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Résumé:	Craniopharyngiomas are rare epithelial tumours situated primarily in the sellar/parasellar region, occurring along the path of the craniopharyngeal duct. Whilst classed as histologically benign tumours, their unpredictable growth pattern and proximity to vital structures including the optic chiasm, hypothalamus, and pituitary gland renders them a considerable threat, with significant associated morbidity and increase in mortality. Occurring both in child and adulthood, their clinical manifestations are broad, commonly with symptoms/signs secondary to hypothalamic-pituitary dysfunction, raised intracranial pressure and visual compromise. They have two distinct histological subtypes (adamantinomatous and papillary), with unique patterns of age distribution, and genetic and molecular make-up. With increasing understanding of their genetic pathogenesis including BRAF V600E mutations in the papillary subtype, and β-catenin mutations in the adamantinomatous, further research provides hope for the discovery of targeted medical therapy that can exploit molecular changes occurring as a result of such alterations. Until then, primary treatment consists of surgery with or without radiotherapy, with intracystic aspiration, chemotherapy or irradiation being alternative options in selected patients. Long term management by an experienced multidisciplinary team is essential, given the breadth of complications, including hypothalamic morbidity, visual compromise, cognitive and neuropsychological sequelae and impairment to quality of life.
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Évaluateurs suggérés:	

Craniopharyngiomas

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Abstract

Craniopharyngiomas are rare epithelial tumours situated primarily in the sellar/parasellar region, occurring along the path of the craniopharyngeal duct. Whilst classed as histologically benign tumours, their unpredictable growth pattern and proximity to vital structures including the optic chiasm, hypothalamus, and pituitary gland renders them a considerable threat, with significant associated morbidity and increase in mortality. Occurring both in child and adulthood, their clinical manifestations are broad, commonly with symptoms/signs secondary to hypothalamic-pituitary dysfunction, raised intracranial pressure and visual compromise. They have two distinct histological subtypes (adamantinomatous and papillary), with unique patterns of age distribution, and genetic and molecular make-up. With increasing understanding of their genetic pathogenesis including *BRAF V600E* mutations in the papillary subtype, and *β-catenin* mutations in the adamantinomatous, further research provides hope for the discovery of targeted medical therapy that can exploit molecular changes occurring as a result of such alterations. Until then, primary treatment consists of surgery with or without radiotherapy, with intracystic aspiration, chemotherapy or irradiation being alternative options in selected patients. Long term management by an experienced multidisciplinary team is essential, given the breadth of complications, including hypothalamic morbidity, visual compromise, cognitive and neuropsychological sequelae and impairment to quality of life.

Introduction

Craniopharyngiomas are histologically benign sellar/suprasellar tumours derived from the embryonic remnants of Rathke's pouch. Close to vital structures, their infiltrative tendency and often aggressive behaviour make them a formidable adversary to both endocrinologists and surgeons alike. Long term morbidity remains high, but recent advancements in surgery and radiotherapy, as well as promising developments in medical therapy, provide optimism for future improvement in what can be devastating outcomes associated with this tumour. Formulating an individualised treatment plan within a multidisciplinary environment is key, recognising that treatment offered, in spite of the local effects of the tumour itself, has the potential to have significant consequences to patient prognosis, including long term sequalae associated with hypothalamic insult. In this review, we start at the discovery of this volatile tumour beginning in the early 19th century, and using the latest available evidence, provide a comprehensive overview to the diagnosis, investigation and management of a craniopharyngioma. Crucially, we provide focus on associated morbidity and mortality, and highlight the potential role of new treatments that may improve future outlook.

History

Whilst the word 'craniopharyngioma' was popularised by Harvey Cushing back in 1932, these 'kaleidoscopic' tumours - as termed by Cushing himself - were first described much earlier, with consistent clinical symptoms and autopsy findings dating back to the 19th century, and case reports arguably suggestive of craniopharyngiomas arising as early as the 16th century [1, 2]. Zenker, a German pathologist, is recognised as first to characterise the tumour in 1857, describing a cystic suprasellar mass he discovered on autopsy containing

squamous epithelium and cholesterol crystals [3]. In 1899, Mott and Barrett reported three cases consistent with a diagnosis of craniopharyngioma, giving a detailed account of the pathophysiology and histology of the tumours, including the case of a 28-year-old man who died with severe fever who, on autopsy, was discovered to have a large multiloculated suprasellar tumour displacing the optic chiasm. Histologically, the tumour represented a papillary craniopharyngioma [1, 3]. In 1904, Erdheim, a pathologist in Vienna, described his findings of squamous epithelial cells in the adenohypophysis on the anterior infundibulum in adult patients [4]. His significant contribution to the understanding of this new entity lead to their branding as 'Erdheim tumours', a term frequently used to describe craniopharyngiomas in the early 20th century [1, 3]. Just 5 years later, in 1909, the first operation for a craniopharyngioma was performed in Chicago by neurosurgeon A.E Halstead. The index patient presented with headache, polyuria and significant visual deficit with bitemporal hemianopia and optic atrophy. The patient made a significant recovery, with complete resolution of headache, as well as sufficient improvement in vision, such that he could resume his work as an express coach driver [5, 6]. Now more than a century from that day, much has changed in our understanding of these tumours, yet the opinion held by Cushing that craniopharyngiomas represent 'the most formidable of intracranial tumours', is still shared by many today.

Epidemiology

Craniopharyngiomas represent approximately 2-5% of adult intracranial tumours [4, 7], and up to 15% of intracranial tumours in children [8]. They are rare, with a reported incident rate of between 0.05-0.2 per 100,000 people [9-12]. Papillary craniopharyngiomas (PCPs) are almost exclusive to adults, peaking between the ages of 40-55 years [9, 13, 14].

Adamantinomatous craniopharyngiomas (ACPs) are more common, and demonstrate a bimodal age distribution, with a peak incidence between ages 5-15 and 45-60 [10, 12], but can occur at any age, and have even been detected in utero [15]. Based on existing population studies, there appears to be equivocal susceptibility for both males and females [9, 12], and whilst there are case reports of craniopharyngiomas occurring in two families, there is no proven underlying genetic susceptibility [16, 17].

Pathology

Craniopharyngiomas are histologically classified as grade 1 tumours by the World Health Organisation [18] and can be divided into 2 subtypes; ACPs and PCPs. [4, 13, 19-21].

Macroscopically, ACPs are characterised by calcification, necrotic debris and fibrous tissue, with sharp and irregular margins. They have cystic and/or solid components, with cystic fluid having the appearance of 'machinery oil' or a 'shimmering' quality, attributed to the high cholesterol content which results from desquamated squamous epithelial cells, and includes membrane lipids and keratin [7].

Microscopically, ACPs contain organised layers of epithelium. The basal layer of palisading epithelium consists of columnar cells, often described as having a 'picket fence' appearance, whilst the intermediate layer- the stellate reticulum- consists of 'star-like' stellate cells, and is pale and microcystic. The top layer - facing into the cyst lumen - contains enlarged, flattened, keratinized squamous cells. Ghost cells - anuclear squamous cells that have lost their basophilic staining - accumulate to form nodules of 'wet keratin', a pathognomonic feature of ACPs. Rosenthal fibres and fibrillary gliosis, occurring in the adjacent normal brain tissue,

are additional characteristic microscopic findings seen in this tumour subtype [4, 7, 13, 22]. Histologically, ACPs are characterised by nodular whorls, anastomosing trabeculae and 'clover leaves' [23].

Figure 1A **Figure 1B**

PCPs consist of mature squamous epithelium forming pseudopapillae. They have a hyalinised stroma, with presence of mucinous cells and individualised or small aggregates of keratin, and are usually well delineated. Microscopically, PCPs lack palisading epithelium, a stellate reticulum and microcystic degeneration, and macroscopically necrosis, calcification and cholesterol are rarely seen. The cystic fluid appears viscous and yellow, providing differentiation from their adamantinomatous counterpart [4, 13]. Additionally, only the cellular membranes of the papillary subtype demonstrate β-catenin immunoreactivity, lacking abnormal nuclear accumulation as seen in ACPs [7].

Pathogenesis

Craniopharyngiomas are thought to arise from neoplastic transformation of ectoderm-derived epithelial cell remnants of Rathke's pouch and the craniopharyngeal duct [24]. This is further supported by the detection of molecular markers of Rathke's pouch precursors in both human and murine craniopharyngiomas [25, 26].

On a molecular level, *BRAF V600E* mutations, present in 77-100% [27-32] of PCPs, have been proposed to be an important driver of tumorigenesis through activation of the MAPK/ERK (Mitogen Activated Protein Kinase/Extracellular signal Regulated Kinases) pathway, a common contributor to tumorigenesis in many cancers. A mutated and constitutively active BRAF V600 phosphorylates MEK and leads to various downstream changes that result in translocation of ERK into the nucleus, causing subsequent activation of various transcription factors involved in cell growth, proliferation and cell survival [33]. Whilst BRAF V600E mutations are seen throughout numerous cell types in PCPs, only a small subset of cells containing the mutation trigger the activation of the MAP/ERK pathway [34]. Such cells are thought to be progenitor cells containing the transcription factor SOX^{2+} (Sex determining region Y- Box 2) and are able to expand and proliferate within human and murine PCPs [34]. Thus, it has been suggested that activation of the MAPK/ERK pathway within SOX progenitor cells is a major driver of tumour formation in PCPs.

Adamantinomatous tumours are associated with mutations in the β-catenin encoding gene *CTNNB1*, found exclusively on exon 3 [35]. β-catenin is a multi-protein complex which plays a prominent role as mediator and activator of the canonical Wnt signalling pathway – a critical regulator of cellular behaviour, homeostasis and cell fate [35]. Mutation in the β-catenin phosphorylation sites results in the accumulation of β-catenin within the cytoplasm which, in turn, is translocated into the nucleus. Excess nuclear β-catenin promotes the activation and transcription of target genes, and thereby leads to increased cellular proliferation [33]. The immune response has also been implicated to play an important role in the pathogenesis of this subtype; ACP tumour cells demonstrate a characteristic pattern of inflammation within the cystic fluid and the solid tumour components, and molecular analyses have discovered increased expression of multiple immunity related genes and

elevated cytokine levels, including IL-6, CXCL-1/GRO (Chemokine Ligand 1 / Growth-Regulated Oncogene), IL-8 and IL-10 [33, 36]. In addition, like in PCPs, activation of the MAPK/ERK pathway has been found to occur within ACP tumour cells, albeit in a ligand dependent manner, without mutation of *BRAF-V600E* [33]. Further to this, administration of trametinib, a MEK inhibitor which targets the MAPK/MEK pathway, has been shown to reduce cellular proliferation, and increase apoptosis in human and murine ACP cell models [37]. Additionally, the immune check point proteins PD-L1 and PD-1 (Programmed Death Ligand 1 and Programmed cell Death protein 1) are expressed in both subtypes of craniopharyngioma [38]. As such, these changes on a cellular and molecular level could be potential targets for medical therapy, including BRAF V600E inhibitors for PCPs, IL-6 inhibitors in ACP's, and both MEK inhibitors and PD-1 immune checkpoint inhibitors for both tumour subtypes [33, 38-40].

Location

Craniopharyngiomas can arise anywhere along the path of the craniopharyngeal duct, but they primarily occur in the suprasellar/sellar area. The vast majority have a suprasellar component, with only around 5% of tumours being solely intrasellar [4]. Rare tumour locations include the paranasal area and nasopharynx, completely in the third ventricle, temporal lobe, ethmoid sinus, sphenoid bone, pineal gland, posterior cranial fossa, midbrain and cerebellopontine angle [4].

Presenting Manifestations

Clinical presentation is dependent on the size, location and growth rate of the tumour[4]. Interval from symptom onset to diagnosis is variable but frequently delayed, ranging from one week to several decades [4, 41-45]. Headaches, visual impairment, as well as nausea and vomiting are the most common presenting symptoms in both children and adults, as are growth failure in children and hypogonadal manifestations in adults [4]. A recent meta-analysis of more than 700 adult patients treated with surgery reported visual impairment, symptoms of raised intracranial pressure and endocrinopathies as the most commonly presenting features in 67%, 37%, and 27% of patients, respectively [46]. In children, visual dysfunction occurs in 55-75% of cases [41, 42, 47-50].

Bitemporal hemianopia affects approximately half of the patients [43, 51, 52]. The degree and direction of the optic chiasm distortion correlates with the type and severity of visual impairment. Downward compression of the optic chiasm is associated with impaired vision in 20% of patients, whereas the respective rate for forward compression of the chiasm is > 90% [53].

Pituitary dysfunction is frequent at diagnosis. Based on series of both adults and children, with different diagnostic tests and criteria applied, GH deficiency is present in 35-95%, FSH/LH deficiency in 38-82%, ACTH deficiency in 21-62%, TSH deficiency in 21-42% and ADH deficiency in 6-38% of patients [4].

