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Unusual Locations of Gangliogliomas: Intraventricular and Posterior Fossa

Adrian Mircea FURTOS[1,2,3], Aurelia Mihaela SANDU[2], Vasile Gheorghe CIUBOTARU[2], Radu Mircea GORGAN[1,2], Ligia Gabriela TĂTĂRANU[1,2]

[1]University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania
[2]Clinic of Neurosurgery, Emergency Clinical Hospital Bagdasar-Arseni, Bucharest, Romania
[3]Clinic of Neurosurgery, University Emergency Hospital Bucharest, Romania

Corresponding author: Aurelia Mihaela SANDU ✉ aurasandu@gmail.com

ABSTRACT

AIM: To report a series of patients diagnosed with gangliogliomas (GG) in unusual locations; and to review the clinical and imaging features as well as surgical treatment and outcomes.

MATERIAL and METHODS: A series of consecutive patients who underwent surgery for GGs at unusual locations, such as intraventricular region and posterior fossa, from 2010 to 2022 were included in the study.

RESULTS: Nine patients with GGs located in unusual areas, one in the intraventricular region and 8 in the posterior fossa, were included. There were 5 males and 4 females, with a mean age 31±8.5 years. We performed GTR in 6 cases and STR in 3 cases. Seven tumors were grade I WHO while the remaining two were anaplastic. Five patients also had preoperative hydrocephalus. We found a positive correlation between midline GG of the posterior fossa and solid aspect of the tumor (p=0.05). Univariate analysis found no other statistically significant associations, but this was due to the small patient sample. Recurrence was seen in 2 cases with STR, after 1 and 10 years, respectively.

CONCLUSION: GG should be considered in the differential diagnosis of patients with tumors in the intraventricular region or posterior fossa. Maximal tumor resection and restoration of CSF flow pathways ensure a good outcome. Growth patterns correlate with resection and can help choose the best candidates for surgery. However, further studies on large patient samples are needed.

KEYWORDS: Brain tumors, Ganglioglioma, Intraventricular, Posterior fossa

ABBREVIATIONS: CPA: Cerebellopontine angle, **CSF:** Cerebrospinal fluid, **GG:** Ganglioglioma, **GTR:** Gross total resection, **LV:** lateral ventricle, **N/S:** Not specified, **STR:** Subtotal resection, **V3:** Third ventricle, **V4:** Fourth ventricle, **WHO:** World Health Organization

INTRODUCTION

Gangliogliomas (GGs) are rare primary brain malignancies, accounting for 0.4% of all central nervous system tumors (3,4,35,41). The majority of GGs are low-grade, well-defined, slow-growing neuroepithelial tumors, but aggressive types of anaplastic GGs can also occur. The first reports of GG in the literature were made by Perkins in 1926 (54), and Courville in 1930 (14). However, brainstem tumors with histopathological features suggestive of GG at autopsy were first described by Bielschowsky and Pick in 1911 (23,62).

GGs have a mixed histologic pattern, consisting of two cellular populations: neoplastic ganglion cells and neoplastic glial cells. Tumor growth is due to proliferation of glial cells. In low-grade GG the glial component is astrocytic,

Adrian Mircea FURTOS : 0000-0002-5248-4743
Aurelia Mihaela SANDU : 0000-0002-0287-5201
Vasile Gheorghe CIUBOTARU : 0000-0002-7559-8241
Radu Mircea GORGAN : 0000-0002-3246-9159
Ligia Gabriela TĂTĂRANU : 0000-0002-3339-5817

pilocytic or fibrillary, with rare mitosis, and stigmas of slow growth, like Rosenthal fibers, eosinophilic granular bodies, microcysts, calcifications, reticulin network, perivascular lymphoid infiltrates and prominent glomeruloid capillary network. In anaplastic GG, the glial part presents mitosis, vascular proliferation, dense capillary network, and necrosis. Ganglionic cells are dysplastic with anaplastic changes being scarce. According to the 2016 WHO classification of tumors of the central nervous system, GGs are mixed neuro-glial tumors, divided into two categories: grade I and anaplastic grade III (39), but the latest 2021 WHO classification acknowledges only one entity of GGs (40). Nevertheless, new classifications have been proposed, dividing them into three histopathological entities: grade I, atypical and anaplastic (38).

