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CLINICAL STUDY

Pediatric posterior fossa ganglioglioma: unique MRI features and correlation with BRAF V600E mutation status

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Abstract Ganglioglioma (GG) is a rare pediatric brain tumor (1–4 %) with neoplastic glial and neuronal cells. Posterior fossa GGs (PF GGs) occur less frequently than supratentorial GGs (ST GGs). The BRAF V600E mutation has been reported in GGs and carries therapeutic implications. We compare the presenting symptoms, magnetic resonance imaging, BRAF V600E mutation status, treatment, and prognosis in children with ST and PF GGs. The neuro-oncology database at a tertiary care Children's Hospital was retrospectively reviewed from 1995 to 2010 for patients with ST and PF GG. All available imaging was reviewed. Symptoms, BRAF V600E mutation status, treatment, and survival data were collected from the electronic medical record and analyzed. Our series consisted of 11 PF GG and 20 ST GG. Children with PF GG presented with ataxia, cranial nerve deficits and long tract signs whereas the majority with ST GGs presented with seizures. On imaging, PF GGs were infiltrative and expansile solid masses with dorsal predominant "paintbrush" enhancement whereas ST GGs were well circumscribed mixed solid and cystic masses with heterogeneous enhancement. Five of 11 (45 %) PF GGs and 6 of 9 (67 %) ST GGs expressed the BRAF V600E mutation. No unique imaging features were identified in BRAF V600E mutation positive tumors. The majority of ST GGs were treated with surgery alone, whereas the majority of PF GGs required multimodality therapy. PF GGs had worse progression-free survival and a higher mortality rate compared with ST GGs. Unlike ST GGs, PF GGs are expansile, infiltrative, show dorsal predominant "paintbrush" enhancement, are not amenable to gross total resection, and have worse progression-free survival and mortality.

Keywords Ganglioglioma · Posterior fossa · Supratentorial · BRAF V600E · Magnetic resonance imaging (MRI)

Introduction

Gangliogliomas (GGs) are tumors of neoplastic ganglion and glial cells [1] and are generally WHO grade I [2, 3], though may occasionally be anaplastic [4–7]. Criteria for WHO grade II tumors have not yet been established [2, 3]. In children, GGs make up 1–4 % of all brain tumors and 6 % of supratentorial (ST) tumors [5, 8]. GGs most commonly occur in the ST brain, with a predilection for the temporal lobe [3, 6, 9, 10]. GGs rarely occur in the posterior fossa (PF) [3, 11–13]. There has been little reported on the difference in presenting symptoms, imaging and course of PF GGs compared with ST GGs.

By magnetic resonance imaging (MRI) ST GGs are well circumscribed, solid or mixed solid and cystic, and demonstrate variable enhancement [5, 8, 13]. In contrast, by

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few published reports, PF GGs are less often cystic and demonstrate a higher rate of enhancement [10, 11].

PF GGs, particularly those affecting the brainstem, have an increased risk of recurrence [11, 14], in part due to tumor location and inability to achieve gross total resection (GTR) as often as ST GGs [11, 12, 15]. PF GGs have a poorer 5-year actuarial survival rate of 73 % compared to that of ST GGs which is 93 % [12]. However, PF GGs may also behave differently due to different tumor biology and have been shown to differentially express genes compared to their ST counterpart [14].

BRAF is a gene implicated in a wide variety of cellular functions, including cell proliferation, cell-cycle arrest, terminal differentiation, and apoptosis [16, 17]. Over 36 different types of mutations in the BRAF gene have been described in human cancers [18–20]. The BRAF V600E mutation in particular has been documented in 18–58 % of GGs [21–28].

Our aim is to report the differing presenting symptoms, MRI characteristics, treatment, and prognosis in ST and PF GGs. The incidence and imaging features of BRAF V600E mutation status in ST GGs and PF GGs are compared.

Materials and methods

Patient population

Following Institutional Review Board approval, a retrospective review of the neuro-oncology database at Children's Hospital Colorado was conducted for patients diagnosed with ST and PF GGs between 1995 and 2010. The patients were defined as pediatric patients if they were 0–18 years of age at the time of diagnosis or if, given the duration of symptoms, the tumors were considered to be present at a pediatric age and the patient was operated on at our institution. Patients without definitive pathology for GG or preoperative imaging were excluded. All included cases were initially confirmed and subsequently re-reviewed by a dedicated neuropathologist at our institution.

BRAF V600E mutational status was recorded. Patient demographics, symptoms, treatment, and survival data were collected from the electronic medical record. All available neuro imaging studies were reviewed, including brain computed tomography (CT), when available, and all available brain and spine MRI exams. All tumors were evaluated on T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), diffusion-weighted, apparent diffusion coefficient, and post contrast T1-weighted MRI sequences.

Statistical analysis

Median values, standard deviations, and confidence intervals (CIs) were calculated for all numerical data. Significance of continuous quantitative data was calculated using the Student's t test. Significance of qualitative data was determined using a χ^2 test.