FIGURE 2

Imaging characteristics of craniopharyngiomas

Craniopharyngiomas usually appear as heterogeneous tumours on imaging. Their appearance varies subject to the presence of solid and cystic components, the level of calcification and the constituents of intra-cystic fluid (cholesterol, keratin or blood) [54]. They often have distinct radiological features that differentiate them from other tumours in the sellar region. Both Magnetic Resonance Imaging (MRI) and Computed Topography (CT) provide are valuable in the diagnostic work-up of a patient with a suspected craniopharyngioma.

MRI and CT

T1-weighted MRI sequences with and without gadolinium, in the coronal and sagittal plane provide optimal assessment of tumour proximity to neighbouring structures including the optic chiasm, hypothalamus and the third ventricle. Contrasted T1-weighted sequences depict solid tumours as hyperintense, and cystic components as iso- or hypointense. The cystic wall also enhances with contrast. [55]. Additionally, protein, cholesterol and methaemoglobin may demonstrate high signal on T1-weighted images [54-56] Obstructive hydrocephalus is often present in intraventricular tumours.

FIGURE 3A

FIGURE 3B

FIGURE 4A

FIGURE 4B

On T2-weighting, cystic features are typically hyperintense, solid components of the tumour are usually of mixed hypo- or hyperintensity, and the presence of high concentrations of protein, cholesterol and methaemoglobin demonstrate a low T2-weighted signal [54].

Microcalcification is visible in approximately 75% of craniopharyngiomas [57], seen more commonly in ACPs and in childhood-onset disease. Whilst high concentrations can be seen on MRI, CT is the superior modality for its detection. Calcification can form 'popcorn-like' foci or more rarely, an egg shell pattern coating the cyst wall [7]. CT is useful to demonstrate the bony anatomy and can also help delineate cystic from solid tumour components, in which cystic fluid has a hypointense appearance, and solid parts enhance following contrast [54].

Whilst imaging cannot accurately differentiate ACPs from PCPs, ACPs commonly contain both cystic and solid components and calcification, whereas PCPs can be entirely solid, do not typically calcify and are usually less locally infiltrative. [7].

Radiological differential diagnosis

The differential diagnosis for craniopharyngiomas is broad, including Rathke's cleft cysts, meningiomas, pituitary adenomas, germinomas, gliomas, hamartomas, dermoid, epidermoid and arachnoid cysts, anterior communicating artery aneurysms, as well as infiltrative diseases including sarcoidosis, tuberculosis and Langerhans histiocytosis [4]. Rathke's cleft cysts can often be differentiated given their lack of calcification, absence of a solid component, oval appearance, as well as minimal to no enhancement of the cyst wall and contents following

gadolinium administration [58]. Likewise, pituitary adenomas are less enhanced compared to the solid parts of craniopharyngiomas following contrast [59]. Despite these differences, intra-sellar craniopharyngiomas or homogeneously enhancing solid craniopharyngiomas (albeit rare), can be challenging when differentiating them from Rathke's cleft cysts or pituitary adenomas.

Tumour topography and image grading systems

Tumour topography, as well as tumour proximity and attachment to the hypothalamus, are important factors determining surgical risks, hypothalamic damage and subsequent hypothalamic morbidity. Both pre- and post-operative tumour classification systems assessing hypothalamic involvement can be helpful in predicting hypothalamic sequelae and risk of hypothalamic morbidity. In a retrospective cohort of 66 patients, Puget *et al.*[60], analysed pre-operative prognosticators that influenced post-operative outcome in paediatric cases with craniopharyngioma. By using pre-operative imaging, they proposed a grading system based on degree of hypothalamic involvement, which was classified into three grades. Grade 0 describes tumours which clearly show no hypothalamic involvement, grade 1 tumours are those where the lesion abuts or elevates the hypothalamus (but the hypothalamus remains visible), and grade 2 are those where the hypothalamus is no longer visible [60]. By applying this system, they found a significant correlation between higher tumour grade and post-operative hypothalamic morbidity and as such, proposed that Gross Total Resection (GTR) should be avoided for grade 2 craniopharyngiomas. They subsequently applied these criteria to a prospective cohort of 22 children (with similar pre-operative imaging and clinical characteristics), and demonstrated significant reduction in hypothalamic morbidity compared

to the retrospective cohort (including mean post-operative BMI, appetite dysregulation and change in post-operative Quality of Life)[60].

Similarly, Muller *et al.*[61], proposed a pre-operative, but also a post-operative, grading system to define pre-operative hypothalamic involvement or post-operative presence of surgical lesions involving the hypothalamus, specifically in reference to hypothalamic mammillary bodies [61]. Craniopharyngioma were graded as 0, if there was no hypothalamic tumour involvement or no surgical lesion visible; grade 1, if there was hypothalamic involvement or a surgical lesion in the anterior hypothalamus (but with sparing of the mammillary bodies and hypothalamic area beyond them), and grade 2, if there was tumour or a surgical lesion involving the anterior and posterior hypothalamus (i.e., involving the mammillary bodies and the area beyond them). They found that pre-operative hypothalamic involvement of the anterior and posterior hypothalamus (grade 2) was associated with higher risk of hypothalamic morbidity, and patients who sustained anterior or posterior hypothalamic lesions following surgery (grades 1 and 2) had higher post-operative BMI and lower health related QOL scores compared to those without hypothalamic lesions (grade 0) [61].

More recently, Prieto *et al.*[62], in a retrospective study of 200 patients with craniopharyngioma, identified several key radiological findings that successfully predicted both craniopharyngioma topography, as well as severity of adherence (the attachment formed between tumour and hypothalamus through adhesions), when using standard sagittal and coronal T1+T2-weighted imaging [62, 63]. In their analysis, they found that adherence severity correlated with poorer outcomes, and subsequently, identified three pre-operative radiological variables which correctly identified those with the greatest severity of intra-

operative adherence in nearly 90% of cases [62]. These included presence of the hypothalamus within the middle portion of the tumour, infiltration of the pituitary stalk and an elliptical tumour shape [62]. A pre-operative grading system predicting adherence severity could facilitate decisions on extent of attempted excision and risk for hypothalamic morbidity.

Management

Surgery

Surgical resection is the first line management option in the vast majority of adult onset craniopharyngiomas. Surgical approach and technique depend on many factors, including size, consistency of the tumour, location and the degree of extension towards neighbouring structures, as well as experience and preference of the surgical team involved [54]. Surgery is particularly challenging due to irregular and jagged tumour borders, often large size and adherence to nearby structures [4]. Additionally, they may lack a distinct dissection plane as they sometimes invade neural tissue and are adherent to the neighbouring neurovascular structures, making safe GTR impossible [59]. Surgery via the transsphenoidal route is generally regarded as the most favourable approach where possible, allowing exposure to the third ventricle floor, hypothalamus and pituitary stalk, whilst avoiding optic nerve and chiasm mobilisation [64].

Extent of Surgical Resection

The extent of tumour clearance, either via GTR or Subtotal/Partial Resection (STR) followed by adjuvant radiotherapy remains controversial. Whilst safe GTR may be possible is some cases performed by experienced surgical hands, STR with adjuvant radiotherapy is arguably considered to be the favourable approach for the majority of craniopharyngiomas. This has been emphasised over the last decade by the increasing appreciation of the impact of hypothalamic morbidity and its relationship with tumour topography and hypothalamic adherence, as well as the ability to achieve comparable rates of tumour control and overall survival with either approach [46, 65, 66]. Notably, in a meta-analysis conducted by Akinduro *et al.* looking at endocrine and visual outcomes in adult craniopharyngioma, found that GTR was associated with lower risk of recurrence compared with STR, nonetheless, GTR had a significantly higher likelihood of panhypopituitarism and permanent diabetes insipidus [67].

Data on risk of hypopituitarism is inconsistent when comparing either approach, with some groups reporting no statistically significant difference [68, 69], yet in other reports, those receiving GTR were more than twice as likely to develop at least one endocrinopathy compared to those who received STR and adjuvant radiotherapy [70]. Despite ongoing debate, in the presence of a clear separation point between tumour and hypothalamus, attempt at GTR during first surgery is generally considered to be the optimal choice, as subsequent surgical attempts can be associated with increased mortality and morbidity [59]. For those tumours with hypothalamic invagination or signs of adherence, subtotal resection with adjuvant radiotherapy is the recommended approach given the increased risk of hypothalamic damage and negative long-term sequelae [59, 71-74].

Cyst aspiration, intracystic drug therapy or radioisotope insertion

Predominantly cystic craniopharyngiomas may be amenable to aspiration, providing rapid resolution of symptoms of mass effect; this approach can be a means of delaying surgery and/or radiotherapy and their potential complications especially in children [54]. The insertion of an Ommaya reservoir - an intraventricular catheter accessed subcutaneously - provides an accessible route for recurrent aspiration, as well as administration of intracystic chemotherapy, radionuclides or biological therapy [75]. Small studies in paediatric populations have demonstrated Ommaya reservoirs to be effective in controlling tumour growth without the need for additional treatment (radiotherapy or surgery) in 43-73% of cases, with an average follow-up of 7 years [75-77].

Localised administration of intracystic drug therapy is more commonly reserved for children and young adults with craniopharyngiomas, where delaying surgery or radiotherapy can be helpful to reduce the risk of associated complications.

Bleomycin, a neurotoxic chemotherapy agent, was first discovered as a potential treatment for craniopharyngiomas as early as 1971 [78], and it's first use in patients was reported in 1985, where it was found to reduce tumour size in patients with cystic craniopharyngiomas, but not in solid or mixed tumours [79]. Multiple small scale reports since then have demonstrated its efficacy, including a study and literature review by Hukin *et al.* [80], who described that > 25% cyst size reduction was seen in up to 90% of patients, and > 90% cyst size reduction in 50% of 70 adults and children with craniopharyngiomas [80]. However, evidence to date is mostly limited to case reports or small non-randomised, retrospective studies, whereas a recent Cochrane review found insufficient evidence to support its use in children, particularly given the risk of side effects [81]. These include (but are not limited to) headache, nausea, vomiting and fever, seen in approximately 70% of recipients [80] , but also

hypothalamic injury, visual loss, peri-tumour oedema, cerebral ischaemia, hemiparesis and death have all been reported [81].

Radioisotopes, including yttrium-90 (90Yt), rhenium-186 (186Rh), and phosphorus-32 (32P) are additional intracystic therapies. Like bleomycin, they have been shown in small studies to reduce cyst size, but the risk of severe side effects including radio-necrosis and visual loss, has been reported in about 5% of patients; its use is, therefore, limited, and this approach is available in few specialist centres [77].

Intracystic delivery of interferon-α, a non-neurotoxic treatment alternative, has a more favourable side benefit-to-risk ratio [82]. Several studies with short follow-up have reported excellent results, including a complete response in a large proportion of patients [83-85]. However, a recent multicentre international study found that 75% of patients had tumour progression at a median time of just 14 months [86], highlighting that for the majority, benefit is limited to a delaying tactic, as opposed to a definitive treatment modality.

Radiotherapy

Radiotherapy is an effective adjunctive treatment modality in the management of craniopharyngiomas. Indeed, adjuvant radiotherapy administered following subtotal/partial resection or after tumour recurrence offers better long-term survival rates when compared to surgery alone [4, 87-89]. Historically, conventional radiation therapy (CRT) has been the standard radiation therapy modality administered to patients with craniopharyngiomas. CRT offers 10 year recurrence rates between 10-63% when given in its adjuvant capacity

following subtotal/partial removal [4]. New or worsening of hypopituitarism is reported in 20-60% of patients who received CRT after 5-10 years of follow-up, and radiation induced optic neuropathy causing visual deficit occurs in 2-8% of patients [88]. Transient cyst enlargement, occurring during or following radiotherapy (within 6 months) is a recognised complication and has been reported in 10-60% of patients [90-93]. This can result in manifestations secondary to mass effect, including hydrocephalus and displacement of the optic chiasm, and thus, patients should be closely monitored both during and after radiotherapy administration. Despite rapid growth requiring urgent surgical decompression in some cases, cystic enlargement is a transient phenomenon necessitating only careful observation in the majority, and is not indicative of disease progression [90].

