Rare endocrine tumour guidelines

Management of craniopharyngioma in children and young people: summary guideline

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Published: October 2021
Next review due: October 2026

Produced in association with the British Society for Paediatric Endocrinology and Diabetes

This is a summary version of the full guideline, ***Craniopharyngioma: Guideline for the management of children and young people (CYP) aged <19 years with craniopharyngioma*** which is available to download from www.cclg.org.uk/guidelines

Citation text
Children's Cancer and Leukaemia Group (CCLG).
Management of craniopharyngioma in children and young people: summary guideline: CCLG; 2021.
Available from https://www.cclg.org.uk/guidelines

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Craniopharyngioma

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Introduction

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 different adult and paediatric, endocrine and oncological, medical and surgical specialists. Largely benign rather than malignant, these tumours have a high survival rate. Since children with tumours have, on average, a further 68 life years ahead, 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. This causes unacceptable inconsistencies and inequalities in care across units and specialties.

In order to achieve high quality care which will improve survival and reduce any secondary, long term, health-related morbidity in this young cohort, there is a need to involve age-specific and tumour-specific multidisciplinary teams (MDTs) from both CYP and adult practice in a coordinated discussion. 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 surveillance. Oncology treatment for CYP in the UK has been centralised for decades to 16 tertiary oncological centres linked to accredited secondary paediatric oncology supportive care units (POSCUs). However, there is no age-appropriate tertiary endocrine or adult tumour-specific MDT always embedded or mandated in this service provision; the latter needs resource and development along a similar model.

Background

Craniopharyngiomas originate from embryological remnants of Rathke's pouch (4), and are rare (1.1-1.7 cases/million/year (5-7)) benign suprasellar tumours, accounting for up to 80% of tumours in this area in childhood (8, 9). They peak in incidence between 5-14 and 65-74 years of age (5, 6), but are histologically different in childhood when they are invariably adamantinomatous (rather than the adult papillary form which is vanishingly rare in childhood) (10-12). Craniopharyngiomas can also present in the neonatal period (13, 14).

Histologically they may be cystic and/ or solid, containing characteristically viscous, "engine-oil" fluid rich in cholesterol crystals (15). Although typically sporadic, human and mouse models have demonstrated that adamatinomatous craniopharyngiomas characteristically demonstrate β-catenin (*CTNNB1*) mutations resulting in hyperactivation of the Wnt signalling pathways, causing β-catenin accumulation in cell clusters over-expressing *SHH*, although increased expression of the *MAPK* pathway and various fibroblast growth

factors, bone morphogenetic proteins, and cytokines have also been reported (16-20). Contrastingly, papillary craniopharyngiomas demonstrate *BRAF* V600E mutations causing hyperactivation of the *MAPK* pathway (12, 21).

As with other suprasellar tumours, symptoms may be present for prolonged durations (8 months to 8 years (22-27)) before diagnosis, most frequently relating to increased intracranial pressure or visual compromise (22, 24-26, 28-31), whilst symptoms of hypothalamo-pituitary dysfunction are often under-recognised and require direct enquiry and/ or examination (Table 1) (32, 33).

Overall 30-year survival rates are high (up to 80% (24, 34)), but this is punctuated by multiple relapses and interventions which, in turn, cause significant long-term neuroendocrine, cognitive and visual morbidity, and premature mortality. Treatment is usually by a combined neurosurgical and/ or radiotherapeutic approach, but treatment strategies vary considerably between centres (35). Optimal management is thus unclear and the first consensus-based guidance for management of craniopharyngiomas was produced in 2005(36). We now aim to update this through a structured review of the literature and a robust Delphi consensus process using AGREE-II methodology, to provide recommendations which will improve and standardise care for such children across the country.

Table 1: Common presenting features of paediatric craniopharyngiomas ranked by median frequency.

