite diagnosis, including complex endocrine and genetic screening of familial cases, acute decision-making and peri-operative care as well as longer term follow-up.

In the United Kingdom, national consensus guidelines for the management of CYP with craniopharyngiomas have been developed to help standardise care, under the auspices of the UK Children's Cancer and Leukaemia Group and the British Society for Paediatric Endocrinology and Diabetes, with the oversight and endorsement of the Royal College of Paediatrics and Child Health, using the Appraisal of Guidelines for Research & Evaluation II methodology.

This talk will highlight the challenges involved in managing craniopharyngiomas whilst trying to reduce their long-term neuroendocrine and neuro-behavioural comorbidities. The main recommendations from the guidelines will be discussed, and the most relevant are summarised.

Recommendations

Generic statements

1. Offer all CYP under 19 years of age with a suspected or confirmed craniopharyngioma management in a specialist paediatric endocrine centre by an age-appropriate endocrinologist with experience in pituitary tumours, liaising with the designated multidisciplinary neuro-oncology team (recommendation: strong; evidence: based on Delphi consensus).

2. Provide age-appropriate hypothalamic–pituitary support from a multidisciplinary team (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, and neuropatho-

logy) including, where appropriate, adult pituitary specialists (eg, endocrinologists and skull base neurosurgeons) (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low).

3. Offer all CYP pituitary surgery performed in an age-appropriate specialist setting with on-site perioperative joint endocrine care (recommendation: strong; evidence: based on Delphi consensus).

4. Offer surgery by the neurosurgeon(s) designated by the adult pituitary or paediatric neuro-oncology multidisciplinary team, which can offer all possible approaches, including transsphenoidal, transcranial, and endoscopic-assisted surgery (recommendation: strong; evidence: based on Delphi consensus).

5. Offer discussion, where necessary, of complex sellar and suprasellar lesions in CYP with a national pituitary tumour multidisciplinary team for a review of radiology, histology, and decision-making (recommendation: strong; evidence: based on Delphi consensus).

6. Offer all CYP treated for craniopharyngiomas ongoing lifelong care and transition to adult pituitary services, on an individualised basis, usually when growth and puberty are complete (recommendation: strong; evidence: based on Delphi consensus).

7. Given the rarity and substantial morbidity of pituitary tumours in CYP, a national clinical database should be created for monitoring outcomes in order to optimise care and prognosis in this patient group (recommendation: strong; evidence: based on Delphi consensus).

Diagnosis and investigations

Radiology

1. MRI with dedicated pituitary views on both the sagittal and coronal planes (as per Children's Cancer and Leukaemia Group guidelines) should be the routine imaging format in the assessment of CYP with suspected craniopharyngioma, but when the diagnosis or extent of calcification is in doubt, additional CT scanning should be considered (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low).

2. Be aware of the option of performing diffusion tensor imaging, perfusion-weighted imaging, and magnetic resonance spectroscopy, although these are not routinely recommended in the preoperative assessment of craniopharyngiomas in CYP and have no clear proven role (recommendation: weak; evidence: based on Delphi consensus).

3. The preoperative MRI report should include grading of the extent of hypothalamic involvement (recommendation: strong; evidence: high).

Endocrinology

1. Offer all CYP baseline plasma endocrine biochemistry at presentation with suspected craniopharyngioma, which should include an urgent analysis of α-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG), and prolactin available before any definitive surgery, as well as insulin-like growth factor 1, thyroid-stimulating hormone (TSH), free thyroxine (FT4), luteinising hormone, follicle-stimulating hormone (FSH), testosterone, and oestradiol, paired early morning plasma and urine osmolalities and electrolytes, and if no dexamethasone has been given, tests to evaluate morning levels of cortisol and adrenocorticotropic hormone (ACTH) (recommendation: strong; evidence: based on Delphi consensus).

2. Be aware that a random cortisol measurement taken before administration of any dexamethasone may be useful in documenting the pretreatment status of the hypothalamic-pituitary-adrenal axis in CYP presenting acutely with raised intracranial pressure. In the absence of treatment with dexamethasone for peritumoral oedema, be aware that morning concentrations of cortisol and ACTH may also be measured before any prophylactic steroid cover (recommendation: weak; evidence: low).

3. In non-acute situations, offer combined dynamic pituitary function tests of growth hormone and cortisol reserve, and if age-appropriate, gonadotrophin secretion when feasible, and before any steroid therapy when possible (recommendation: strong; evidence: based on Delphi consensus).

4. Be aware that deteriorating serial thyroid function test scores (low or normal TSH concentrations with repeatedly low, borderline low, or falling FT4 concentrations at least 1–2 weeks apart) are sufficient for a diagnosis of central hypothyroidism, with no need for a thyrotropin releasing hormone test that does not adequately discriminate between hypothalamic and pituitary causes of thyroid dysfunction (recommendation: weak; evidence: low).

5. Be aware that a formal water deprivation test may help to confirm AVP-deficiency in CYP with a known suprasellar tumour and a history of polydipsia or polyuria when other metabolic causes have been excluded, and in the absence of an

inappropriately dilute polyuria with plasma hyperosmolality (urine to plasma osmolality ratio <1·0), especially if the posterior pituitary bright spot is absent in MRI (recommendation: weak; evidence: low).