Intensity Modulated Radiation Therapy (IMRT), Fractionated Stereotactic Radiotherapy (FSRT), Stereotactic Radiosurgery (SRS) and proton beam therapy are newer modalities used increasingly in the management of craniopharyngiomas. Such routes allow delivery of precise, targeted therapy, thereby reducing exposure of healthy tissue to radiation, and in turn, may reduce risk of radiation toxicity. Choice of modality is largely influenced by tumour size, as well as proximity to nearby vital structures. Tumour control rates after SRS are negatively associated with tumour volume [94], and those patients with smaller sized residuum at least 3-5mm away from the optic chiasm and nerves are likely to be more suitable candidates of SRS [95]. For SRS, tumour control rates of between 67 and 86% at 5 years have been reported [96, 97]. For FRST, reported rates of local control are between 92% [98] and 95% [99] at 5 years and 100% at 10 years [100]. Long term data after proton beam therapy are limited, but local control rates appear to be comparable with FSRT, and may reduce the potential for neurocognitive decline, hypopituitarism and secondary brain tumours in the paediatric population [101, 102].

Medical Management

Use of systemic interferon in craniopharygiomas has shown mixed results. Jackacki *et al*.[103] were first to evaluate its use in a cohort of 15 children with craniopharyngiomas. Of the 12 evaluated following subcutaneous interferon administration, three showed evidence of tumour response to treatment, however 25% demonstrated disease progression on treatment, and whilst transient, 60% of patients developed hepatic, cutaneous or neurological toxicities in the first 8 weeks [103]. A further analysis by the same group in 2012 reported the use of pegylated interferon – a derivative of interferon with a longer half-life – in 5 patients with craniopharyngioma. Interestingly, all showed radiological evidence of tumour response, including two who demonstrated a complete response to treatment [104]. This was followed by a recent multi-centre study examining the effect of pegylated interferon in a cohort of 18 children and young adults with recurrent craniopharyngiomas who had all received surgery, but prior use of radiotherapy was variable. Although treatment was well tolerated, treatment response was disappointing, with only two patients demonstrating response, of which only one had a sustained response to systemic pegylated interferon beyond 3 months [105].

Drugs targeting the MAPK/ERK pathway are a promising and evolving approach at the forefront of current research in the management of craniopharyngiomas. *BRAF V600E* mutation specific inhibitors have been shown to be effective in numerous cancers containing the V600E mutation, and are often supplemented with MEK inhibitors, agents that override resistance to BRAF inhibition [33, 106]. For the papillary subtype, in which the *BRAF V600E* mutation triggers activation of the MAPK/ERK pathway, use of BRAF inhibitors has been

shown in a number of case reports to have led to a dramatic reduction in tumour size, both when used alone or in combination with MEK inhibitors, applied neoadjuvantly or following surgery, with or without radiotherapy [39, 107-115]. More recently, Patel *et al.* [116] reported a case of a 26 year old patient with the adamantinomatous subtype, who, after 8 surgeries, chemotherapy and radiotherapy, received binimetinib, a MEK inhibitor used off licence in effort to relieve the progressive disease. The authors reported a significant reduction in tumour size, as well as stable disease following a year of medical therapy [116]. Grob *et al.* [40] reported two cases of paediatric cystic craniopharyngioma successfully controlled with tocilizumab, an IL-6 inhibitor, used alone or in conjunction with bevacizumab, a Vascular Endothelial Growth Factor (VEGF) inhibitor. Both children had extensive treatment prior to initiation, and were confirmed to have IL-6 in cystic tumour fluid. Both patients achieved a reduction in cyst size, and at the time of publication, were undergoing MRI surveillance alone [40].

Whilst evidence to date is limited to case reports and small case series (summarised in Table 1), randomised control trials involving combination therapy with both BRAF V600E and MEK inhibitors for PCPs, and IL-6 inhibitors for children and adolescents with ACPs are currently underway [117, 118].

TABLE ONE

Morbidity

Craniopharyngiomas carry significant morbidity attributed to direct invasion of the primary tumour and its recurrence(s), and/or to the sequelae of therapeutic intervention(s). Endocrine and metabolic dysfunction frequently result, but compromise to cerebrovascular, ophthalmic, cardiovascular, and respiratory function can also occur. Neurological, psychological and psychosocial complications may also follow, all summarised below.

Endocrine sequalae

Hypopituitarism, either partial or complete, is encountered in the vast majority of patients with craniopharyngiomas. Numerous case series, with different diagnostic criteria, as well as variable management and follow-up periods, report loss of at least three hormone axes in 54-100% of patients [4]. Individual hormone deficits range from 88-100% for GH, 80-95% for FSH/LH, 55-88% for ACTH, 39-95% for TSH and 25-86% for ADH [4]. Both panhypopituitarism and permanent diabetes insipidus are more likely in adults who have received GTR compared with STR [67]. Unlike anterior pituitary tumours, reversal of hormone deficit following treatment is extremely uncommon, with any hormone deficit being permanent for nearly all patients [4].

Hormone replacement therapy is vital, and the aims of replacement are the same for those with craniopharyngiomas and those who have hypopituitarism due to a different aetiology [119]. GH replacement therapy has been shown to be safe in numerous retrospective studies with adults and children, resulting in neither tumour growth nor tumour recurrence [120, 121]. A recent prospective study with follow-up of approximately 12 years showed that in addition to benefiting growth, childhood patients who received GH replacement had improved weight and quality of life outcomes when compared to those who did not receive

this treatment, or received GH only in adulthood [122]. Despite this, GH replacement does not prevent obesity [123-125]. Furthermore, unlike other hypopituitary patients in whom GH replacement leads to mortality risk that is comparable to the background population [126], GH replacement therapy has not been shown to reduce mortality for those with craniopharyngiomas [122, 127-129].

Vision

Visual disturbances represent one of the most commonly observed long term complications, irrespective of treatment choice in both adults and children alike. In a recent study of 128 treated craniopharyngioma patients with a median follow-up of 13 years, 75% of them had evidence of visual disturbance, with no significant difference in visual outcomes between children or adults, or in relation to initial treatment modality (including GTR, STR with or without radiotherapy, cyst aspiration or use of yttrium-90) [68]. These findings are in keeping with previous studies analysing long term health outcomes based on initial treatment approach [130-132], with exception of Karavitaki *et al.* [41] who found that deterioration in visual fields was more likely after initial treatment with STR alone, when compared to GTR, and GTR or STR with adjuvant radiotherapy [41].

Hypothalamic morbidity and metabolic complications

Insult to the hypothalamus, via treatment or tumour, can have a profound impact on morbidity. Obesity, sleep disturbance, dysregulated temperature homeostasis, disruption to normal thirst and electrolyte regulation including diabetes insipidus, as well as neurocognitive, psychosocial and behavioural issues can all result. In fact, 35% of patients

with craniopharyngiomas will have symptoms and signs consistent with hypothalamic impairment at time of diagnosis, rising to between 65 and 80% following surgery [133].

Hypothalamic obesity (HO) is a common and significant sequalae encountered in 40-66% of patients with childhood-onset craniopharyngiomas [134]. Weight gain, which may have arisen by the time of diagnosis, predominantly presents within the first year after surgery [135], before levelling off, but remains sustained [133]. Craniopharyngiomas with hypothalamic involvement have been shown in numerous studies to correlate with the severity of obesity [134, 136, 137], which in turn, has been shown to result in increased likelihood of impaired QOL [138]. HO contributes to the increased risk of cardiovascular disease, type 2 diabetes, metabolic syndrome and obstructive sleep apnoea in patients with craniopharyngiomas [139-142].

The causes of HO in patients with craniopharyngiomas are multifactorial, including increased energy intake, reduced energy expenditure, dysregulation of the autonomic nervous system, behavioural changes, sleep disturbance, hypopituitarism and hyperinsulinaemia [143]. On a biochemical level, damage to the paraventricular and suprachiasmic nuclei disrupts the vagal tone, triggering excess vagal stimulation, which in turn, causes a rise in insulin secretion, and energy storage [144]. Interestingly, rates of hyperinsulinaemia and insulin resistance have been found to be higher in those with craniopharyngiomas when compared to those without, matched to BMI, sex and stage of puberty [145]. Whilst chronic hyperinsulinaemia triggers a compensatory rise in leptin and suppression of ghrelin [146], damage to the ventromedial nuclei within the hypothalamus leads to impaired processing of afferent signals including insulin, leptin and Glucagon-Like Peptide-1 (GLP-1) [144]. Insensitivity to endogenous leptin [147] and impaired processing of these other afferent signalling are recognised factors

leading to disordered appetite and impaired satiety. Somnolence, visual impairment, neurological defects, hypopituitarism and psychological disorders represent additional exacerbating factors [7].

Management of HO is particularly challenging. To date, drug therapy has not been proven to be of benefit in a randomised control trial setting. Small studies have looked at various agents, including GLP-1 analogues [148-150], metformin combined with diazoxide [151], fenofibrate [152] and pioglitazone [153], central nervous system stimulants [154-156], somatostatin analogues [157], supraphysiological doses of liothyronine [158, 159], and oxytocin [160], most with variable, and modest results. A recent systematic review recommended an individualised patient approach following assessment for likely contributing factors, including use of GLP-1 analogues in those with insulin resistance, GLP-1 analogues and/or methylphenidate in those with hyperphagia, or dextro-amphetamine in patients with psychosocial disorders or decreased energy expenditure [143].

Bariatric surgery, including sleeve gastrectomy, Roux-en-Y gastric bypass and biliopancreatic diversion, were found to be the most effective surgical methods resulting in weight loss in a systematic review published in 2013, analysing outcomes at one year following surgery [161]. A case control study by Wijnen *et al*. in 2017 supported the use of Roux-en-Y gastric bypass, reporting comparable weight loss outcomes between craniopharyngioma patients and 'common obesity' subjects. However, unlike the earlier systematic review, the study found no significant weight loss in those who had sleeve gastrectomy [162].

Ultimately, treatments for hypothalamic obesity are of limited efficacy, and can be associated with significant side effects and may not be appropriate for children [133]. As such, in addition to further research into pharmacological therapy, focus on prevention by avoiding hypothalamic injury where at all possible, remains key.

Neurobehavioral impact, Cognitive Impairment and Quality of life

Childhood survivors of craniopharyngioma are frequently found to have some degree of social, emotional or neurobehavioral impairment [163]. Patients are more likely to develop deficits in memory (episodic long term memory in particular), executive function, attention, as well as processing speed, with hypothalamic involvement being an increased risk factor for poorer outcomes [164]. It is, therefore, unsurprising that this, in turn, can impact on relationships, day to day functioning and result in changes in behaviour [165]. Problems at school are frequently reported, and, unfortunately, poorer health related quality of life scores are seen in comparison to healthy controls [166]. Depressive symptoms and increased apathy are also more likely [163, 167], and in an analysis by Karavitaki *et al.*, 15% of 121 patients with craniopharyngiomas had psychological disorders requiring treatment [41]. Pre-operative hypothalamic involvement or surgically induced damage to the hypothalamus has been linked to a lower quality of life in children and adolescents with craniopharyngioma, as well as GTR and radiotherapy [73].

Mortality

Mortality rates have been reported as nearly 6 times higher than the general population [168]. In cohorts of both adults and children, overall survival rates range from 40-93% and 66-85%

at 10 and 20 years, respectively [169]. Cardiovascular, cerebrovascular and respiratory related mortality have all been shown to be increased [11, 168, 170-173]. Recent advances in neurosurgical techniques and apparatus used, in addition to the wider variety of radiotherapy modalities offered, may be starting to turn the tide. A meta-analysis published in 2018 including 2,802 patients who had received treatment for a craniopharyngioma found the pooled Standardised Mortality Ratio (SMR) pre 2000 to be 6.2, (CI 4.1-9.4), dropping to 2.9 after 2010 (CI 2.2-3.8) [174]. Evidence to support one initial treatment modality in favour of another based on improved survival rates alone is inconsistent, with overall survival being comparable between GTR *vs* STR with radiotherapy [41, 66, 68]. Female sex [11, 168, 170, 175, 176], as well as childhood-onset disease [11, 72, 127, 170], have been linked to increase in mortality, but other studies have not confirmed this [21, 41, 89]. Similarly, histology type and hydrocephalus are other poor prognosticators identified by some [170, 177], but not others [13, 21, 41, 89]. Tumour recurrence however, is widely accepted as a negative influencing factor on mortality, with survival rates of 29-70%, depending on subsequent treatment modality offered [4].

The association between increased mortality and hypopituitarism due to any cause is long established, but those that have craniopharyngiomas have mortality rates nearly 10 times higher than other hypopituitary patients in some reports [172, 178]. A Swedish based population study involving 307 patients with craniopharyngiomas, followed-up for a mean of 9 years reported a SMR of 2.7 (CI 1.4-4.6) in patients with craniopharyngiomas who lacked any hormone deficit, compared with an SMR of 4.3 (CI 3.1-5.8) in craniopharyngioma patients with hypopituitarism, and an SMR of 6.1 (CI 3.5-9.7) in those with diabetes insipidus [11]. In those with hypopituitarism (with or without diabetes insipidus), increased mortality was attributable to circulatory diseases (including cerebrovascular disease), not seen in the

small number who had normal pituitary function [11]. From this study, 67 patients were also included in a hospital based retrospective study, involving a total of 224 patients followed for 13 years. Again, panhypopituitarism was linked to excess mortality, with circulatory diseases, cerebrovascular disease and respiratory infections being the main causes of death [170].