Sex distribution for GGs is even (37) or with minimal preference for males (41). GGs occur in children and young adults, at a mean age of 26-36 years. (37,41) Classically, most patients present with long-term seizures (41), and symptoms that are indicative of the tumor's location. Imaging of GG is not definitive. A typical imaging result shows a well-circumscribed cystic lesion with a mural nodule. The solid part enhances contrast. No surrounding edema is usually observed but calcifications can sometimes be seen. Hemorrhagic transformation is unusual. Meanwhile, anaplastic GGs have a heterogenous pattern, have strong contrast enhancement and are associated with surrounding edema.

Differential diagnosis is made in the case of pilocytic astrocytomas, oligodendrogliomas, dysembryoplastic neuroepithelial tumors, pleomorphic xanthoastrocytomas, desmoplastic infantile astrocytomas, gangliocytomas, astrocytomas,ependymomas, cortical dysplasias and hemangioblastomas.

GGs are usually found in the cerebral parenchyma, with the temporal lobe being the most common location (37,41,58). Unusual locations, such as the ventricular system, the cerebellum and the brainstem account for 4.3%, 7.7%, and 3% of all GG cases, respectively (37).

The treatment of choice is surgery, with the goal of complete tumor resection. Adjuvant therapies, like radiotherapy and chemotherapy, have been shown to be ineffective (58).

The aim of this study is to report a series of cases of GG with unusual locations, such as the intraventricular region and posterior fossa, and to review clinical and imaging features, surgical treatment and outcomes.

MATERIAL and METHODS

We report a series of consecutive patients who underwent surgery for GGs at unusual locations, such as intraventricular region and posterior fossa. We included cases with positive histopathological exams for GG (histology codes M9505/1, and M9505/3 – ICD-O-3 International Classification of Diseases for Oncology, 3rd edition), from 2010 to 2022. Cases with GG arising from the parenchyma and extending into the intraventricular region and patients who underwent surgery solely for hydrocephalus were excluded. Patients with dysplastic gangliocytoma of the cerebellum Lhermitte-Duclos were also excluded. The study was approved by the hospital Ethics Committee of Spitalul Clinic de Urgenta "Bagdasar-Arseni" (No: 42914, Date: December 2022). Statistical analysis was done using SPSS IBM®.

RESULTS

Nine patients with unusual GG locations were identified. Specifically, we found one case of intraventricular GG (Case 1, Figures 1-3) and 8 cases of GG in the posterior fossa (Cases 2-9, Figures 4-6). The main features of these patients are summarized in Table I. There were 5 males and 4 females and the mean age was 31 ± 8.5 years (ranging from 20 - 46 years of age). Mean hospital stay was 16.89 ± 6.214 months. Timing from onset to positive diagnosis varied from one month to 24 years.

According to tumor location, we divided patients with posterior fossa GGs into three categories: cerebellar midline (vermian and paravermian), brainstem (brainstem and V4), and lateral posterior fossa (cerebellar hemisphere and CPA). We found a correlation between location and imaging features: solid vs. solid-cystic (U=1.5, p=0.05), solid GG being more likely found in the midline (brainstem and cerebellar midline), while solid-cystic tumors were found in lateral locations. All GGs displayed

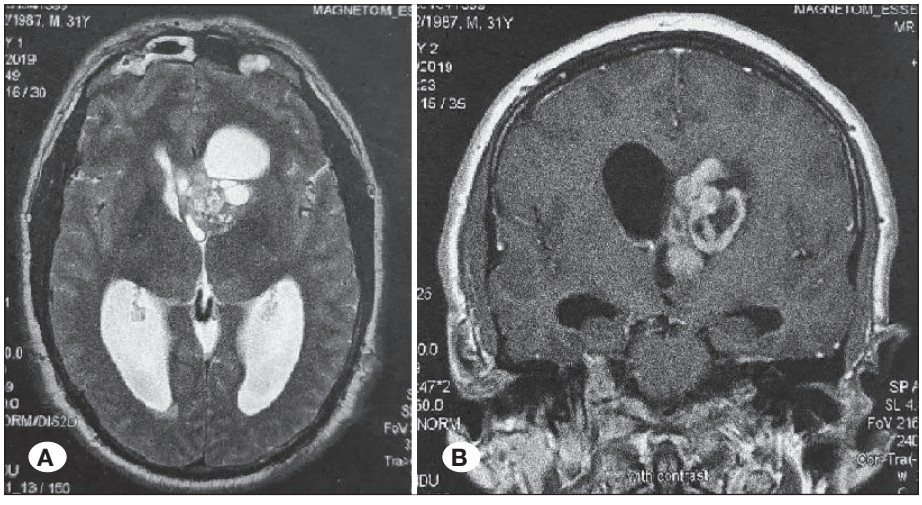

Figure 1: Case 1 - intraventricular ganglioglioma. Preoperative axial T2W **(A)** and coronal T1W contrast enhanced **(B)** MRI scans: left LV tumor, extending into V3, ventriculomegaly.

