

## Childhood and Adolescent Chordoid Gliomas: A Review

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### Abstract

Chordoid glioma (CG) is a rare benign tumour of glial origin, arising from the anterior third ventricle and hypothalamus. Common presentations are headaches, endocrine and visual disturbance. Of 100 CGs described since 1998, only six children and adolescents have had this condition. Gross total resection is curative. A high postsurgical mortality makes partial resection and gamma-knife radio-surgery an acceptable alternative. There is suggestion CGs in children and adolescents are different to that of the adult population. This review explores such a thesis.

Of six tumours in this study group, aged five to 18-years, three have arisen from the third ventricle and suprasellar regions while the rest are within the cerebral hemispheres. One 5-year-old boy succumbed to an unexplained cardiac event 48 hours following total resection of a temporal-parietal lesion. The other five are alive and well post-surgery; among them is a 13-year-old girl with two repeat surgeries for recurrences over a 9-year period. Lesions in both the children and adolescents are preoperatively mistaken for the better-known chordomas, intraventricular meningiomas and pilocytic astrocytomas.

There is inadequate clinical, morphological and ultra-structural evidence to substantiate childhood and adolescent CGs is distinct from their adult counterparts. CGs uncertain biological nature exists in all age groups.

**Keywords:** Chordoid Glioma; Adolescent; Childhood

### Abbreviations

CG: Chordoid Glioma; CT: Computed Tomography; EMA: Epithelial Membrane Antigen; GFAP: Glial Fibrillary Acidic Protein; GTR: Gross Total Tumour Resection; MRI: Magnetic Resonance Imaging; PA: Pilocytic Astrocytoma; STR: Subtotal Resection; WHO: World Health Organisation

### Introduction

In 1998 Brat, *et al.* [1] published a landmark paper by describing eight tumours arising from the anterior third ventricle and hypothalamus. They named the lesion chordoid glioma (CG) after the almost identical “chordoma-like” appearance initially described in a child with a cranial chordoid meningioma [2]. On histology a CG composes of epithelioid cells, arranged in clusters; there are eosinophilic cytoplasm admixed with extracellular mucinous substance and peripheral lymphoplasmacytic infiltrates.

Morphologically, CGs are solid and well defined with the occasional cyst formation and fine calcifications [1,3,4]. There is therefore a similarity to an intraventricular meningioma or probably a suprasellar chordoma except meningotheial cells and nuclear pseudo-inclusions are present in the former while physaliferous cells characterise the latter [3]. Immunohistochemical studies show CGs stain positively for glial fibrillary acidic protein (GFAP), vimentin, CD34, and epithelial membrane antigen (EMA) [3]. The latest World Health Organisation (WHO) report classifies CG as a grade II glioma on account of the high incidence of postsurgical complications and mortality [5]. Opinion from major and influential publications, regard damage to the hypothalamus as a causative factor [6,7], with pulmonary thrombo-embolism the commonest cause of death in the first two weeks following gross total tumour resection (GTR) [7].

Research into histogenesis of CG indicates that ultra-structurally the cells of this neoplasm are derived from embryonic tanycytic cells [8]. This theory is strengthened by the constant origin of CGs from the infundibulum and lamina terminalis of the anterior third ventricle, regions rich in tanycytes. Besides supporting the concept that CGs have ependymal origins, another group further proposed a minority also derived from multi-potential stem cells [9]). Thus CGs have both neuronal and ependymal origins. The earlier thesis by Pasquier, et al. [10] that CG is a sub-type of ependymoma seems justified.

The key breakthrough in the genetic nature of CGs occurred in 2018. By studying the genomic profiling of 13 CGs of adult patients, Goode, et al. [11] have identified a mutation in a singular gene; the PRKCA in all 13 tumour samples tested. The PRKCA gene is part of the growth pathway named MAP kinase; in normal circumstances this pathway is turned off in brain cells. Mutation of the PRKCA genome activates the MAP kinase pathway, resulting in cellular growth into a tumour. By manipulating this MAP kinase pathway, scientists are discovering specific medications to treat tumours such as a melanoma.

Instead, what insight we possess of CG's nature has not been translated into clinical practice since clinicians rarely encounter this condition. Moreover, there are situations in which a CG can be overly aggressive, when a patient would succumb to rapid tumour recurrence within eight months following initial presentation despite adequate surgical resection [12]. Furthermore, a young woman of 27-years-old died unaccountably of respiratory failure on the third day after GTR of a CG arising from the pulvina of the thalamus [13]. On the contrary, a middle-aged woman with an anterior third ventricle CG infiltrating the optic chiasm had shown no change in clinical status and tumour size 18 months following exploratory biopsy; the patient nominated not to have surgery or any other forms of therapy [14].