Presenting feature	Median frequency (range)
Headaches(22, 24, 25, 28-30)	64% (51-78)
Reduction in visual acuity(22, 24-26, 28-31)	51% (23-73)
Restriction in visual fields(22, 24-26, 28-30)	46% (17-61)
Nausea/ vomiting(22, 24, 25, 28-30)	43% (31-61)
Linear growth failure/ short stature(22, 24-26, 28, 29, 32, 37, 38)	33% (14-86)
Papilloedema(29)	29%
Lethargy/ somnolence(22, 24, 32)	21% (5-22)
Cranial nerve palsy(22, 24, 29)	20% (11-27)
Weight loss(22, 24, 26, 32)	17% (5-31)
Polyuria/ polydipsia(22, 24, 26, 28, 29, 32)	16% (9-28)
Pubertal delay/ arrest(22, 24, 28, 29, 32)	10% (5-24)
Cognitive impairment(24)	10%
Blindness(24, 26)	9% (3-15)
Ataxia(4, 22, 29)	8% (7-18)
Hemiparesis(4, 22, 26, 29)	8% (7-12)
Decreased consciousness(24, 29)	8% (5-10)
Hyperphagia/ weight gain(22, 24, 26, 32)	6% (5-30)
Seizures(22, 26, 29)	5% (5-6)
Optic atrophy(24)	5%
Behaviour change/ psychiatric symptoms(22, 24, 26)	4% (3-10)
Gynaecomastia/ galactorrhoea(22)	4%
Cold intolerance(22, 24)	3% (0-5)
Precocious puberty(26, 28, 29, 32)	2% (0-3)
Sleep/ wake cycle disturbance(22)	2%

Scope & target population

This guideline covers the management of all CYP diagnosed before their 19th birthday with a confirmed adamantinomatous craniopharyngioma. It does not cover the management of patients over 19 years of age, or the management of papillary craniopharyngiomas when presenting in childhood.

Disclaimer

Healthcare providers need to use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here is the responsibility of the treating clinician and must be made in the light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

Target users of this guideline: healthcare professionals from a variety of disciplines (including paediatric endocrinology, oncology, neurosurgery, radiology, histopathology, and genetics) involved in the management and long-term follow-up of childhood and adolescent craniopharyngioma within the UK.

Recommendations

Recommendation	Evidence for recommendation or consensus
Generic statements	
Offer management in a specialist paediatric endocrine centre by an age-appropriate endocrinologist with experience in pituitary tumours, in liaison with the designated multidisciplinary neuro-oncology team to all children and young people under 19 years of age (CYP) with a suspected or confirmed craniopharyngioma.	Strong recommendation, Delphi consensus (95%)
Age-appropriate hypothalamo-pituitary multidisciplinary team (MDT) support (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, neuropathology), including adult pituitary specialists (e.g. endocrinologists and skull base neurosurgeons) should be provided where appropriate.	Strong recommendation, low quality evidence, GDG consensus (100%)
Offer pituitary surgery performed in an age-appropriate specialist setting with on-site perioperative joint endocrine care to all CYP.	Strong recommendation, Delphi consensus (95%)
Offer surgery by the neurosurgeon(s) nominated by the adult pituitary or paediatric neuro-oncology MDT, which can offer all possible approaches, including transsphenoidal, transcranial and endoscopic-assisted surgery.	Strong recommendation, Delphi consensus (83%)
Offer discussion, where necessary, of complex sellar/ suprasellar lesions in CYP at a national pituitary tumour MDT for review of radiology, histology and decision-making.	Strong recommendation, Delphi consensus (83%)
Offer continued lifelong care and transition to adult pituitary services, on an individualised basis, usually when growth and puberty are complete, to all CYP treated for craniopharyngiomas.	Strong recommendation, Delphi consensus (100%)
Given the rarity and significant morbidity of pituitary tumours in CYP, a national clinical database should be created for monitoring outcomes to optimise care and prognosis in this patient group.	Strong recommendation, Delphi consensus (100%)
Diagnosis and investigations	
Radiology	
MRI with dedicated pituitary views in both sagittal and coronal planes (as per CCLG guidelines) should be the routine imaging modality in assessment of CYP with suspected craniopharyngioma, but where the diagnosis and/ or extent of calcification is in doubt, consider additional CT scanning.	Strong recommendation, low quality evidence, GDG consensus (100%)
Be aware of the option of performing diffusion tensor imaging (DTI), perfusion-weighted imaging (PWI) and magnetic resonance spectroscopy	Weak recommendation, Delphi consensus (100%)