Conclusions and future perspectives

Craniopharyngiomas remain a challenging tumour to manage. With increasing recognition of the impacts of both tumour and the consequences of its management, the need to focus on treatments that not only improve survival, but also reduce the significant impact of hypothalamic morbidity, remain a priority. Until such treatments come to light, attempt to prevent hypothalamic insult with subtotal resection and adjuvant radiotherapy, currently appears to be the optimal treatment approach in the majority of patients. Cystic aspiration and delivery of intracystic drug therapy represent alternative treatment options that may be appropriate in cystic tumours, particularly in paediatric cases. Regardless of treatment choice, life-long multidisciplinary care is essential to surveil for recurrence, as well as to manage and offer rehabilitation to those who are left with endocrine, metabolic, visual, neurocognitive and psychosocial sequalae. Improved understanding of tumour pathogenesis and molecular targets for drug therapy are exciting areas at the forefront of translational research. The use of BRAF V600 and MEK inhibitors in particular, described in an increasing number of case reports, offer a glimmer of hope for a novel and beneficial treatment option, with the results of randomised, prospective trials eagerly awaited.

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Figure 1A. *Histology of ACP. Well-differentiated epithelium with palisading, nodular whorls (top half of image), and the intermediate layer – the stellate reticulum- consisting of pale, microcystic areas. A 'wet keratin' nodule can be seen in the bottom right of the image. HE x200 magnification.*

Figure 1B. *Histology of PCP. Papillae lined by non-keratinising squamous epithelium and containing loosely structured connective tissue; HE x20 magnification* [Reproduced with permission from Endotext.org. Lithgow K, Pohl U, Karavitaki N. Craniopharyngiomas. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2019 Mar 14.]

Figure 2. *Data from Karavitaki et al [41]. Presenting clinical features of 119 patients with craniopharyngioma (41 children + 78 adults) recorded in medical notes of patients reviewed in adult and paediatric services over a 40-year period. *In those ≥ 13 years, n=91. ** In adult women, n=37.*

Figure 3A. *T1-weighted MRI with contrast, coronal section*

Figure 3B. *T1-weighted MRI with contrast, sagittal section. The cystic rim of the craniopharyngioma is enhanced, whilst the inner contents are isointense.* [Reproduced with permission from Endotext.org. Lithgow K, Pohl U, Karavitaki N. Craniopharyngiomas. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2019 Mar 14.]

Figure 4A. *T2-weighted coronal section showing a solid craniopharyngioma enhanced following contrast*

Figure 4B. *T2-weighted coronal section depicting mixed signal intensities consistent with a solid and cystic craniopharyngioma.* [Reproduced with permission from Endotext.org. Lithgow K, Pohl U, Karavitaki N. Craniopharyngiomas. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2019 Mar 14.]

TABLE I: A summary of selected case reports of medical therapy used in craniopharyngiomas

Author and year	CP Type	Previous Treatment	Medical Treatment	Treatment Duration	Radiological Outcome	Additional information
Aylwin [107] et al 2015	PCP	TSS X2 RT	Vemurafenib 960mg BD	3 months initially (Held following CSF leak and meningitis), then a further 7 months	Near CR after 3 months, then regrowth 3 months after stopping, Tumour control for 7 months on therapy then progression	Treatment stopped after a total of 10 months of treatment due to progression and reduction in PS. Patient died 6 months after [115]
Brastianos et al [108] 2015	PCP	Craniotomy x 3	Dabrafenib 150 mg BD, and at week 3, trametinib 2mg OD	1 month	PR -85% decrease	Surgery and RT following medical treatment, tumour free at one year [115]
Roque et al [110] 2017	PCP	Craniotomy Ommaya reservoir and RT	Dabrafenib 150mg BD, trametinib 2mg OD	2 years and 9 months*, continues on treatment	CR by 7 months	CR maintained since treatment began [115]
Rostami et al [109] 2017	PCP	TSS	Dabrafenib 150 mg BD, and at week 3 trametinib 2mg OD	4 months	PR - 91% decrease	
Himes et al [111] 2019	PCP	Craniotomy + RT	Dabrafenib 150mg BD, changed to OD, then trametinib 2mg OD	9 months	CR	No tumour recurrence 18 months after stopping therapy [115]
Juratli et al [115] 2019	PCP	Nil	Dabrafenib 150mg BD, trametinib 2mg OD	6 months	PR >80% decrease	
Bernstein et al [39] 2019	PCP	TSS+RT	Dabrafenib 150mg BD, trametinib 2mg OD		CR at 28 months	
Grob et al [40] 2019	ACP x 2	Case 1+2: multiple cystic aspirations, INF-α, bleomycin. Case 2: Craniotomy and RTX	Case 1: tocilizumab + bevacizumab at 8 months Case 2: Tocilizumab alone	14 months of combination therapy Case 2: 7 months	Significant reduction in cyst size PR	

Khaddour et al 2020 [113]	PCP	TSS	Dabrafenib 150mg BD, trametinib 2mg OD	9 months, then RT	PR >70% decrease (pre-RT)	Remission for 2 years
Stefano et al [114] 2020	PCP	TSS	Dabrafenib 150mg BD, trametinib 2mg OD	208 days, then RT	>94% decrease at day 72 (pre-RT)	At 385 days, sustained control
Patel et al [116] 2020	ACP	Surgery x 8, RT x 2 + Chemotherapy	Binimetinib 45mg BD, reduced to 30mg BD, then 30mg OM and 15mg OE	April 2019 to August 2020 (publication submission date) 16 months with occasional interruptions	PR -Decrease from 3.5 x 2.5 x 2.5cm to 2.8 X 2.1 X 2.8cm (after 6 months of treatment)	Stable disease

*CP = Craniopharyngioma, TSS = Transphenoidal Surgery, RT= Radiotherapy, CR= Complete Response, PR = Partial Response, PS = Performance Status, INF-α = Interferon-α, * 7 months of treatment completed by publication of April 2017 [110], and remains on treatment at time of update in June 2019 [115].*

Glossary of abbreviations:

ACP - Adamantinomatous Craniopharyngioma

PCP - Papillary Craniopharyngioma

MAPK/ERK - Mitogen Activated Protein Kinase/Extracellular signal Regulated Kinases

SOX^{2+} - Sex determining region Y- Box 2

CXCL-1/GRO - Chemokine Ligand 1 / Growth-Regulated Oncogene

IL-6/8/10 – Interleukin 6/8/10

PD-L1 and PD-1 -Programmed Death Ligand 1 and Programmed cell Death protein 1

MEK – Mitogen activated Extracellular signal-regulated Kinase

FSH- Follicle Stimulating Hormone

LH – Luteinizing Hormone

GH – Growth Hormone

TSH – Thyroid Stimulating Hormone

ACTH – Adrenocorticotropic Hormone

ADH – Anti-Diuretic Hormone

T3- Triiodothyronine

GLP-1 - Glucagon- Like Peptide-1

90Yt -Yttrium-90

186Rh- Rhenium-186

32P - Phosphorus-32

CRT – Conventional Radiotherapy

IMRT - Intensity Modulated Radiation Therapy

FSRT- Fractionated Stereotactic Radiotherapy

SRS - Stereotactic Radiosurgery

MRI - Magnetic Resonance Imaging

CT- Computed Topography

GTR - Gross Total Resection

STR - Sub Total/Partial Resection

HO - Hypothalamic Obesity

SMR - Standardised Mortality Ratio

QOL – Quality Of Life

Craniopharyngiomas

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Abstract

Craniopharyngiomas are rare epithelial tumours situated primarily in the sellar/parasellar region, occurring along the path of the craniopharyngeal duct. Whilst classed as histologically benign tumours, their unpredictable growth pattern and proximity to vital structures including the optic chiasm, hypothalamus, and pituitary gland renders them a considerable threat, with significant associated morbidity and increase in mortality. Occurring both in child and adulthood, their clinical manifestations are broad, commonly with symptoms/signs secondary to hypothalamic-pituitary dysfunction, raised intracranial pressure and visual compromise. They have two distinct histological subtypes (adamantinomatous and papillary), with unique patterns of age distribution, and genetic and molecular make-up. With increasing understanding of their genetic pathogenesis including *BRAF V600E* mutations in the papillary subtype, and *β-catenin* mutations in the adamantinomatous, further research provides hope for the discovery of targeted medical therapy that can exploit molecular changes occurring as a result of such alterations. Until then, primary treatment consists of surgery with or without radiotherapy, with intracystic aspiration, chemotherapy or irradiation being alternative options in selected patients. Long term management by an experienced multidisciplinary team is essential, given the breadth of complications, including hypothalamic morbidity, visual compromise, cognitive and neuropsychological sequelae and impairment to quality of life.

Introduction

Craniopharyngiomas are histologically benign sellar/suprasellar tumours derived from the embryonic remnants of Rathke's pouch. Close to vital structures, their infiltrative tendency and often aggressive behaviour make them a formidable adversary to both endocrinologists and surgeons alike. Long term morbidity remains high, but recent advancements in surgery and radiotherapy, as well as promising developments in medical therapy, provide optimism for future improvement in what can be devastating outcomes associated with this tumour. Formulating an individualised treatment plan within a multidisciplinary environment is key, recognising that treatment offered, in spite of the local effects of the tumour itself, has the potential to have significant consequences to patient prognosis, including long term sequalae associated with hypothalamic insult. In this review, we start at the discovery of this volatile tumour beginning in the early 19th century, and using the latest available evidence, provide a comprehensive overview to the diagnosis, investigation and management of a craniopharyngioma. Crucially, we provide focus on associated morbidity and mortality, and highlight the potential role of new treatments that may improve future outlook.

History

Whilst the word 'craniopharyngioma' was popularised by Harvey Cushing back in 1932, these 'kaleidoscopic' tumours - as termed by Cushing himself - were first described much earlier, with consistent clinical symptoms and autopsy findings dating back to the 19th century, and case reports arguably suggestive of craniopharyngiomas arising as early as the 16th century [1, 2]. Zenker, a German pathologist, is recognised as first to characterise the tumour in 1857, describing a cystic suprasellar mass he discovered on autopsy containing

squamous epithelium and cholesterol crystals [3]. In 1899, Mott and Barrett reported three cases consistent with a diagnosis of craniopharyngioma, giving a detailed account of the pathophysiology and histology of the tumours, including the case of a 28-year-old man who died with severe fever who, on autopsy, was discovered to have a large multiloculated suprasellar tumour displacing the optic chiasm. Histologically, the tumour represented a papillary craniopharyngioma [1, 3]. In 1904, Erdheim, a pathologist in Vienna, described his findings of squamous epithelial cells in the adenohypophysis on the anterior infundibulum in adult patients [4]. His significant contribution to the understanding of this new entity lead to their branding as 'Erdheim tumours', a term frequently used to describe craniopharyngiomas in the early 20th century [1, 3]. Just 5 years later, in 1909, the first operation for a craniopharyngioma was performed in Chicago by neurosurgeon A.E Halstead. The index patient presented with headache, polyuria and significant visual deficit with bitemporal hemianopia and optic atrophy. The patient made a significant recovery, with complete resolution of headache, as well as sufficient improvement in vision, such that he could resume his work as an express coach driver [5, 6]. Now more than a century from that day, much has changed in our understanding of these tumours, yet the opinion held by Cushing that craniopharyngiomas represent 'the most formidable of intracranial tumours', is still shared by many today.

Epidemiology

Craniopharyngiomas represent approximately 2-5% of adult intracranial tumours [4, 7], and up to 15% of intracranial tumours in children [8]. They are rare, with a reported incident rate of between 0.05-0.2 per 100,000 people [9-12]. Papillary craniopharyngiomas (PCPs) are almost exclusive to adults, peaking between the ages of 40-55 years [9, 13, 14].

Adamantinomatous craniopharyngiomas (ACPs) are more common, and demonstrate a bimodal age distribution, with a peak incidence between ages 5-15 and 45-60 [10, 12], but can occur at any age, and have even been detected in utero [15]. Based on existing population studies, there appears to be equivocal susceptibility for both males and females [9, 12], and whilst there are case reports of craniopharyngiomas occurring in two families, there is no proven underlying genetic susceptibility [16, 17].

Pathology

Craniopharyngiomas are histologically classified as grade 1 tumours by the World Health Organisation [18] and can be divided into 2 subtypes; ACPs and PCPs. [4, 13, 19-21].