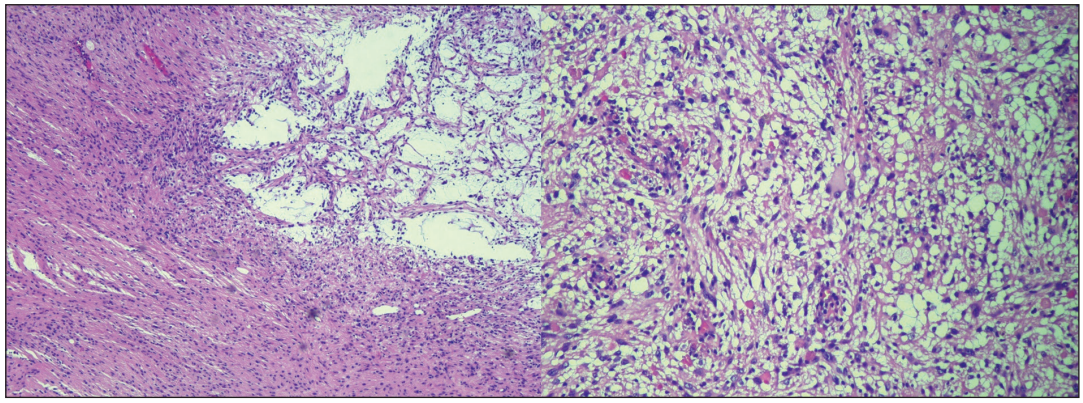

Figure 2: Case 1- intraventricular ganglioglioma. Histopathological examination revealed anaplastic GG WHO Grade III. Biphasic aspect, large, multinucleate tumor cells.

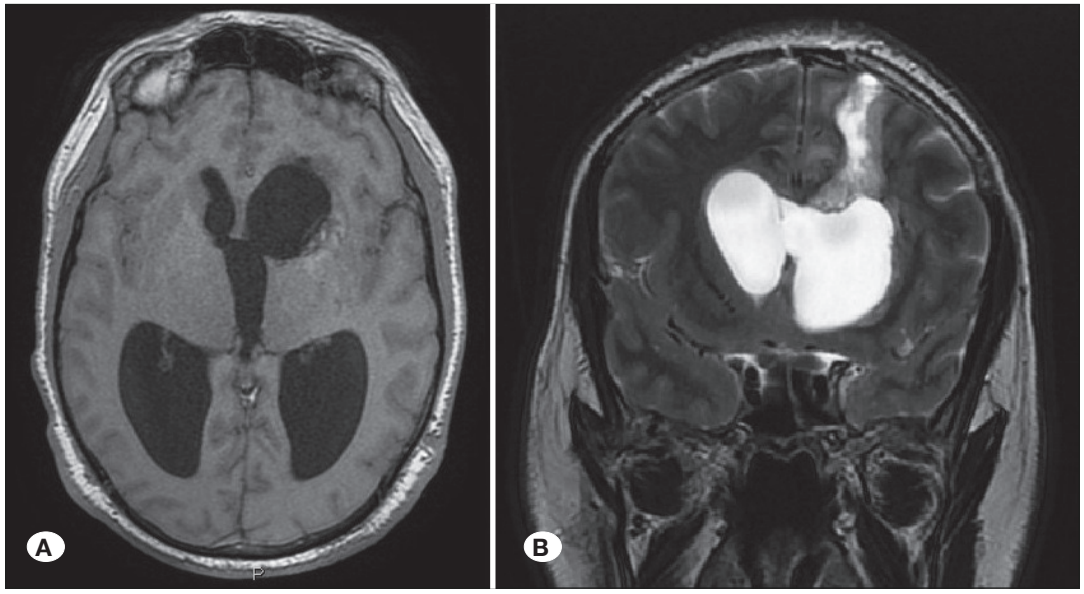

Figure 3: Case 1 - intraventricular ganglioglioma. Postoperative T1W axial **(A)** and T2W coronal **(B)** MRI scans showing: complete resection via transcortical approach.