(MRS), although these are not routinely recommended in the pre-operative assessment of craniopharyngiomas in CYP and have no clear proven role.	
The pre-operative MRI report should include grading of the extent of hypothalamic involvement according to the Paris system.	Strong recommendation, high quality evidence
Vision	
Offer visual acuity, visual fields and fundoscopy before treatment in all cooperative CYP. Consider pattern visual evoked potentials in infants or disabled children but these should not be used for surveillance in the longer-term.	Strong recommendation, low quality evidence, GDG consensus (100%)
Be aware of optical coherence tomography (OCT) as a method of assessing retinal nerve fibre layer thinning in CYP with more severe degrees of visual acuity or field loss.	Weak recommendation, Low quality evidence
Endocrinology	
Offer baseline plasma endocrine biochemistry in all CYP at presentation of suspected craniopharyngioma which should include urgently analysed AFP, β-hCG and prolactin available before any definitive surgery; as well as IGF-1, TSH, free T_4, LH, FSH, testosterone/ oestradiol, paired early morning plasma/ urine osmolalities and electrolytes, and, if no dexamethasone has been instituted, a morning cortisol +/- ACTH.	Strong recommendation, Delphi consensus (100%)
Be aware that a random cortisol measurement taken before administration of any dexamethasone may be useful in documenting pre-treatment status of the hypothalamo-pituitary-adrenal axis in CYP presenting acutely with raised intracranial pressure. In the absence of treatment with dexamethasone for peri-tumoral oedema, be aware that morning cortisol concentrations +/- ACTH may also be measured prior to any prophylactic steroid cover.	Weak recommendation, low quality evidence
In the non-acute situation, offer combined dynamic pituitary function tests of growth hormone (GH) and cortisol reserve and, if age-appropriate, gonadotrophin secretion when feasible, before any steroid therapy when possible, as the results inform the treatment decision-making process.	Strong recommendation, Delphi consensus (100%)
Be aware that deteriorating serial thyroid function tests (low or inadequately elevated TSH concentrations with repeatedly low/ borderline low/ falling free T_4 concentrations at least 1-2 weeks apart) are sufficient for diagnosis in CYP with craniopharyngioma, without the need for a TRH test which does not adequately discriminate between hypothalamic and pituitary causes of thyroid dysfunction.	Weak recommendation, low quality of evidence
Be aware that a formal water deprivation test may help confirm central diabetes insipidus (CDI) in CYP with a known suprasellar tumour and a history of polydipsia and/ or polyuria, where other metabolic causes have been excluded, in the absence of a confirmed inappropriately dilute polyuria in the presence of plasma hyperosmolality (urine: plasma osmolality ratio <1.0) responsive to desmopressin, especially if the posterior pituitary bright spot is absent on MRI.	Weak recommendation, low quality of evidence
Be aware of the presence of the hypothalamic syndrome, and the possibility of performing a formal psychological assessment at diagnosis, as this may help separate disease- and future treatment-related morbidity.	Weak recommendation, low quality of evidence
Neuropsychology	
Offer all CYP with craniopharyngioma a baseline neurocognitive assessment around the time of diagnosis against which to monitor future progress.	Strong recommendation, Delphi consensus (92%)
Pathology	
Except in occasional surgical emergencies, offer delayed definitive surgical or radiotherapeutic treatment until confirmatory pre- or perioperative tissue histopathology or cyst fluid cytology is available.	Strong recommendation, Delphi consensus (91%)