By 2017, an estimated 86 cases of CG have been described [15], mostly in small case-series and case-reports. A predominance of adult females is stricken with a female to male ratio of 1.6:1 [15]. CGs affecting children and adolescents are uncommon; their unusual clinical course and morphological features have stimulated discussion [7]. Points of interest include fewer lesions arising from the anterior third ventricle and rapid onset and death of a young child despite surgical intervention. Perhaps for patients in their first two decades of life the disease expresses itself in different forms. This review explores such thesis, describes the clinico-morphological features and the role of imaging in therapeutic management.

### Material and Methods

A search of the Medline database on publications (in English) in childhood and adolescent chordoid gliomas from 1998 to January 2019 was performed. Search terms used on this theme include the following keywords: "childhood/adolescent", "chordoid glioma", "imaging", and "therapy".

The primary search yielded 37 papers. Only 34 of these meet the criteria of which five review papers are retained as sources of reference.

### Results and Discussion

The core material consists of six case-reports on CGs in children and adolescents. In accordance with the tumour's site of origin, each of the respective six patients is placed into two subgroups; namely the "hemispheric group" and the "third ventricle/suprasellar group".

### Hemispheric group

The clinical presentations of the three children here range from asymptomatic [15] to sudden headaches and abnormal body movements [16]. In the latter instance, a 5-year-old boy, the illness' abrupt onset was mistaken as a viral encephalopathy and treated accordingly. Plain cranial computed tomography (CT) depicted a huge 7 x 5.5 x 5 cm mixed density lesion in the left temporo-parietal lobe and despite complete surgical resection he succumbed to cardiac arrest 48-hours later.

Contrarily, the right anterior horn lesion described by Chen., *et al.* [15] on magnetic resonance imaging (MRI) was moderately well circumscribed. The patient had no symptoms or positive physical signs. CG's rarity led to a pre-surgical diagnosis of giant cell subependymal astrocytoma since both tumours share similar imaging characteristics. Surgical exploration found tumour adherence to the ventricular walls and septum pellucidum, limiting the procedure to a subtotal excision. It exemplifies the apparent indolence of CG but neuro-imaging can on occasions belie the true surgical pathology.

The third case concerns a 7-year old girl with progressive headaches, vomiting, lower limb weakness and a past history of healed tuberculous cervical lymphadenitis [17]. Cranial CT revealed a moderate sized mixed density mass within the corona radiata extending to the adjacent right thalamic region. An unexpected increase in lesional vascularity did not prevent its GTR. She has remained alive and well two years post-surgery. Of the six CGs studied, this is the only instance in which its histogenesis was discussed. Ultra-structurally the tumour cells resemble ependymal cells. The abundance of cytoplasmic intermediate filaments and local basal lamina suggests its cellular origin is derived from tanyocytes, supporting earlier arguments by Sato., *et al* [8].

### Third ventricular/suprasellar group

This group consists of two female and one male patient. The latter, a 12-year-old boy, had complained of progressive visual disturbance. The causative factor as confirmed by MRI was optic chiasm compression by a moderate-sized hypothalamic tumour extending towards the suprasellar region [18]. Contrary to the commonly described homogeneous enhancement on MRI, this tumour was inhomogeneous after intravenous contrast injection. This might correspond to a mix of glial cells and chondroid and cartilaginous tissues. Though it was the first case of a CG with chondroid metaplasia, the list of conditions with similar morphology and sites of origin includes a retroclival chordoma [19], craniopharyngioma, germinoma, teratoid tumour and pilocytic astrocytoma [20]. A successful tumour debulking was performed through a right pterion approach though his follow-up data went unrecorded.

Both female patients in this group give a long history of headaches though the elder girl had presented with visual impairment and endocrine dysfunction; her amenorrhoea had lasted a few years [4]. She harboured a solid and homogeneously enhancing 3.5cm diameter suprasellar tumour. Despite its size MRI revealed the pituitary contents were intact. Only a subtotal resection (STR) was achievable for reasons of lesional size and adhesions to adjacent structures. Her endocrine problems persisted due to residual tumour that was successfully treated with a course of gamma knife radio-surgery. Apart from receiving hormonal replacement therapy she was well and symptom-free 18 months post-surgery.

The third patient in this group highlighted a tale of ultimate survival by researchers from Brazil [21]. This 13-year-old girl's illness has stretched from 2003 to 2012 and she has been well at the latest follow-up. Surprisingly it was not until surgery for the third time that the tumour in the hypothalamus was confirmed as a CG. In 2003 she underwent surgery for excision of a "chordoid meningioma" followed by an asymptomatic period of 8-years. But a first recurrence at the hypothalamus followed; this was reported as a gliosarcoma after STR. A GTR on the second recurrence in 2012 confirmed the lesion to be a chordoid glioma but without signs of malignancy [21].