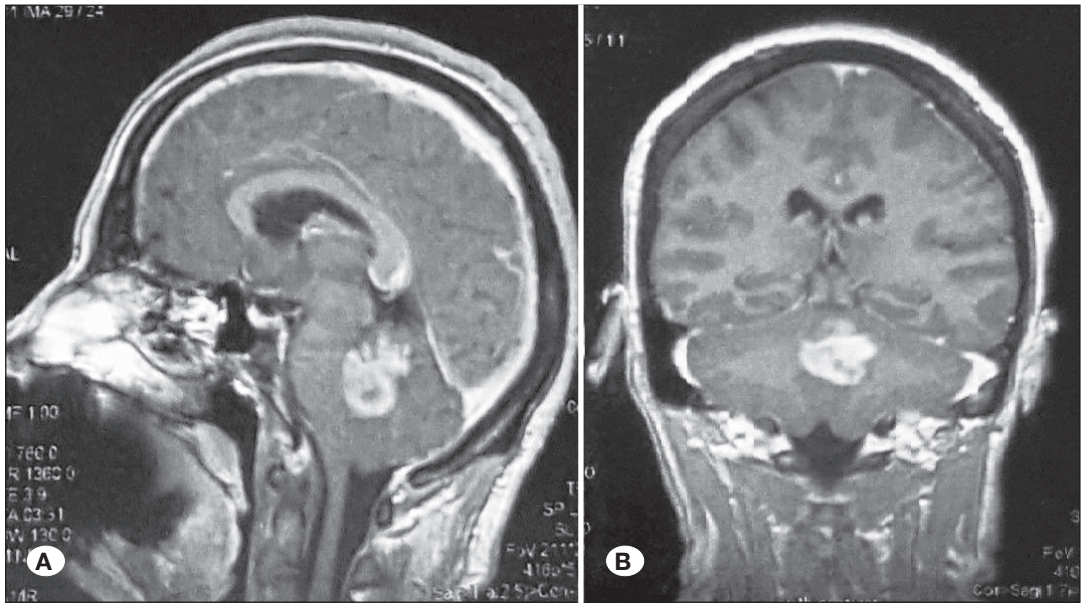

Figure 4: Case 7 - posterior fossa ganglioglioma. Preoperative sagittal **(A)** and coronal **(B)** T1W contrast enhanced MRI scans. Midline contrast enhancing vermian tumor.

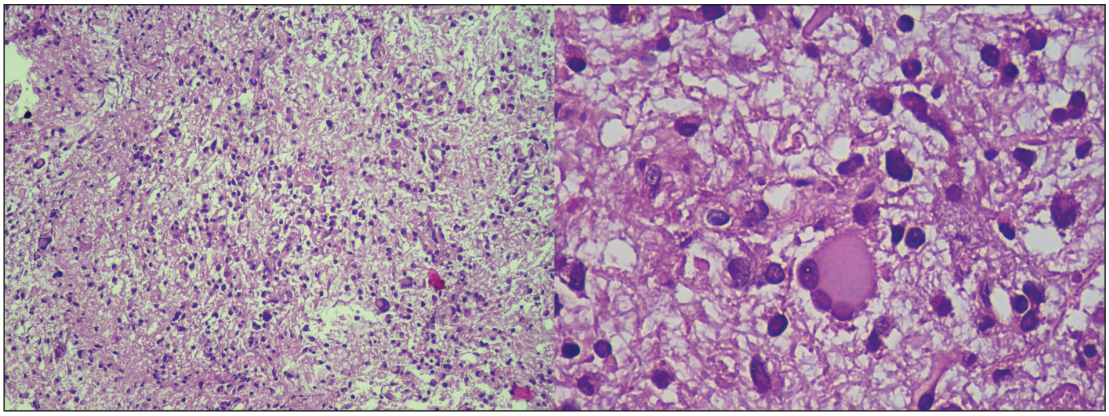

Figure 5: Case 7 - posterior fossa ganglioglioma. Histopathological examination revealed GG WHO Grade I. Ganglionic cells in glial stroma, ganglionic multinucleate tumor cell (detail).