Be aware that Ki67 labelling or CTNNB1 mutation analysis of tissue have poor prognostic value.	Weak recommendation, low quality of evidence
Treatment	
Surgery	
Be aware that access to a surgeon with specific experience in paediatric craniopharyngioma surgery may improve overall outcomes.	Weak recommendation, low quality of evidence
Consider surgery (complete or subtotal resection or cyst aspiration) in all CYP with craniopharyngioma given the better overall and progression-free survival compared with conservative (watch and wait) management alone.	Moderate recommendation, moderate quality of evidence
Consider not proceeding with complete resection of paediatric craniopharyngiomas where there is clear evidence of hypothalamic involvement on Paris grading.	Moderate recommendation, moderate quality of evidence
Be aware of the spectrum of options available for surgical management of hydrocephalus, including but not limited to insertion of ventriculo-peritoneal shunts, external ventricular drains, transventricular endoscopic cyst drainage, transsphenoidal endoscopic cyst drainage or insertion of an Ommaya reservoir into a craniopharyngioma cyst, tailoring these to each patient.	Weak recommendation, low quality of evidence
Be aware of the option of using solely primary cyst drainage to treat hydrocephalus due to a craniopharyngioma cyst, rather than ventriculo-peritoneal shunt or external ventricular drain insertion.	Weak recommendation, Delphi consensus (67%)
Be aware of the option of transventricular or transsphenoidal cyst drainage with/ without insertion of an Ommaya reservoir to control cyst size in cystic craniopharyngiomas.	Weak recommendation, low quality of evidence
Be aware of the option of a two-staged surgical approach involving minimally invasive surgery, relief of hydrocephalus and intracranial pressure, further neuroradiological assessment and MDT discussion before any definitive surgery of large mixed cystic/ solid craniopharyngiomas with/ without hydrocephalus.	Weak recommendation, low quality of evidence
Be aware of the option of using high-field intraoperative MRI, although this may not improve outcomes of craniopharyngioma surgery.	Weak recommendation, low quality of evidence
Perioperative management	
Offer CYP with cerebral oedema and those undergoing craniotomy or wide opening of the cerebrospinal fluid space transsphenoidally rapidly tapered perioperative (48-72 hours), dexamethasone neuroprotection.	Strong recommendation, Delphi consensus (100%)
Be aware that perioperative hydrocortisone at stress doses could be given to CYP undergoing surgery without dexamethasone cover. If commenced consider tapering post-operatively to maintenance doses until the integrity of the hypothalamo-pituitary-adrenal axis has been established.	Weak recommendation, low quality of evidence
Be aware of the diagnoses of central diabetes insipidus (CDI, which may progress to a triphasic response), iatrogenic intravenous hyperhydration, glycosuria, and/ or cerebral salt-wasting syndrome in the presence of post-operative polyuria.	Weak recommendation, low quality of evidence
Be aware of the diagnoses of central adrenal insufficiency, the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (possibly as part of a triphasic response), iatrogenic water overload and/ or cerebral salt-wasting syndrome in the presence of post-operative hyponatraemia.	Weak recommendation, low quality of evidence
Radiotherapy	
Offer deferment of adjuvant radiotherapy in CYP where the surgical impression of complete resection has been confirmed on post-operative MRI and/ or CT.	Strong recommendation, low quality of evidence, GDG consensus (100%)