On the evidence provided, CGs in children and adolescents are not specifically different from that of adults. Some may have different morphological expressions [16,17]. But as illustrated in the other four cases, there are similarities in clinical presentations and modes of therapy as that of the adult population. Yet our limited insight on the nature of paediatric CG is exemplified in the 12-year-old boy whose-

anterior third ventricle/ hypothalamic lesion [18] is a mix of glial and chondroid metaplasia, findings that also typify the WHO grade I pilocytic astrocytoma (PA). Children with CGs and PAs may share similar symptoms such as progressive visual loss and headaches. In a series of 14 cases of PA affecting the optic pathway/hypothalamus [22], surgical excision resulted in tumour control; their success hinged on precise histology following biopsy. Contrariwise, those tasked with managing the uncommon paediatric CGs may not recognise this condition preoperatively [21]. It must be stressed that surgical removal of the occasional vascular third ventricular tumour is difficult, and complications are due to the lesion's histopathology rather than a surgeon's experience [23]. Additionally, there is the mucinous adhesive property of a CG, akin to that of an intraventricular chordoid meningioma: the causative factor of tumour recurrences [24].

To assess a large mixed density hemispheric lesion in a child based purely on plain cranial CT, the magnitude of the undertaking verges on enormous [16]. Such an enigmatic situation might stem from diseases ranging from viral encephalopathy to the rare secondary deposit. But in an acute setting, involving a 5-year-old, the imaging findings maybe in keeping with a high-grade vascular glioma [25]. In a similar vein, the patchy enhancing mass in the right corona radiata [17] is morphologically comparable to the surgically curable hemispheric low grade glioma [26]. However, with a past history of cervical tuberculous lymphadenitis the presence of a tuberculoma is a possibility [27].

Although GTR is curative for CGs, the high postsurgical mortality rate has made some to trial safer alternatives [6]. The same group used microsurgical biopsy to confirm tumour histology prior to STR and gamma-knife radio-surgery to irradiate the tumours, taking precautions to minimise exposure to the optic apparatus. The adverse effects of irradiation cannot be over-emphasized. A recent series describes a total of 142 children who received central nervous system irradiation; of these, 57% developed a malignant brain tumour over a mean period of 8-years [28]. Nevertheless, there had been gradual acceptance of the safety and effectiveness of gamma-knife radio-surgery. This is attested by suggestions on its use in treating residual disease affecting adolescents [21].

Contrast enhanced MRI counts as the most invaluable in preoperative assessment and postsurgical management of CGs. Consider the value of diffusion tensor tractography in mapping the cortico-spinal tract prior to GTR of a neoplasm in the thalamic region. And although there is doubt of MRI's absolute diagnostic accuracy in some quarters [29], much has been written about the characteristic features of an anterior third ventricular CG [30,31]. These include its oval shape with its longest diameter along the vertical axis and causing posterior displacement of the infundibulum compared to a tuber-cinereum lesion that pushes the infundibular stalk anteriorly. MRI's excellent spatial resolution makes it possible to distinguish the true relationship between a CG that had apparently infiltrated the optic chiasm [32] preoperatively. Surgical exploration revealed the lesion was only adhering to the optic nerve enabling its STR. The scenario in which a large suprasellar CG had not invaded the pituitary gland was emphasised by Danilowicz., et al. [4]) for sparing an adolescent more surgery substantiating the value of MRI in therapeutic planning.

High resolution CT with 3D reconstructions of the skull and facial bones is one of the essential tools in planning skull base surgery. With a developing skull the focus of entry for a craniotomy or burr hole has potential impact on the procedure's outcome. Therefore, instead of the child's pterion, the correct point of a pterion burr hole is located 2 cm more posteriorly [33]. Other essentials consist of digital subtraction cerebral angiography, a technique that depicts the full anatomical configuration and variations of the anterior communicating artery. Should the width of the vessel be narrow it may not be feasible to excise an anterior third ventricular tumour successfully and safely [6,34].

Various surgical routes are described to access CGs in the third ventricle or other third ventricular tumours in children. Preventing damage to the hypothalamus is the prime objective and access through the lamina terminalis the most acceptable [29]. The interhemispheric route counts as the safest since no postsurgical mortality was reported among 100 children afflicted with anterior ventricular tumours, craniopharyngiomas and gliomas [34]. Of the 10 childhood hypothalamic gliomas excised, none suffered postoperative endocrine disturbance. Such good outcome is due in part to use of the endoscopic technique

### Conclusion

There is inadequate evidence to validate that paediatric and adolescent CGs are different from that in the adult population. By studying the lesion's varied morphology and clinical course one is more cognisant of its biological behaviour and therapeutic options. We should be sensitive to the emotional effects of repeated therapies on children since those with less resilience may carry a psychological burden to adulthood.

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