6. Be aware of the presence of hypothalamic syndrome and the possibility of performing a formal psychological assessment at diagnosis (recommendation: weak; evidence: low).

Neuropsychology

1. Offer all CYP with craniopharyngioma a baseline neurocognitive assessment around the time of diagnosis to monitor future progress (recommendation: strong; evidence: based on Delphi consensus).

Pathology

1. Except in occasional surgical emergencies, offer delayed definitive surgical or radiotherapeutic treatment until confirmatory preoperative or perioperative tissue histopathology or cyst fluid cytology is available (recommendation: strong; evidence: based on Delphi consensus).

2. Be aware that Ki67 labelling and CTNNB1 mutation analysis of tissue have poor prognostic value (recommendation: weak; evidence: low).

Treatment

Surgery

1. Be aware that access to a surgeon with specific experience in paediatric craniopharyngioma surgery may improve overall outcomes (recommendation: weak; evidence: low).

2. Consider surgery (complete or subtotal resection or cyst aspiration), given the better overall and progression-free survival compared to conservative management alone (recommendation: moderate; evidence: moderate).

3. Consider not proceeding with complete resection of paediatric craniopharyngiomas when there is clear evidence of hypothalamic involvement on grading (recommendation: moderate; evidence: moderate).

4. Be aware of the spectrum of options available for surgical management of hydrocephalus, including but not limited to insertion of ventricular-peritoneal shunts, external ventricular drains, transventricular endoscopic cyst drainage, transsphenoidal endoscopic cyst drainage, and insertion of an Ommaya reservoir into a craniopharyngioma cyst, tailoring these to each patient (recommendation: weak; evidence: low).

5. Be aware of the option of using solely primary cyst drainage to treat hydrocephalus due to a craniopharyngioma cyst, rather than a ventricular-peritoneal shunt or external ventricular drain insertion (recommendation: weak; evidence: based on Delphi consensus).

6. Be aware of the option of transventricular or transsphenoidal cyst drainage with optional insertion of an Ommaya reservoir to control cyst size in cystic craniopharyngiomas (recommendation: weak; evidence: low).

7. Be aware of the option of a two-stage surgical approach involving minimally invasive surgery, relief of hydrocephalus and intracranial pressure, further neuroradiological assessment, and multidisciplinary team discussion before any definitive surgery on large mixed cystic or solid craniopharyngiomas with or without hydrocephalus (recommendation: weak; evidence: low).

8. Be aware of the option of using high-field intraoperative MRI, although intraoperative imaging may not improve outcomes of craniopharyngioma surgery (recommendation: weak; evidence: low).

Perioperative management

1. Offer CYP with cerebral oedema and those undergoing craniotomy or wide opening of the cerebrospinal fluid space transsphenoidally rapidly tapered perioperative dexamethasone neuroprotection (recommendation: strong; evidence: based on Delphi consensus).

2. Be aware that perioperative hydrocortisone at stress doses could be administered without dexamethasone cover. If it has commenced, consider tapering postoperatively to maintenance doses until integrity of the hypothalamic–pituitary–adrenal axis has been established (recommendation: weak; evidence: low).

3. Be aware of the diagnosis of AVP deficiency (which may progress to a triphasic response), iatrogenic intravenous hyperhydration, glycosuria, and cerebral salt-wasting syndrome in the presence of postoperative polyuria (recommendation: weak; evidence: low).

4. Be aware of the diagnosis of central adrenal insufficiency, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (possibly as part of a triphasic response), iatrogenic water overload, and cerebral salt-wasting syndrome in

the presence of postoperative hyponatraemia (recommendation: weak; evidence: low).

Radiotherapy

1. Offer deferral of adjuvant radiotherapy where the surgical impression of complete resection has been confirmed in postoperative imaging (eg, MRI or CT) (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low).

2. Consider upfront external beam radiotherapy where tumour resection is incomplete (recommendation: moderate; evidence: moderate).

3. Offer deferral of radiation until tumour progression is evident on a case-by-case basis when the multidisciplinary team considers that the morbidity of radiation may outweigh its benefits in very young children or those with minimal residual disease (recommendation: strong; evidence: based on Delphi consensus).

4. Offer radiotherapy using the gross tumour volume, defined as the dimensions of the postoperative solid and cystic tumour complex (recommendation: strong; evidence: based on Delphi consensus).

5. Offer radiotherapy using the clinical target volume margin, defined as 5 mm modified to barriers of natural spread (recommendation: strong; evidence: based on Delphi consensus).

6. Offer radiotherapy using a dose fractionation of 50·4–54·0 Gy (or the cobalt gray equivalent for proton beam therapy) administered in 28–30 fractions over 6 weeks to the planning target volume (recommendation: strong; evidence: based on Delphi consensus).

7. Consider high-energy proton beam therapy as a radiation treatment modality. (Guideline Development Group consensus recommendation; recommendation: moderate; evidence: low).