Macroscopically, ACPs are characterised by calcification, necrotic debris and fibrous tissue, with sharp and irregular margins. They have cystic and/or solid components, with cystic fluid having the appearance of 'machinery oil' or a 'shimmering' quality, attributed to the high cholesterol content which results from desquamated squamous epithelial cells, and includes membrane lipids and keratin [7].

Microscopically, ACPs contain organised layers of epithelium. The basal layer of palisading epithelium consists of columnar cells, often described as having a 'picket fence' appearance, whilst the intermediate layer- the stellate reticulum- consists of 'star-like' stellate cells, and is pale and microcystic. The top layer - facing into the cyst lumen - contains enlarged, flattened, keratinized squamous cells. Ghost cells - anuclear squamous cells that have lost their basophilic staining - accumulate to form nodules of 'wet keratin', a pathognomonic feature of ACPs. Rosenthal fibres and fibrillary gliosis, occurring in the adjacent normal brain tissue,

are additional characteristic microscopic findings seen in this tumour subtype [4, 7, 13, 22]. Histologically, ACPs are characterised by nodular whorls, anastomosing trabeculae and 'clover leaves' [23].

Figure 1A **Figure 1B**

PCPs consist of mature squamous epithelium forming pseudopapillae. They have a hyalinised stroma, with presence of mucinous cells and individualised or small aggregates of keratin, and are usually well delineated. Microscopically, PCPs lack palisading epithelium, a stellate reticulum and microcystic degeneration, and macroscopically necrosis, calcification and cholesterol are rarely seen. The cystic fluid appears viscous and yellow, providing differentiation from their adamantinomatous counterpart [4, 13]. Additionally, only the cellular membranes of the papillary subtype demonstrate β-catenin immunoreactivity, lacking abnormal nuclear accumulation as seen in ACPs [7].

Pathogenesis

Craniopharyngiomas are thought to arise from neoplastic transformation of ectoderm-derived epithelial cell remnants of Rathke's pouch and the craniopharyngeal duct [24]. This is further supported by the detection of molecular markers of Rathke's pouch precursors in both human and murine craniopharyngiomas [25, 26].

On a molecular level, *BRAF V600E* mutations, present in 77-100% [27-32] of PCPs, have been proposed to be an important driver of tumorigenesis through activation of the MAPK/ERK (Mitogen Activated Protein Kinase/Extracellular signal Regulated Kinases) pathway, a common contributor to tumorigenesis in many cancers. A mutated and constitutively active BRAF V600 phosphorylates MEK and leads to various downstream changes that result in translocation of ERK into the nucleus, causing subsequent activation of various transcription factors involved in cell growth, proliferation and cell survival [33]. Whilst BRAF V600E mutations are seen throughout numerous cell types in PCPs, only a small subset of cells containing the mutation trigger the activation of the MAP/ERK pathway [34]. Such cells are thought to be progenitor cells containing the transcription factor SOX^{2+} (Sex determining region Y- Box 2) and are able to expand and proliferate within human and murine PCPs [34]. Thus, it has been suggested that activation of the MAPK/ERK pathway within SOX progenitor cells is a major driver of tumour formation in PCPs.

Adamantinomatous tumours are associated with mutations in the β-catenin encoding gene *CTNNB1*, found exclusively on exon 3 [35]. β-catenin is a multi-protein complex which plays a prominent role as mediator and activator of the canonical Wnt signalling pathway – a critical regulator of cellular behaviour, homeostasis and cell fate [35]. Mutation in the β-catenin phosphorylation sites results in the accumulation of β-catenin within the cytoplasm which, in turn, is translocated into the nucleus. Excess nuclear β-catenin promotes the activation and transcription of target genes, and thereby leads to increased cellular proliferation [33]. The immune response has also been implicated to play an important role in the pathogenesis of this subtype; ACP tumour cells demonstrate a characteristic pattern of inflammation within the cystic fluid and the solid tumour components, and molecular analyses have discovered increased expression of multiple immunity related genes and

elevated cytokine levels, including IL-6, CXCL-1/GRO (Chemokine Ligand 1 / Growth-Regulated Oncogene), IL-8 and IL-10 [33, 36]. In addition, like in PCPs, activation of the MAPK/ERK pathway has been found to occur within ACP tumour cells, albeit in a ligand dependent manner, without mutation of *BRAF-V600E* [33]. Further to this, administration of trametinib, a MEK inhibitor which targets the MAPK/MEK pathway, has been shown to reduce cellular proliferation, and increase apoptosis in human and murine ACP cell models [37]. Additionally, the immune check point proteins PD-L1 and PD-1 (Programmed Death Ligand 1 and Programmed cell Death protein 1) are expressed in both subtypes of craniopharyngioma [38]. As such, these changes on a cellular and molecular level could be potential targets for medical therapy, including BRAF V600E inhibitors for PCPs, IL-6 inhibitors in ACP's, and both MEK inhibitors and PD-1 immune checkpoint inhibitors for both tumour subtypes [33, 38-40].

Location

Craniopharyngiomas can arise anywhere along the path of the craniopharyngeal duct, but they primarily occur in the suprasellar/sellar area. The vast majority have a suprasellar component, with only around 5% of tumours being solely intrasellar [4]. Rare tumour locations include the paranasal area and nasopharynx, completely in the third ventricle, temporal lobe, ethmoid sinus, sphenoid bone, pineal gland, posterior cranial fossa, midbrain and cerebellopontine angle [4].

Presenting Manifestations

Clinical presentation is dependent on the size, location and growth rate of the tumour[4]. Interval from symptom onset to diagnosis is variable but frequently delayed, ranging from one week to several decades [4, 41-45]. Headaches, visual impairment, as well as nausea and vomiting are the most common presenting symptoms in both children and adults, as are growth failure in children and hypogonadal manifestations in adults [4]. A recent meta-analysis of more than 700 adult patients treated with surgery reported visual impairment, symptoms of raised intracranial pressure and endocrinopathies as the most commonly presenting features in 67%, 37%, and 27% of patients, respectively [46]. In children, visual dysfunction occurs in 55-75% of cases [41, 42, 47-50].

Bitemporal hemianopia affects approximately half of the patients [43, 51, 52]. The degree and direction of the optic chiasm distortion correlates with the type and severity of visual impairment. Downward compression of the optic chiasm is associated with impaired vision in 20% of patients, whereas the respective rate for forward compression of the chiasm is > 90% [53].

Pituitary dysfunction is frequent at diagnosis. Based on series of both adults and children, with different diagnostic tests and criteria applied, GH deficiency is present in 35-95%, FSH/LH deficiency in 38-82%, ACTH deficiency in 21-62%, TSH deficiency in 21-42% and ADH deficiency in 6-38% of patients [4].

FIGURE 2

Imaging characteristics of craniopharyngiomas

Craniopharyngiomas usually appear as heterogeneous tumours on imaging. Their appearance varies subject to the presence of solid and cystic components, the level of calcification and the constituents of intra-cystic fluid (cholesterol, keratin or blood) [54]. They often have distinct radiological features that differentiate them from other tumours in the sellar region. Both Magnetic Resonance Imaging (MRI) and Computed Topography (CT) provide are valuable in the diagnostic work-up of a patient with a suspected craniopharyngioma.

MRI and CT

T1-weighted MRI sequences with and without gadolinium, in the coronal and sagittal plane provide optimal assessment of tumour proximity to neighbouring structures including the optic chiasm, hypothalamus and the third ventricle. Contrasted T1-weighted sequences depict solid tumours as hyperintense, and cystic components as iso- or hypointense. The cystic wall also enhances with contrast. [55]. Additionally, protein, cholesterol and methaemoglobin may demonstrate high signal on T1-weighted images [54-56] Obstructive hydrocephalus is often present in intraventricular tumours.

FIGURE 3A **FIGURE 3B**

FIGURE 4A **FIGURE 4B**

On T2-weighting, cystic features are typically hyperintense, solid components of the tumour are usually of mixed hypo- or hyperintensity, and the presence of high concentrations of protein, cholesterol and methaemoglobin demonstrate a low T2-weighted signal [54].

Microcalcification is visible in approximately 75% of craniopharyngiomas [57], seen more commonly in ACPs and in childhood-onset disease. Whilst high concentrations can be seen on MRI, CT is the superior modality for its detection. Calcification can form 'popcorn-like' foci or more rarely, an egg shell pattern coating the cyst wall [7]. CT is useful to demonstrate the bony anatomy and can also help delineate cystic from solid tumour components, in which cystic fluid has a hypointense appearance, and solid parts enhance following contrast [54].

Whilst imaging cannot accurately differentiate ACPs from PCPs, ACPs commonly contain both cystic and solid components and calcification, whereas PCPs can be entirely solid, do not typically calcify and are usually less locally infiltrative. [7].

Radiological differential diagnosis

The differential diagnosis for craniopharyngiomas is broad, including Rathke's cleft cysts, meningiomas, pituitary adenomas, germinomas, gliomas, hamartomas, dermoid, epidermoid and arachnoid cysts, anterior communicating artery aneurysms, as well as infiltrative diseases including sarcoidosis, tuberculosis and Langerhans histiocytosis [4]. Rathke's cleft cysts can often be differentiated given their lack of calcification, absence of a solid component, oval appearance, as well as minimal to no enhancement of the cyst wall and contents following

gadolinium administration [58]. Likewise, pituitary adenomas are less enhanced compared to the solid parts of craniopharyngiomas following contrast [59]. Despite these differences, intra-sellar craniopharyngiomas or homogeneously enhancing solid craniopharyngiomas (albeit rare), can be challenging when differentiating them from Rathke's cleft cysts or pituitary adenomas.

Tumour topography and image grading systems

Tumour topography, as well as tumour proximity and attachment to the hypothalamus, are important factors determining surgical risks, hypothalamic damage and subsequent hypothalamic morbidity. Both pre- and post-operative tumour classification systems assessing hypothalamic involvement can be helpful in predicting hypothalamic sequelae and risk of hypothalamic morbidity. In a retrospective cohort of 66 patients, Puget *et al.*[60], analysed pre-operative prognosticators that influenced post-operative outcome in paediatric cases with craniopharyngioma. By using pre-operative imaging, they proposed a grading system based on degree of hypothalamic involvement, which was classified into three grades. Grade 0 describes tumours which clearly show no hypothalamic involvement, grade 1 tumours are those where the lesion abuts or elevates the hypothalamus (but the hypothalamus remains visible), and grade 2 are those where the hypothalamus is no longer visible [60]. By applying this system, they found a significant correlation between higher tumour grade and post-operative hypothalamic morbidity and as such, proposed that Gross Total Resection (GTR) should be avoided for grade 2 craniopharyngiomas. They subsequently applied these criteria to a prospective cohort of 22 children (with similar pre-operative imaging and clinical characteristics), and demonstrated significant reduction in hypothalamic morbidity compared

to the retrospective cohort (including mean post-operative BMI, appetite dysregulation and change in post-operative Quality of Life)[60].

Similarly, Muller *et al.*[61], proposed a pre-operative, but also a post-operative, grading system to define pre-operative hypothalamic involvement or post-operative presence of surgical lesions involving the hypothalamus, specifically in reference to hypothalamic mammillary bodies [61]. Craniopharyngioma were graded as 0, if there was no hypothalamic tumour involvement or no surgical lesion visible; grade 1, if there was hypothalamic involvement or a surgical lesion in the anterior hypothalamus (but with sparing of the mammillary bodies and hypothalamic area beyond them), and grade 2, if there was tumour or a surgical lesion involving the anterior and posterior hypothalamus (i.e., involving the mammillary bodies and the area beyond them). They found that pre-operative hypothalamic involvement of the anterior and posterior hypothalamus (grade 2) was associated with higher risk of hypothalamic morbidity, and patients who sustained anterior or posterior hypothalamic lesions following surgery (grades 1 and 2) had higher post-operative BMI and lower health related QOL scores compared to those without hypothalamic lesions (grade 0) [61].

More recently, Prieto *et al.*[62], in a retrospective study of 200 patients with craniopharyngioma, identified several key radiological findings that successfully predicted both craniopharyngioma topography, as well as severity of adherence (the attachment formed between tumour and hypothalamus through adhesions), when using standard sagittal and coronal T1+T2-weighted imaging [62, 63]. In their analysis, they found that adherence severity correlated with poorer outcomes, and subsequently, identified three pre-operative radiological variables which correctly identified those with the greatest severity of intra-

operative adherence in nearly 90% of cases [62]. These included presence of the hypothalamus within the middle portion of the tumour, infiltration of the pituitary stalk and an elliptical tumour shape [62]. A pre-operative grading system predicting adherence severity could facilitate decisions on extent of attempted excision and risk for hypothalamic morbidity.