Consider upfront external beam radiotherapy where tumour resection is incomplete.	Moderate recommendation, moderate quality of evidence
Offer deferment of radiation until tumour progression is evident on a case-by-case basis where the MDT considers that the morbidity of radiation may outweigh its benefits in very young children or those with minimal residual disease.	Strong recommendation, Delphi consensus (93%)
Offer radiotherapy using the gross tumour volume (GTV) defined as the dimensions of the post-operative solid and cystic tumour complex.	Strong recommendation, Delphi consensus (86%)
Offer radiotherapy using the clinical target volume (CTV) margin defined as 5 mm modified to barriers of natural spread.	Strong recommendation, Delphi consensus (100%)
Offer radiotherapy using a dose fractionation of 54 Gy (or equivalent CGE for proton beam therapy) administered in 30 fractions over 6 weeks to the planning target volume (PTV).	Strong recommendation, Delphi consensus (100%)
Consider high-energy proton beam therapy (PBT) as a radiation treatment modality for CYP with craniopharyngiomas.	Moderate recommendation, low quality of evidence, GDG consensus (100%)
Be aware that gamma knife radiosurgery should only be considered as a primary treatment for craniopharyngiomas in CYP within a research setting as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence
Other therapies	
Be aware that intracystic chemotherapies should only be considered as a primary treatment for craniopharyngiomas in CYP within a research setting as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence
Post-treatment follow-up surveillance	
Be aware that a follow-up MRI within 3-6 months of treatment may be needed assess response.	Weak recommendation, low quality of evidence
Offer MRI surveillance imaging at intervals guided by patient symptoms, definitive therapy (i.e. degree of resection and/ or radiotherapy) and by the MDT.	Strong recommendation, Delphi consensus (94%)
Offer repeat formal visual acuity and, if age-appropriate, visual field assessment within three months of definitive tumour treatment (i.e. resection +/- radiotherapy).	Strong recommendation, Delphi consensus (94%)
Offer ongoing visual follow-up at a frequency individualised according to age, residual visual function, symptoms and likelihood of tumour/ cyst regrowth.	Strong recommendation, Delphi consensus (81%)
Offer basal and combined dynamic anterior pituitary function tests off any replacement therapy within 6 weeks of completion of initial treatment to assess the integrity of the GH, ACTH, TSH, and, if age-appropriate, gonadotrophin axes, if not already found definitively abnormal at diagnosis	Strong recommendation, Delphi consensus (100%)
Offer lifelong endocrinology follow-up for evolving hypopituitarism, with the frequency determined on an individual patient basis.	Strong recommendation, Delphi consensus (100%)
Consider recombinant human growth hormone (rhGH) in replacement doses in CYP with confirmed GH deficiency to re-establish normal linear growth, as this does not increase the risk of tumour progression.	Moderate recommendation, moderate quality of evidence
Consider using dynamic function testing as per local guidelines on several occasions over time to differentiate long-term recovery from dexamethasone-induced ACTH suppression from permanent ACTH deficiency.	Strong recommendation, Delphi consensus (100%)

Consider access to a designated MDT with specialist dietary, exercise, psychological and endocrine input for the management of hypothalamic obesity.	Moderate recommendation, moderate quality of evidence
Be aware of specialist sleep laboratory and behavioural neuropsychopharmacology services for CYP with hypothalamic injury and disturbed sleep and/ or behaviour.	Weak recommendation, low quality of evidence
Offer interval neuropsychological assessments until adulthood to inform clinical and educational neurorehabilitation and vocation in CYP with identified neuropsychological and neurological deficits (e.g. seizures, stroke, visual impairment) and those who have undergone cranial radiotherapy.	Strong recommendation, Delphi consensus (100%)
Management of recurrence	
Offer further surgery to avoid or reduce the radiation field before radiotherapy in CYP with cystic and/ or solid recurrences after a radiologically complete resection without previous irradiation.	Strong recommendation, Delphi consensus (100%)
Offer further cyst drainage before radiotherapy in CYP with progressive, primarily cystic recurrences following initial incomplete resection without radiotherapy.	Strong recommendation, Delphi consensus (100%)
Offer radiotherapy with further surgery to reduce the radiation field in CYP with progressive, primarily solid recurrences following initial incomplete resection without radiotherapy.	Strong recommendation, Delphi consensus (100%)
Offer a repeat course of conventional radiotherapy for the treatment of disease progression or recurrence after previous radiotherapy only in exceptional cases and only after all other therapeutic modalities have been explored, given its high morbidity.	Strong recommendation, Delphi consensus (100%)
Be aware that gamma knife radiosurgery for recurrent or progressive craniopharyngiomas should only be considered in a research setting, as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence
Be aware that repeated courses of intracystic interferon-α via an indwelling catheter could be considered instead of aspiration alone in CYP with recurrent cystic craniopharyngiomas.	Weak recommendation, low quality of evidence
Be aware that systemic IFNα in CYP with recurrent craniopharyngiomas should only be considered in the context of a research trial as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence

*Based on GRADE system and Delphi consensus process (1, 2)

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