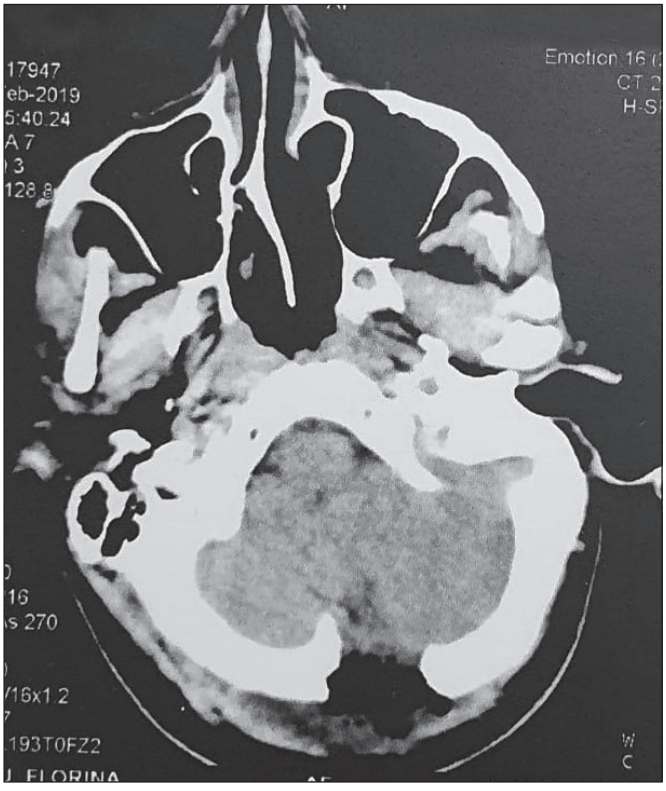

Figure 6: Case 7 - posterior fossa ganglioglioma. Postoperative axial CT scan showed complete resection via suboccipital craniectomy.

enhanced contrast, either homogenous or inhomogeneous. There was no correlation between tumor location and the pattern of contrast enhancement (U=2, p=0.061). We found no associations between tumor volume and imaging aspect (U=3, p=0.180) or contrast enhancement (U=3, p=0.149). None of the tumors presented with surrounding edema.

Extent of resection was defined as GTR (complete resection of the whole tumor as detected on postoperative MRI) or STR (resection of > 50% of tumor). The resection grade was not associated with tumor size (U=8, p=0.796), but rather with the tumor location. GTR was achieved in all patients with cerebellar tumors while STR was done in challenging locations such as the brainstem, and in a very large tumor from the CPA. Further, tumor size was not associated with hydrocephalus (U=4, p=0.142), histopathological grade (U=2, p=0.143) or postoperative complications (U=8, p=0.796). Five patients had enlarged ventricles at diagnosis; one required ventriculoperitoneal shunt before tumor surgery due to acute hydrocephalus, and in another one it was done after tumor surgery due to the persistence of symptoms of intracranial hypertension. Two patients developed early complications. One patient developed a CSF fistula, which resolved in a few days with CSF drainage. Another patient with brainstem GG had a less favorable outcome. Immediately after surgery the patient was fully awake, without any motor deficits, but with transient respiratory failure, which required mechanical ventilation. After a few days she was extubated, with no signs of respiratory failure, but on the 13th day of hospitalization she suffered a sudden and irreversible cardiac arrest. Finally, another patient developed late hydrocephalus 4 months after surgery, which required a ventriculoperitoneal shunt, with good outcome. The follow-up period varied from 2 to 11 years. During this period of time, tumor recurrence was noticed in two patients with STR. Recurrence timing was 1 year in grade III GG and 10 years in grade I GG.

DISCUSSION

In the literature there are few large cohort studies on GGs. So far, the largest study included 703 adult patients with low-grade GG, from the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2016 (37). Another large study reviewed all reports published from 1978 to 2007 and included 402 patients, both children and adults, harboring both low and high grade tumors (58). Other large studies gathering information on hundreds of cases were published by Blümcke and Wiestler (6), Luyken et al. (41), Dudley et al. (21), and Varshneya et al. (73), among others.

GGs are intriguing tumors with a histopathological hallmark of dual cellularity, consisting of both glial and neuronal cells. The tumor may exhibit either mainly neuronal or glial phenotype. The latest theory regarding the origin of GGs is that they arise from prior malformative or dyplastic lesions, in which neoplastic transformation of the glial component occurs (6). This theory is supported by a low-malignancy,