Management

Surgery

Surgical resection is the first line management option in the vast majority of adult onset craniopharyngiomas. Surgical approach and technique depend on many factors, including size, consistency of the tumour, location and the degree of extension towards neighbouring structures, as well as experience and preference of the surgical team involved [54]. Surgery is particularly challenging due to irregular and jagged tumour borders, often large size and adherence to nearby structures [4]. Additionally, they may lack a distinct dissection plane as they sometimes invade neural tissue and are adherent to the neighbouring neurovascular structures, making safe GTR impossible [59]. Surgery via the transsphenoidal route is generally regarded as the most favourable approach where possible, allowing exposure to the third ventricle floor, hypothalamus and pituitary stalk, whilst avoiding optic nerve and chiasm mobilisation [64].

Extent of Surgical Resection

The extent of tumour clearance, either via GTR or Subtotal/Partial Resection (STR) followed by adjuvant radiotherapy remains controversial. Whilst safe GTR may be possible is some cases performed by experienced surgical hands, STR with adjuvant radiotherapy is arguably considered to be the favourable approach for the majority of craniopharyngiomas. This has been emphasised over the last decade by the increasing appreciation of the impact of hypothalamic morbidity and its relationship with tumour topography and hypothalamic adherence, as well as the ability to achieve comparable rates of tumour control and overall survival with either approach [46, 65, 66]. Notably, in a meta-analysis conducted by Akinduro *et al.* looking at endocrine and visual outcomes in adult craniopharyngioma, found that GTR was associated with lower risk of recurrence compared with STR, nonetheless, GTR had a significantly higher likelihood of panhypopituitarism and permanent diabetes insipidus [67].

Data on risk of hypopituitarism is inconsistent when comparing either approach, with some groups reporting no statistically significant difference [68, 69], yet in other reports, those receiving GTR were more than twice as likely to develop at least one endocrinopathy compared to those who received STR and adjuvant radiotherapy [70]. Despite ongoing debate, in the presence of a clear separation point between tumour and hypothalamus, attempt at GTR during first surgery is generally considered to be the optimal choice, as subsequent surgical attempts can be associated with increased mortality and morbidity [59]. For those tumours with hypothalamic invagination or signs of adherence, subtotal resection with adjuvant radiotherapy is the recommended approach given the increased risk of hypothalamic damage and negative long-term sequelae [59, 71-74].

Cyst aspiration, intracystic drug therapy or radioisotope insertion

Predominantly cystic craniopharyngiomas may be amenable to aspiration, providing rapid resolution of symptoms of mass effect; this approach can be a means of delaying surgery and/or radiotherapy and their potential complications especially in children [54]. The insertion of an Ommaya reservoir - an intraventricular catheter accessed subcutaneously - provides an accessible route for recurrent aspiration, as well as administration of intracystic chemotherapy, radionuclides or biological therapy [75]. Small studies in paediatric populations have demonstrated Ommaya reservoirs to be effective in controlling tumour growth without the need for additional treatment (radiotherapy or surgery) in 43-73% of cases, with an average follow-up of 7 years [75-77].

Localised administration of intracystic drug therapy is more commonly reserved for children and young adults with craniopharyngiomas, where delaying surgery or radiotherapy can be helpful to reduce the risk of associated complications.

Bleomycin, a neurotoxic chemotherapy agent, was first discovered as a potential treatment for craniopharyngiomas as early as 1971 [78], and it's first use in patients was reported in 1985, where it was found to reduce tumour size in patients with cystic craniopharyngiomas, but not in solid or mixed tumours [79]. Multiple small scale reports since then have demonstrated its efficacy, including a study and literature review by Hukin *et al.* [80], who described that > 25% cyst size reduction was seen in up to 90% of patients, and > 90% cyst size reduction in 50% of 70 adults and children with craniopharyngiomas [80]. However, evidence to date is mostly limited to case reports or small non-randomised, retrospective studies, whereas a recent Cochrane review found insufficient evidence to support its use in children, particularly given the risk of side effects [81]. These include (but are not limited to) headache, nausea, vomiting and fever, seen in approximately 70% of recipients [80] , but also

hypothalamic injury, visual loss, peri-tumour oedema, cerebral ischaemia, hemiparesis and death have all been reported [81].

Radioisotopes, including yttrium-90 (90Yt), rhenium-186 (186Rh), and phosphorus-32 (32P) are additional intracystic therapies. Like bleomycin, they have been shown in small studies to reduce cyst size, but the risk of severe side effects including radio-necrosis and visual loss, has been reported in about 5% of patients; its use is, therefore, limited, and this approach is available in few specialist centres [77].

Intracystic delivery of interferon-α, a non-neurotoxic treatment alternative, has a more favourable side benefit-to-risk ratio [82]. Several studies with short follow-up have reported excellent results, including a complete response in a large proportion of patients [83-85]. However, a recent multicentre international study found that 75% of patients had tumour progression at a median time of just 14 months [86], highlighting that for the majority, benefit is limited to a delaying tactic, as opposed to a definitive treatment modality.

Radiotherapy

Radiotherapy is an effective adjunctive treatment modality in the management of craniopharyngiomas. Indeed, adjuvant radiotherapy administered following subtotal/partial resection or after tumour recurrence offers better long-term survival rates when compared to surgery alone [4, 87-89]. Historically, conventional radiation therapy (CRT) has been the standard radiation therapy modality administered to patients with craniopharyngiomas. CRT offers 10 year recurrence rates between 10-63% when given in its adjuvant capacity

following subtotal/partial removal [4]. New or worsening of hypopituitarism is reported in 20-60% of patients who received CRT after 5-10 years of follow-up, and radiation induced optic neuropathy causing visual deficit occurs in 2-8% of patients [88]. Transient cyst enlargement, occurring during or following radiotherapy (within 6 months) is a recognised complication and has been reported in 10-60% of patients [90-93]. This can result in manifestations secondary to mass effect, including hydrocephalus and displacement of the optic chiasm, and thus, patients should be closely monitored both during and after radiotherapy administration. Despite rapid growth requiring urgent surgical decompression in some cases, cystic enlargement is a transient phenomenon necessitating only careful observation in the majority, and is not indicative of disease progression [90].

Intensity Modulated Radiation Therapy (IMRT), Fractionated Stereotactic Radiotherapy (FSRT), Stereotactic Radiosurgery (SRS) and proton beam therapy are newer modalities used increasingly in the management of craniopharyngiomas. Such routes allow delivery of precise, targeted therapy, thereby reducing exposure of healthy tissue to radiation, and in turn, may reduce risk of radiation toxicity. Choice of modality is largely influenced by tumour size, as well as proximity to nearby vital structures. Tumour control rates after SRS are negatively associated with tumour volume [94], and those patients with smaller sized residuum at least 3-5mm away from the optic chiasm and nerves are likely to be more suitable candidates of SRS [95]. For SRS, tumour control rates of between 67 and 86% at 5 years have been reported [96, 97]. For FRST, reported rates of local control are between 92% [98] and 95% [99] at 5 years and 100% at 10 years [100]. Long term data after proton beam therapy are limited, but local control rates appear to be comparable with FSRT, and may reduce the potential for neurocognitive decline, hypopituitarism and secondary brain tumours in the paediatric population [101, 102].

Medical Management

Use of systemic interferon in craniopharygiomas has shown mixed results. Jackacki *et al*.[103] were first to evaluate its use in a cohort of 15 children with craniopharyngiomas. Of the 12 evaluated following subcutaneous interferon administration, three showed evidence of tumour response to treatment, however 25% demonstrated disease progression on treatment, and whilst transient, 60% of patients developed hepatic, cutaneous or neurological toxicities in the first 8 weeks [103]. A further analysis by the same group in 2012 reported the use of pegylated interferon – a derivative of interferon with a longer half-life – in 5 patients with craniopharyngioma. Interestingly, all showed radiological evidence of tumour response, including two who demonstrated a complete response to treatment [104]. This was followed by a recent multi-centre study examining the effect of pegylated interferon in a cohort of 18 children and young adults with recurrent craniopharyngiomas who had all received surgery, but prior use of radiotherapy was variable. Although treatment was well tolerated, treatment response was disappointing, with only two patients demonstrating response, of which only one had a sustained response to systemic pegylated interferon beyond 3 months [105].

Drugs targeting the MAPK/ERK pathway are a promising and evolving approach at the forefront of current research in the management of craniopharyngiomas. *BRAF V600E* mutation specific inhibitors have been shown to be effective in numerous cancers containing the V600E mutation, and are often supplemented with MEK inhibitors, agents that override resistance to BRAF inhibition [33, 106]. For the papillary subtype, in which the *BRAF V600E* mutation triggers activation of the MAPK/ERK pathway, use of BRAF inhibitors has been

shown in a number of case reports to have led to a dramatic reduction in tumour size, both when used alone or in combination with MEK inhibitors, applied neoadjuvantly or following surgery, with or without radiotherapy [39, 107-115]. More recently, Patel *et al.* [116] reported a case of a 26 year old patient with the adamantinomatous subtype, who, after 8 surgeries, chemotherapy and radiotherapy, received binimetinib, a MEK inhibitor used off licence in effort to relieve the progressive disease. The authors reported a significant reduction in tumour size, as well as stable disease following a year of medical therapy [116]. Grob *et al.* [40] reported two cases of paediatric cystic craniopharyngioma successfully controlled with tocilizumab, an IL-6 inhibitor, used alone or in conjunction with bevacizumab, a Vascular Endothelial Growth Factor (VEGF) inhibitor. Both children had extensive treatment prior to initiation, and were confirmed to have IL-6 in cystic tumour fluid. Both patients achieved a reduction in cyst size, and at the time of publication, were undergoing MRI surveillance alone [40].

Whilst evidence to date is limited to case reports and small case series (summarised in Table 1), randomised control trials involving combination therapy with both BRAF V600E and MEK inhibitors for PCPs, and IL-6 inhibitors for children and adolescents with ACPs are currently underway [117, 118].

TABLE ONE

Morbidity

Craniopharyngiomas carry significant morbidity attributed to direct invasion of the primary tumour and its recurrence(s), and/or to the sequelae of therapeutic intervention(s). Endocrine and metabolic dysfunction frequently result, but compromise to cerebrovascular, ophthalmic, cardiovascular, and respiratory function can also occur. Neurological, psychological and psychosocial complications may also follow, all summarised below.

Endocrine sequalae

Hypopituitarism, either partial or complete, is encountered in the vast majority of patients with craniopharyngiomas. Numerous case series, with different diagnostic criteria, as well as variable management and follow-up periods, report loss of at least three hormone axes in 54-100% of patients [4]. Individual hormone deficits range from 88-100% for GH, 80-95% for FSH/LH, 55-88% for ACTH, 39-95% for TSH and 25-86% for ADH [4]. Both panhypopituitarism and permanent diabetes insipidus are more likely in adults who have received GTR compared with STR [67]. Unlike anterior pituitary tumours, reversal of hormone deficit following treatment is extremely uncommon, with any hormone deficit being permanent for nearly all patients [4].

Hormone replacement therapy is vital, and the aims of replacement are the same for those with craniopharyngiomas and those who have hypopituitarism due to a different aetiology [119]. GH replacement therapy has been shown to be safe in numerous retrospective studies with adults and children, resulting in neither tumour growth nor tumour recurrence [120, 121]. A recent prospective study with follow-up of approximately 12 years showed that in addition to benefiting growth, childhood patients who received GH replacement had improved weight and quality of life outcomes when compared to those who did not receive

this treatment, or received GH only in adulthood [122]. Despite this, GH replacement does not prevent obesity [123-125]. Furthermore, unlike other hypopituitary patients in whom GH replacement leads to mortality risk that is comparable to the background population [126], GH replacement therapy has not been shown to reduce mortality for those with craniopharyngiomas [122, 127-129].

Vision

Visual disturbances represent one of the most commonly observed long term complications, irrespective of treatment choice in both adults and children alike. In a recent study of 128 treated craniopharyngioma patients with a median follow-up of 13 years, 75% of them had evidence of visual disturbance, with no significant difference in visual outcomes between children or adults, or in relation to initial treatment modality (including GTR, STR with or without radiotherapy, cyst aspiration or use of yttrium-90) [68]. These findings are in keeping with previous studies analysing long term health outcomes based on initial treatment approach [130-132], with exception of Karavitaki *et al.* [41] who found that deterioration in visual fields was more likely after initial treatment with STR alone, when compared to GTR, and GTR or STR with adjuvant radiotherapy [41].

Hypothalamic morbidity and metabolic complications

Insult to the hypothalamus, via treatment or tumour, can have a profound impact on morbidity. Obesity, sleep disturbance, dysregulated temperature homeostasis, disruption to normal thirst and electrolyte regulation including diabetes insipidus, as well as neurocognitive, psychosocial and behavioural issues can all result. In fact, 35% of patients

with craniopharyngiomas will have symptoms and signs consistent with hypothalamic impairment at time of diagnosis, rising to between 65 and 80% following surgery [133].