8. Be aware that gamma knife radiosurgery should only be considered as a primary treatment within a research setting, as there is currently insufficient evidence for its efficacy (recommendation: weak; evidence: low).

Post-treatment follow-up

1. Be aware that a follow-up MRI within 3-6 months of treatment may be needed to assess the response (recommendation: weak; evidence: low).

2. Offer MRI surveillance imaging at intervals guided by patient symptoms, definitive therapy (eg, degree of resection or radiotherapy), and by the multidisciplinary team (recommendation: strong; evidence: based on Delphi consensus).

3. Offer repeat formal visual acuity and if age-appropriate, visual field assessment within 3 months of the definitive tumour treatment (recommendation: strong; evidence: based on Delphi consensus).

4. Offer ongoing visual follow-up at a frequency individualised according to age, residual visual function, symptoms, and the likelihood of tumour or cyst regrowth (recommendation: strong; evidence: based on Delphi consensus).

5. Offer basal and combined dynamic anterior pituitary function tests of any replacement therapy within 6 weeks of completion of initial treatment to assess the integrity of the growth hormone, ACTH, TSH, and if age-appropriate, gonadotrophin axes, if not already definitively abnormal at diagnosis (recommendation: strong; evidence: based on Delphi consensus).

6. Consider using dynamic function testing as per local guidelines on several occasions over time to differentiate long-term recovery from dexamethasone-induced ACTH suppression due to permanent ACTH deficiency (recommendation: moderate; evidence: based on Delphi consensus).

7. Offer lifelong endocrinology follow-up for evolving hypopituitarism, with the frequency determined on an individual basis for the patient (recommendation: strong; evidence: based on Delphi consensus).

8. Consider recombinant human growth hormone in replacement doses in CYP with confirmed growth hormone deficiency to re-establish normal linear growth, as this treatment does not increase the risk of tumour progression (recommendation: moderate; evidence: moderate).

9. Consider access to a designated multidisciplinary team with specialist dietary, exercise, psychological, and endocrine input for the management of hypothalamic obesity (recommendation: moderate; evidence: moderate).

10. Be aware of specialist sleep laboratory and behavioural neuropsychopharmacology services for CYP with hypothalamic injury and disturbed sleep or behaviour (recommendation: weak; evidence: low).

11. Offer interval neuropsychological assessments until adulthood to inform clinical and educational neurorehabilitation and vocation in CYP with identified neuropsychology and neurological deficits,

and those who have undergone cranial radiotherapy (recommendation: strong; evidence: based on Delphi consensus).

Management of recurrence

1. Offer CYP with cystic or solid recurrences further surgery to avoid or reduce the radiation field before radiotherapy after a radiologically complete resection without previous irradiation (recommendation: strong; evidence: based on Delphi consensus).

2. Offer further cyst drainage before radiotherapy to CYP with progressive, primarily cystic recurrences following initial incomplete resection without previous irradiation (recommendation: strong; evidence: based on Delphi consensus).

3. Offer CYP with progressive, primarily solid recurrences following initial incomplete resection without previous irradiation radiotherapy with further surgery to reduce the radiation field (recommendation: strong; evidence: based on Delphi consensus).

4. Offer a repeat course of conventional radiotherapy for the treatment of disease progression or recurrence after previous irradiation only in exceptional cases, and only after all other types of therapy have been explored, given its high morbidity levels (recommendation: strong; evidence: based on Delphi consensus).

References

1. Hoong-Wei Gan, Paul Morillon, Assunta Albanese, et al. National UK guidelines for the management of paediatric craniopharyngioma. *Lancet Diabetes Endocrinol* 2023; 11: 694–706.

2. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol* 2005; 62: 397–409.

3. Puget S, Garnett M, Wray A, et al. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg* 2007; 106 (suppl): 3–12.

4. Müller HL. Childhood craniopharyngioma—current concepts in diagnosis, therapy and follow-up. *Nat Rev Endocrinol* 2010; 6: 609–18.

5. Mallucci C, Pizer B, Blair J, et al. Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. *Childs Nerv Syst* 2012; 28: 1181–92.

6. Mortini P, Gagliardi F, Bailo M, et al. Magnetic resonance imaging as predictor of functional outcome in craniopharyngiomas. *Endocrine* 2016; 51: 148–62.

7. Edate S, Albanese A. Management of electrolyte and fluid disorders after brain surgery for pituitary/suprasellar tumours. *Horm Res Paediatr* 2015; 83: 293–301.

8. van Santen HM, van Schaik J, van Roessel IMAA, Beckhaus J, Boekhoff S, Müller HL. Diagnostic criteria for the hypothalamic syndrome in childhood. *Eur J Endocrinol* 2023; published online Feb 14.

9. Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer* 20 Hoffman LM, Jaimes C, Mankad K, et al. Response assessment in pediatric craniopharyngioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Neuro-oncol* 2023; 25: 224–33. 08; 51: 110–17.

10. Karavitaki N, Warner JT, Marland A, et al. GH replacement does not increase the risk of recurrence in patients with craniopharyngioma. *Clin Endocrinol (Oxf)* 2006; 64: 556–60.

11. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018; 103: 2761–84.

12. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol* 2004; 5: 399–408.