Table I: Patients with GG with Unusual Locations

No	Sex, age	Location	Signs & symptoms	Tumor size (mm)	Imaging	Hydro-cephalus	Resection type	HP grade	Postoperative complications	Recurrence
1	M, 31 y	LV + V3	Headache, gait disturbances, brachial paresthesia, memory loss, singultus	40/40/20	Solid-cystic, inhomogeneous, contrast enhancing	+	GTR	III	-	-
2	M, 22 y	cerebellum paravermian	Headache, vertigo, gait ataxia	28/24/23	Solid, homogenous, contrast enhancing	-	GTR	I	-	-
3	M, 22 y	cerebellum, vermis	Headache, nausea, vomiting, gait ataxia	20/20/25	Solid, homogenous, contrast enhancing	+	GTR	I	-	-
4	F, 34 y	brainstem, V4	Headache, nausea, tinnitus, otalgia, visual loss	24/22/20	Solid, homogenous, contrast enhancing	-	STR	I	death	n/a
5	M, 31 y	cerebellum	Headache, limb ataxia, dysmetria, dysfonia	30/25/20	Solid-cystic, inhomogeneous, contrast enhancing	-	GTR	I	-	-
6	M, 36 y	cerebellum paravermian	Headache, vomiting, truncal and limb ataxia, gait disturbance, dysmetria, hypotonia, hypokinesia, urinary incontinence, memory loss	47/45/43	Solid-cystic, inhomogeneous, contrast enhancing	+	GTR	I	CSF fistula	-
7	F, 46 y	vermis	Headache, dizziness, gait disturbance, truncal ataxia	33/30/26	Solid, inhomogeneous, contrast enhancing	-	GTR	I	hydrocephalus	-
8	F, 20 y	CPA	Headache, vomiting, facial palsy, dysmetria	57/40/26	Solid-cystic, inhomogeneous, contrast enhancing	+	STR	III	-	+
9	F, 37 y	brainstem, V4	Headache, dizziness, nausea, vomiting, memory loss, Parinauld syndrome	33/30/26	Solid, homogeneous, contrast enhancing	+	STR	I	-	+

M: *Male,* ***F:*** *Female,* ***y:*** *years.*

well-differentiated glioneuronal phenotype, immunoreactivity for stem cell epitope CD34, a slow-growing pattern, and a long-term, benign history (6). GGs exhibit a broad variety of morphological changes, with three types of histological growth patterns: relatively well-circumscribed, infiltrative and combined model (1). Most GGs express the stem cell epitope CD34 (6). Further, molecular analyses have shown that GG harbor genetic mutations that activate the MAP kinase pathway (53). BRAF p.V600E mutations are often encountered and are associated with tumor regrowth (13,26). In addition, genetic studies using trypsin-Giemsa staining and spectral karyotyping, found deletions on chromosomes 10, 13 and 22, gains in chromosomes 5, 7, 8 and 12, the unbalanced non-reciprocal translocation t(1;18)(q21;q21) and a ring chromosome 1 (75).

In addition to their typical temporal lobe location, GG can occur less frequently in other parts of the brain, such as parietal or frontal lobes, thalamus and hypothalamus, ventricular system, pituitary stalk, optic pathways, pineal gland, cerebellum, brainstem and spinal cord (52,53,59,62). Regarding unusual locations, current knowledge is limited to case reports or very small series of patients. Hence, reports on the correlation of GG and unusual locations provide better understanding of tumor behavior. GGs with unusual locations also present a specific clinical pattern, characterized by the absence of long-term epilepsy, and the presence of symptoms that mirror tumor locations. In our series of cases, age, sex ratio and imaging features are consistent with the literature.

Intraventricular GGs

Supratentorial pure intraventricular GGs are very rare. They can be located in one or both LV and/or in V3. A literature review found only 40 cases published so far, with our case being the 41st (Table II). This is the most comprehensive literature review so far.

The origin of pure intraventricular GG is believed to be from the ventricular walls or choroid plexus (32). The clinical pattern of intraventricular GGs is primarily dominated by obstruction of CSF pathways and resulting intracranial hypertension. Other clinical features are memory loss, fatigue, loss of vision, pituitary failure, and diabetes insipidus. Rarely intraventricular GGs may present with sudden onset due to acute spontaneous intratumoral bleeding (5,9,74). Dissemination along the CSF pathways is unusual. Few and far between case reports with synchronous GG, such as LV and optic chiasm (18), or LV and sacral drop metastases(69), have been published.

Technical challenges include a long and narrow surgical corridor. We recommend maximal tumor resection with restoration of CSF flow as the first stage of surgery, as in most cases hydrocephalus resolves on its own. The persistence of acute hydrocephalus after tumor surgery is caused by intraventricular bleeding, remaining tumor tissue or infection. Treatment for secondary hydrocephalus can be carried out as a first step surgery in patients with acute symptoms, but it carries risks such as cerebral herniation, tumor bleeding, and tumor swelling, among others.

Posterior Fossa GGs

Posterior fossa GGs are also rare, with most findings being case reports. However, many authors have conducted comprehensive literature reviews. In 2007, Safavi-Abbasi et al. reported one case and found another 70 patients with posterior fossa GGs, from 1911 to 2007 (62). In 2013, Gopalakrishnan et al. reported one case of brainstem GG in a child and found another 33 previously reported cases of brainstem GGs in children, from 1932 to 2009 (25). Puget et al. performed a comprehensive review of the literature and found 100 brainstem GGs and 80 cerebellar GGs in children (56). In 2014, Gupta et al. reported a histologic study in 22 patients with posterior fossa GGs (26). Janjua et al. performed a systematic review over 50 years, and found 142 brainstem GGs across 46 studies (33). Posterior fossa GGs are more frequent among the pediatric population (27,57).