Hypothalamic obesity (HO) is a common and significant sequalae encountered in 40-66% of patients with childhood-onset craniopharyngiomas [134]. Weight gain, which may have arisen by the time of diagnosis, predominantly presents within the first year after surgery [135], before levelling off, but remains sustained [133]. Craniopharyngiomas with hypothalamic involvement have been shown in numerous studies to correlate with the severity of obesity [134, 136, 137], which in turn, has been shown to result in increased likelihood of impaired QOL [138]. HO contributes to the increased risk of cardiovascular disease, type 2 diabetes, metabolic syndrome and obstructive sleep apnoea in patients with craniopharyngiomas [139-142].

The causes of HO in patients with craniopharyngiomas are multifactorial, including increased energy intake, reduced energy expenditure, dysregulation of the autonomic nervous system, behavioural changes, sleep disturbance, hypopituitarism and hyperinsulinaemia [143]. On a biochemical level, damage to the paraventricular and suprachiasmic nuclei disrupts the vagal tone, triggering excess vagal stimulation, which in turn, causes a rise in insulin secretion, and energy storage [144]. Interestingly, rates of hyperinsulinaemia and insulin resistance have been found to be higher in those with craniopharyngiomas when compared to those without, matched to BMI, sex and stage of puberty [145]. Whilst chronic hyperinsulinaemia triggers a compensatory rise in leptin and suppression of ghrelin [146], damage to the ventromedial nuclei within the hypothalamus leads to impaired processing of afferent signals including insulin, leptin and Glucagon-Like Peptide-1 (GLP-1) [144]. Insensitivity to endogenous leptin [147] and impaired processing of these other afferent signalling are recognised factors

leading to disordered appetite and impaired satiety. Somnolence, visual impairment, neurological defects, hypopituitarism and psychological disorders represent additional exacerbating factors [7].

Management of HO is particularly challenging. To date, drug therapy has not been proven to be of benefit in a randomised control trial setting. Small studies have looked at various agents, including GLP-1 analogues [148-150], metformin combined with diazoxide [151], fenofibrate [152] and pioglitazone [153], central nervous system stimulants [154-156], somatostatin analogues [157], supraphysiological doses of liothyronine [158, 159], and oxytocin [160], most with variable, and modest results. A recent systematic review recommended an individualised patient approach following assessment for likely contributing factors, including use of GLP-1 analogues in those with insulin resistance, GLP-1 analogues and/or methylphenidate in those with hyperphagia, or dextro-amphetamine in patients with psychosocial disorders or decreased energy expenditure [143].

Bariatric surgery, including sleeve gastrectomy, Roux-en-Y gastric bypass and biliopancreatic diversion, were found to be the most effective surgical methods resulting in weight loss in a systematic review published in 2013, analysing outcomes at one year following surgery [161]. A case control study by Wijnen *et al*. in 2017 supported the use of Roux-en-Y gastric bypass, reporting comparable weight loss outcomes between craniopharyngioma patients and 'common obesity' subjects. However, unlike the earlier systematic review, the study found no significant weight loss in those who had sleeve gastrectomy [162].

Ultimately, treatments for hypothalamic obesity are of limited efficacy, and can be associated with significant side effects and may not be appropriate for children [133]. As such, in addition to further research into pharmacological therapy, focus on prevention by avoiding hypothalamic injury where at all possible, remains key.

Neurobehavioral impact, Cognitive Impairment and Quality of life

Childhood survivors of craniopharyngioma are frequently found to have some degree of social, emotional or neurobehavioral impairment [163]. Patients are more likely to develop deficits in memory (episodic long term memory in particular), executive function, attention, as well as processing speed, with hypothalamic involvement being an increased risk factor for poorer outcomes [164]. It is, therefore, unsurprising that this, in turn, can impact on relationships, day to day functioning and result in changes in behaviour [165]. Problems at school are frequently reported, and, unfortunately, poorer health related quality of life scores are seen in comparison to healthy controls [166]. Depressive symptoms and increased apathy are also more likely [163, 167], and in an analysis by Karavitaki *et al.*, 15% of 121 patients with craniopharyngiomas had psychological disorders requiring treatment [41]. Pre-operative hypothalamic involvement or surgically induced damage to the hypothalamus has been linked to a lower quality of life in children and adolescents with craniopharyngioma, as well as GTR and radiotherapy [73].

Mortality

Mortality rates have been reported as nearly 6 times higher than the general population [168]. In cohorts of both adults and children, overall survival rates range from 40-93% and 66-85%

at 10 and 20 years, respectively [169]. Cardiovascular, cerebrovascular and respiratory related mortality have all been shown to be increased [11, 168, 170-173]. Recent advances in neurosurgical techniques and apparatus used, in addition to the wider variety of radiotherapy modalities offered, may be starting to turn the tide. A meta-analysis published in 2018 including 2,802 patients who had received treatment for a craniopharyngioma found the pooled Standardised Mortality Ratio (SMR) pre 2000 to be 6.2, (CI 4.1-9.4), dropping to 2.9 after 2010 (CI 2.2-3.8) [174]. Evidence to support one initial treatment modality in favour of another based on improved survival rates alone is inconsistent, with overall survival being comparable between GTR *vs* STR with radiotherapy [41, 66, 68]. Female sex [11, 168, 170, 175, 176], as well as childhood-onset disease [11, 72, 127, 170], have been linked to increase in mortality, but other studies have not confirmed this [21, 41, 89]. Similarly, histology type and hydrocephalus are other poor prognosticators identified by some [170, 177], but not others [13, 21, 41, 89]. Tumour recurrence however, is widely accepted as a negative influencing factor on mortality, with survival rates of 29-70%, depending on subsequent treatment modality offered [4].

The association between increased mortality and hypopituitarism due to any cause is long established, but those that have craniopharyngiomas have mortality rates nearly 10 times higher than other hypopituitary patients in some reports [172, 178]. A Swedish based population study involving 307 patients with craniopharyngiomas, followed-up for a mean of 9 years reported a SMR of 2.7 (CI 1.4-4.6) in patients with craniopharyngiomas who lacked any hormone deficit, compared with an SMR of 4.3 (CI 3.1-5.8) in craniopharyngioma patients with hypopituitarism, and an SMR of 6.1 (CI 3.5-9.7) in those with diabetes insipidus [11]. In those with hypopituitarism (with or without diabetes insipidus), increased mortality was attributable to circulatory diseases (including cerebrovascular disease), not seen in the

small number who had normal pituitary function [11]. From this study, 67 patients were also included in a hospital based retrospective study, involving a total of 224 patients followed for 13 years. Again, panhypopituitarism was linked to excess mortality, with circulatory diseases, cerebrovascular disease and respiratory infections being the main causes of death [170].

Conclusions and future perspectives

Craniopharyngiomas remain a challenging tumour to manage. With increasing recognition of the impacts of both tumour and the consequences of its management, the need to focus on treatments that not only improve survival, but also reduce the significant impact of hypothalamic morbidity, remain a priority. Until such treatments come to light, attempt to prevent hypothalamic insult with subtotal resection and adjuvant radiotherapy, currently appears to be the optimal treatment approach in the majority of patients. Cystic aspiration and delivery of intracystic drug therapy represent alternative treatment options that may be appropriate in cystic tumours, particularly in paediatric cases. Regardless of treatment choice, life-long multidisciplinary care is essential to surveil for recurrence, as well as to manage and offer rehabilitation to those who are left with endocrine, metabolic, visual, neurocognitive and psychosocial sequalae. Improved understanding of tumour pathogenesis and molecular targets for drug therapy are exciting areas at the forefront of translational research. The use of BRAF V600 and MEK inhibitors in particular, described in an increasing number of case reports, offer a glimmer of hope for a novel and beneficial treatment option, with the results of randomised, prospective trials eagerly awaited.

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Figure 1A. *Histology of ACP. Well-differentiated epithelium with palisading, nodular whorls (top half of image), and the intermediate layer – the stellate reticulum- consisting of pale, microcystic areas. A 'wet keratin' nodule can be seen in the bottom right of the image. HE x200 magnification.*

Figure 1B. *Histology of PCP. Papillae lined by non-keratinising squamous epithelium and containing loosely structured connective tissue; HE x20 magnification* [Reproduced with permission from Endotext.org. Lithgow K, Pohl U, Karavitaki N. Craniopharyngiomas. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2019 Mar 14.]

Figure 2. *Data from Karavitaki et al [41]. Presenting clinical features of 119 patients with craniopharyngioma (41 children + 78 adults) recorded in medical notes of patients reviewed in adult and paediatric services over a 40-year period. *In those ≥ 13 years, n=91. ** In adult women, n=37.*

Figure 3A. *T1-weighted MRI with contrast, coronal section*

Figure 3B. *T1-weighted MRI with contrast, sagittal section. The cystic rim of the craniopharyngioma is enhanced, whilst the inner contents are isointense.* [Reproduced with permission from Endotext.org. Lithgow K, Pohl U, Karavitaki N. Craniopharyngiomas. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2019 Mar 14.]

Figure 4A. *T2-weighted coronal section showing a solid craniopharyngioma enhanced following contrast*

Figure 4B. *T2-weighted coronal section depicting mixed signal intensities consistent with a solid and cystic craniopharyngioma.* [Reproduced with permission from Endotext.org. Lithgow K, Pohl U, Karavitaki N. Craniopharyngiomas. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2019 Mar 14.]

TABLE I: A summary of selected case reports of medical therapy used in craniopharyngiomas

Author and year	CP Type	Previous Treatment	Medical Treatment	Treatment Duration	Radiological Outcome	Additional information
Aylwin [107] et al 2015	PCP	TSS X2 RT	Vemurafenib 960mg BD	3 months initially (Held following CSF leak and meningitis), then a further 7 months	Near CR after 3 months, then regrowth 3 months after stopping, Tumour control for 7 months on therapy then progression	Treatment stopped after a total of 10 months of treatment due to progression and reduction in PS. Patient died 6 months after [115]
Brastianos et al [108] 2015	PCP	Craniotomy x 3	Dabrafenib 150 mg BD, and at week 3, trametinib 2mg OD	1 month	PR -85% decrease	Surgery and RT following medical treatment, tumour free at one year [115]
Roque et al [110] 2017	PCP	Craniotomy Ommaya reservoir and RT	Dabrafenib 150mg BD, trametinib 2mg OD	2 years and 9 months*, continues on treatment	CR by 7 months	CR maintained since treatment began [115]
Rostami et al [109] 2017	PCP	TSS	Dabrafenib 150 mg BD, and at week 3 trametinib 2mg OD	4 months	PR - 91% decrease	
Himes et al [111] 2019	PCP	Craniotomy + RT	Dabrafenib 150mg BD, changed to OD, then trametinib 2mg OD	9 months	CR	No tumour recurrence 18 months after stopping therapy [115]
Juratli et al [115] 2019	PCP	Nil	Dabrafenib 150mg BD, trametinib 2mg OD	6 months	PR >80% decrease	
Bernstein et al [39] 2019	PCP	TSS+RT	Dabrafenib 150mg BD, trametinib 2mg OD		CR at 28 months	
Grob et al [40] 2019	ACP x 2	Case 1+2: multiple cystic aspirations, INF-α, bleomycin. Case 2: Craniotomy and RTX	Case 1: tocilizumab + bevacizumab at 8 months Case 2: Tocilizumab alone	14 months of combination therapy Case 2: 7 months	Significant reduction in cyst size PR	

Khaddour et al 2020 [113]	PCP	TSS	Dabrafenib 150mg BD, trametinib 2mg OD	9 months, then RT	PR >70% decrease (pre-RT)	Remission for 2 years
Stefano et al [114] 2020	PCP	TSS	Dabrafenib 150mg BD, trametinib 2mg OD	208 days, then RT	>94% decrease at day 72 (pre-RT)	At 385 days, sustained control
Patel et al [116] 2020	ACP	Surgery x 8, RT x 2 + Chemotherapy	Binimetinib 45mg BD, reduced to 30mg BD, then 30mg OM and 15mg OE	April 2019 to August 2020 (publication submission date) 16 months with occasional interruptions	PR -Decrease from 3.5 x 2.5 x 2.5cm to 2.8 X 2.1 X 2.8cm (after 6 months of treatment)	Stable disease

*CP = Craniopharyngioma, TSS = Transphenoidal Surgery, RT= Radiotherapy, CR= Complete Response, PR = Partial Response, PS = Performance Status, INF-α = Interferon-α, * 7 months of treatment completed by publication of April 2017 [110], and remains on treatment at time of update in June 2019 [115].*

Glossary of abbreviations:

ACP - Adamantinomatous Craniopharyngioma

PCP - Papillary Craniopharyngioma

MAPK/ERK - Mitogen Activated Protein Kinase/Extracellular signal Regulated Kinases