Posterior fossa GGs may originate in the cerebellar hemispheres, vermis, cerebellar peduncles, CPA, brainstem, fourth ventricle, and cervicomedullary junction. Clinical presentation depends on the location of the tumor, and includes cerebellar syndrome, ataxia, gait disturbances, incoordination, cranial nerves deficits, long tract dysfunctions, nystagmus, and intracranial hyperpressure. As in intraventricular GG, classic symptoms, such as long-term epilepsy are not found. A few cases of epilepsy have been reported in the literature with a particular seizure (11,28,46,47,49). Development of cerebellar seizures is still debatable, but EEG monitoring shows seizure discharges arising from cerebellum (11,28,47). Intratumoral hemorrhage is rare (34).

Regarding location and tumor type, we found correlation between tumor site and imagistic appearance. However, while we observed a higher prevalence of solid tumors in the midline, other authors have reported a positive association between midline tumors and a cystic appearance (26). Nevertheless, midline tumors were associated with glial matrix composed by neoplasticastrocytes and presence of BRAF p.V600E mutation (26,53). Immunoreactivity for stem cell epitope CD34 also varies with location; most CD34 positive tumors have been found in the temporal lobe, whereas GGs in other brain regions were CD34 negative (6).

As a grade I, slow-growing tumor, GGs have good survival outcomes. Optimal treatment should be the top priority, with the goal of achieving maximal resection and restoring normal CSF flow, gold standard objectives, which ensure a good outcome. While cerebellar GGs are easily accessible for surgery, GTR of brainstem lesions is challenging. Our study found that tumor size was not a factor in determining the extent of resection. The ability to achieve complete resection was related to the tumor's location and the difficulty of the surgery. Locations that are more accessible, such as the cerebellum, do not pose significant challenges for GTR, while resection of brainstem GGs may be hindered by the vicinity of eloquent cortex. In our study, in both patients with brainstem GGs, the tumors had a dorsal exophytic component protruding into the V4. Surgery was possible through a transvermian approach, for resecting only the exophytic component occupying the V4. This provided a tissue sample for histopathological examination

Table II: Supratentorial Intraventricular GG – Review of the Literature

No.	Author	Year	No. of cases	Patients' features	Location	Surgery
1	Doyle and Kernohan (20)	1931	1	F, 13 y	V3	N/S
2	Anderson ve Adelstein (2)	1942	1	-	V3	N/S
3	Russell and Rubinstein (61)	1962	1	F, 26 y	LV	N/S
4	Silver et al. (68)	1991	1	M, 33 y	LV	STR
5	Majós et al. (43)	1998	1	M, 71 y	LV	GTR
6	Matsumoto et al. (45)	1999	2	M, 10 y	LV	STR
7				F, 31 y	LV	STR
8	Yin Foo Lee et al. (76)	2001	1	F, 25 y	LV	GTR
9	Jaeger et al. (32)	2001	1	F, 20 y	LV	GTR
10	Nair et al. (51)	2004	1	F, 65 y	LV	N/S
11	Shono et al. (67)	2007	2	F, 34 y	V3	GTR
12				M, 52 y	V3	GTR
13	Hauck et al. (29)	2008	1	F, 20 y	V3	GTR
14	Samdani et al. (64)	2009	1	M, 18 y	LV	GTR
15	Bhat et al. (5)	2010	1	M, 27 y	LV	GTR
16	d'Andrea et al. (15)	2011	1	M, 22 y	LV	GTR
17	Deling et al. (19)	2013	7	M, 28 y	LV	GTR
18				M, 15 y	V3	GTR
19				F, 15 y	LV	GTR
20				M, 54 y	LV	GTR
21				F, 13 y	LV	GTR
22				M, 27 y	V3	GTR
23				M, 13 y	LV	GTR
24	Gonçalves et al. (24)	2014	2	M, 38 y	V3	N/S
25				F, 10 y	LV	N/S
26	de Castro et al. (18)	2014	1	F, 10 y	LV	N/S
27	Zhao et al. (77)	2015	1	M, 12 y	V3+LV	STR
28	Prasad et al. (55)	2016	1	F, 15 y	V3	STR
29	Higa et al. (31)	2016	1	F, 38 y	V3	STR
30	Syed et al. (69)	2016	1	M, 49 y	LV	GTR
31	Maiti et al. (42)	2016	1	M, 20 y	V3	GTR
32	Warnica and Provias (74)	2017	1	F, 23 y	LV	STR
33	Miyake et al. (50)	2017	1	M, 21 y	V3	STR
34	de Abreu et al. (17)	2018	1	F, 26 y	V3+LV	N/S
35	Campos et al. (9)	2018	1	M, 33 y	LV	GTR
36	Chatrath et al. (12)	2019	1	F, 13 y	LV	STR
37				F, 10 y	V3+LV	STR
38	Timble et al. (71)	2020	1	F, 67 y	LV	GTR
39	Salge-Arrieta et al. (63)	2021	3	M, 41 y	LV	STR
40				M, 25 y	V3	STR
41	Our case	2022	1	M, 31 y	V3+LV	GTR