SOX^{2+} - Sex determining region Y- Box 2

CXCL-1/GRO - Chemokine Ligand 1 / Growth-Regulated Oncogene

IL-6/8/10 – Interleukin 6/8/10

PD-L1 and PD-1 -Programmed Death Ligand 1 and Programmed cell Death protein 1

MEK – Mitogen activated Extracellular signal-regulated Kinase

FSH- Follicle Stimulating Hormone

LH – Luteinizing Hormone

GH – Growth Hormone

TSH – Thyroid Stimulating Hormone

ACTH – Adrenocorticotropic Hormone

ADH – Anti-Diuretic Hormone

T3- Triiodothyronine

GLP-1 - Glucagon- Like Peptide-1

90Yt -Yttrium-90

186Rh- Rhenium-186

32P - Phosphorus-32

CRT – Conventional Radiotherapy

IMRT - Intensity Modulated Radiation Therapy

FSRT- Fractionated Stereotactic Radiotherapy

SRS - Stereotactic Radiosurgery

MRI - Magnetic Resonance Imaging

CT- Computed Topography

GTR - Gross Total Resection

STR - Sub Total/Partial Resection

HO - Hypothalamic Obesity

SMR - Standardised Mortality Ratio

QOL – Quality Of Life

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Figure1A

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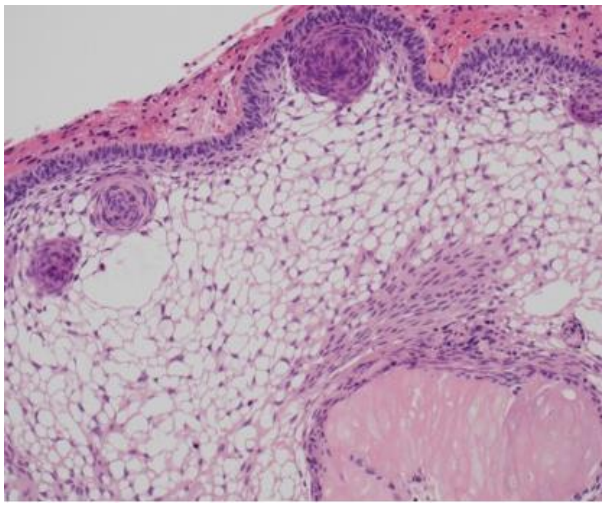

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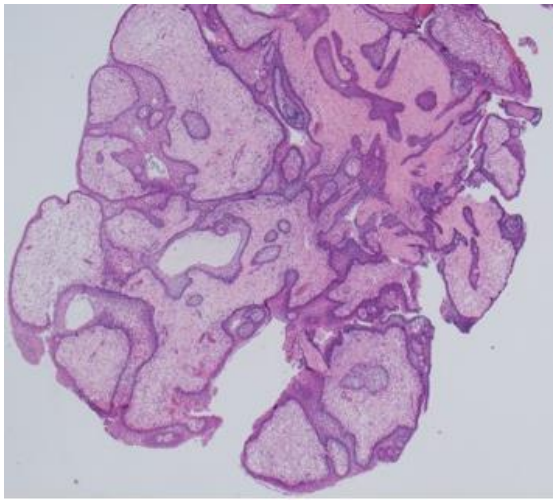

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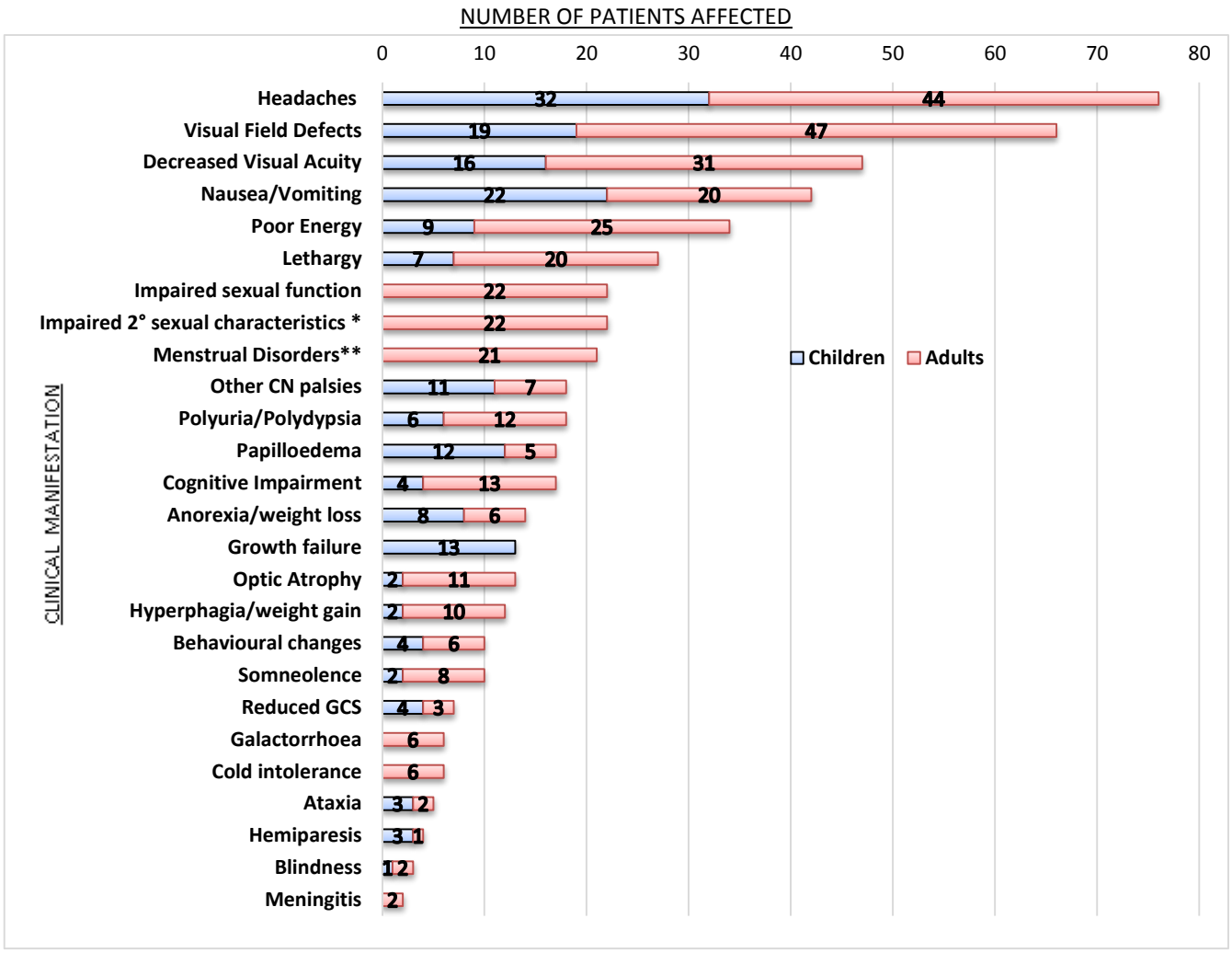

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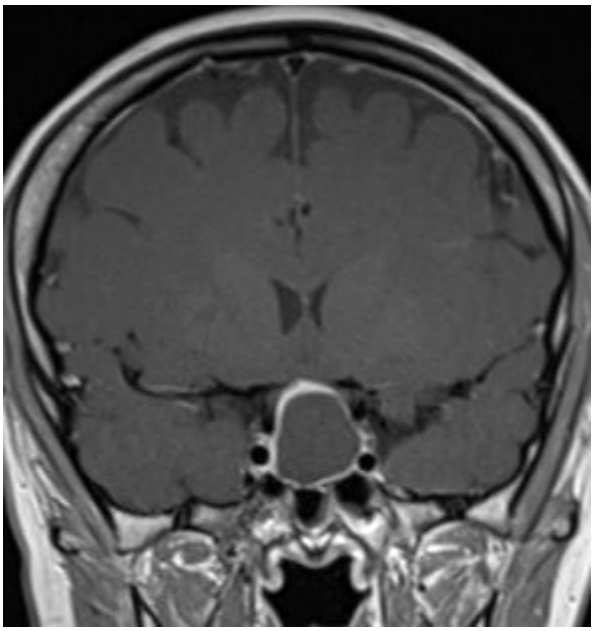

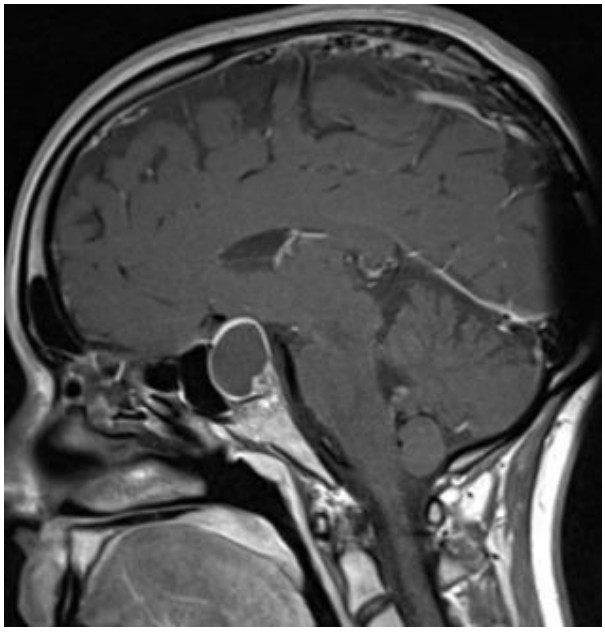

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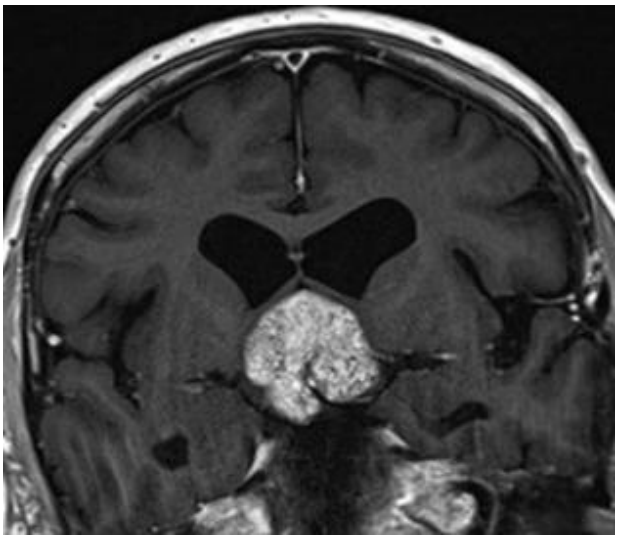

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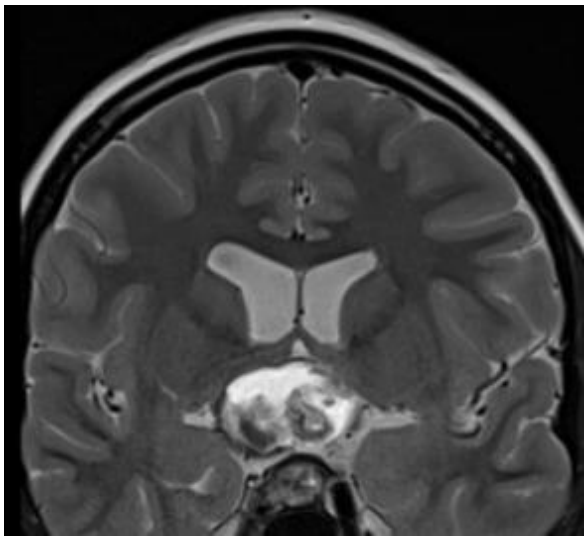

Dear Dr. Bodossian,

Thank you for looking at our manuscript and for the comments of the reviewers. Please have our responses for each point raised. Changes in the text have been highlighted in yellow.

Évaluateur nº1

Thank you for your positive comments.

- Page 3 Patholgy: tell that craniopharygioma are not neoplasic, but dysembryoplasic tumors

Response:

Thank you for raising this point. Based on the WHO classification of tumours of the Central Nervous System, craniopharyngiomas are considered to be tumours (neoplasms) of the sellar region. Although their pathogenesis has not been completely elucidated, the recent discovery of mutations (e.g., in the BRAF gene) driving tumorigenesis through activation of the various pathways (e.g., MAPK/ERK) favours using the term neoplastic.

- Page 21 Disparities between pituitary deficiencies: are they explained by the diagnostic criteria?

Response:

Different diagnostic criteria can indeed also explain the disparities between the reported pituitary hormone deficits. We have added this in page 21.

Évaluateur nº2 : Excellent review

No comment, no change necessary

Response:

We are grateful for the positive comments.