M: *Male,* ***F:*** *Female,* ***y:*** *year.*

and prevented the development of hydrocephalus. Resection of the focal endophytic or diffuse infiltrative tumors can be done but with high risks due to the long surgical corridor, vicinity of eloquent brain and lack of a clear boundary around the tumor. Grade I GGs and GTR are associated with a low risk of recurrence (41). Even if complete resection is not possible, prognosis remains good for grade I gliomas. Moreover, GTR has no impact on survival in these cases (41). Considering the slow-growing nature of the tumor, in patients with incomplete resection, we recommend a wait-and-watch approach for diffuse infiltrative or endophytic brainstem GG. Radiotherapy is not recommended. The seizure-free period, a common indicator for quality of life after surgery in classic GG (7), does not apply to these locations.

Anaplastic GG can appear de novo or through dedifferentiation of the glial part of a preexisting tumor. Neuroblastomatous malignant transformation is exceptionally rare (16,70). In 2018, Bouali et al. reported a malignant posterior fossa GG and found another 11 patients with the same histological features in the literature, from 1992 to 2012 (8). Grade III anaplastic gliomas exhibit a more aggressive behavior compared to other types of gliomas. However, they have a better prognosis than other high-grade brain gliomas (22). Anaplastic GGs have a tendency to recur after STR (36). After STR, adjuvant treatment should be tailored according to histological grade and growth kinetics studies (36). In our series of cases, one of the two patients with grade III GG had 1-year recurrence and the second had a short follow-up period of only 2 years, so we cannot conclude whether he will be a long-term survivor.

However, if the role of surgery is undebatable, the efficiency of other therapeutical options is inconclusive. Initially, radiotherapy was proposed for brainstem GG, but nowadays its use has been limited because of its poor radiosensitivity and the long-term deleterious side-effects of irradiation in young patients. Some authors even describe malignant dedifferentiation of the glial (30,60,66), or neuronal components (70) after radiotherapy. Radiotherapy has a negative impact on prognosis and survival (10,37). It is limited only to patients with unresectable progressive disease or anaplastic GG (56,65). Stereotactic radiosurgery seems to improve results in residual, recurrent or inaccessible GG (44,72). Genetic studies may be useful for developing target therapies. Lately, targeted therapies against BRAF p.V600E mutation seem to be promising (48), and they may be used in selected patients with a high surgical risk or to prolong recurrence-free survival.

The main limitation of this study is the small patient sample size without a comparison group, making it prone to bias which results in a lack of statistical significance. Our study has level IV evidence. However, the paucity of intraventricular or posterior fossa GG limits the possibility of conducting large studies. To gain a better understanding, systematic reviews that include case reports or series of cases may be useful.

CONCLUSION

GG should be considered in the differential diagnosis of patients with intraventricular tumors or in the posterior fossa. Patients with GGs in these unusual locations have a different clinical pattern, such as the fact that a solid aspect is common in midline GGs of the posterior fossa. Regarding treatment, successful outcomes are more likely with maximal tumor resection and restoration of CSF flow pathways. The growth pattern of the tumor is related to the extent of resection and can aid in selecting the best candidates for surgery. Cerebellar GGs are suitable for complete resection. Further, surgery may also be beneficial for exophytic brainstem GGs growing through the floor of the V4. However, further studies on larger samples are needed.

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AUTHORSHIP CONTRIBUTION

Study conception and design: AMF, AMS, LGT

Data collection: AMF, AMS

Analysis and interpretation of results: AMF, AMS

Draft manuscript preparation: AMF, AMS

Critical revision of the article: AMF, AMS, VGC, RMG

Other (study supervision, fundings, materials, etc...): VGC, RMG, LGT

All authors (AMF, AMS, VGC, RMG, LGT) reviewed the results and approved the final version of the manuscript.

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