DNA sequencing for BRAF exon 15 mutations

DNA was extracted either from snap frozen or formalin fixed paraffin embedded (FFPE) material using the DNeasy extraction kit or DNeasy FFPE extraction kit, respectively (Qiagen, Inc., Valencia, CA) according to manufacturer's instructions. DNA yields were then quantified using a Nanodrop spectrophotometer ND-1000 (Thermo Fisher Scientific, Inc., Waltham, MA). For direct sequencing, approximately 10 ng of template DNA were PCR amplified by a hemi-nested procedure using 10 pmol each of forward (5′-TGCTTGCTCTGATAGGAAAAT-3′) and reverse (5′-AGCATCTCAGGGCCAAAAAT-3′ external and 5′-TCAGGGCCAAAAATTTAATCA-3′ internal) BRAF exon 15 primers and Taq polymerase PCR master mix (Promega cat# M750) in a 25 µl reaction. PCR was performed on an ABI 9700 thermocycler with 20 cycles of touchdown PCR (starting annealing temperature of 65 °C, decremented 0.5 °C per cycle) and 15 cycles for both first and second amplification rounds at 94 °C denaturation, 55 °C annealing and 72 °C extension. The resultant PCR products were purified with the QIAquick 96 well PCR cleanup kit (Qiagen, Inc., Valencia, CA). The purified PCR products were sequenced in forward and reverse directions using an ABI 3730 automated sequencer. Each chromatogram was visually inspected for any abnormalities, using NM_004333.4 as a reference sequence, with particular attention directed to codon 600. Sequences were also evaluated using Mutation Surveyor software (Soft Genetics, State College, PA) using reference sequence NM_004333.4 for comparison. Mutations were determined to be present when peaks reached a threshold value above baseline calculated from background level, combined with visual inspection of the chromatogram.

RNA sequencing for BRAF exon 15 mutations and immunohistochemical staining were also performed to help confirm BRAF V600E mutation status and the methods for these techniques performed on the same patient samples at the same institution are fully described in a separate study recently published by Donson et al. [23] and involving current author (SZR).

Results

Eleven PF GGs and 20 ST GGs met inclusion criteria for the current study. Of note, the current imaging focused study includes 9 of the 13 brainstem GGs (patients 1–7 and 12–13 in Table 1 of the referenced study) and 9 of the 11

Table 1 Imaging characteristics of patients with supratentorial and posterior fossa gangliogliomas

Imaging characteristics	ST GG	PF GG	*p* Value
Solid	8/20 (40 %)	9/11 (82 %)	0.025*
Mixed solid and cystic	12/20 (60 %)	2/11 (18 %)	0.025*
Infiltrative and expansile	3/20 (15 %)	8/11 (73 %)	0.001*
Well-circumscribed	10/20 (50 %)	0/11 (0 %)	0.004*
Hydrocephalus	3/20 (15 %)	5/11 (45 %)	0.064
Enhancement[b]	15/18 (83 %)	11/11 (100 %)	0.15
Dorsal "paintbrush" enhancement[b]	0/18 (0 %)	6/11 (55 %)	<0.001*
T1 hypointense[a, b]	12/18 (67 %)	10/11 (91 %)	0.14
T1 isointense[a, b]	5/18 (28 %)	0/11 (0 %)	0.055
T2 hyperintense[a, b]	19/19 (100 %)	11/11 (100 %)	1

ST supratentorial, *PF* posterior fossa, *GG* ganglioglioma

* Indicates statistical significance

[a] T1- and T2- weighted intensity of tumor is relative to normal gray matter

[b] Two ST GG patients lacked post contrast T1-weighted imaging and one patient lacked T2-weighted imaging

non-brainstem GGs (patients 14 and 17–24 in Table 1 of the referenced study) in a recent study published by Donson et al. [23]. Four patients with brainstem GGs and two patients with non-brainstem GGs lacked adequate preoperative imaging and were not included. Eleven additional ST GGs which were not evaluated for BRAF V600E mutation status are included in the present study as their imaging provides a control group for comparison. The Donson et al. study includes histology and immunohistochemistry images for the same patient population and compares histologic patterns for brainstem and nonbrainstem GGs. Correlating BRAF mutation status with histologic pattern was not possible for our cohort given small sample size [23].

PF GG patients ranged in age from 1 day to 23 years (5 of 11 male; median age 4 years; 95 % CI 7.7 ± 4.2 years) and ST GG patients from 10 months to 19 years (11 of 20 male; median age 10.2 years; 95 % CI 9.5 ± 2.4 years). Pathology results (initially reviewed and subsequently re-reviewed by a dedicated neuropathologist) for all patients confirmed WHO grade I GG.

Presenting symptoms differed between ST and PF GG patients. The majority of ST GG patients (17 of 20, 85 %) presented with seizures, which were absent in all patients with PF GGs. PF GG patients presented with ataxia (7 of 11), long tract signs (sensory loss in 4, weakness in 5), and cranial nerve deficits (soft voice in 4, dysphagia in 3). Three PF GG patients had speech delay and one had hearing loss. Of note, all PF GG patients had two or more symptoms at diagnosis.

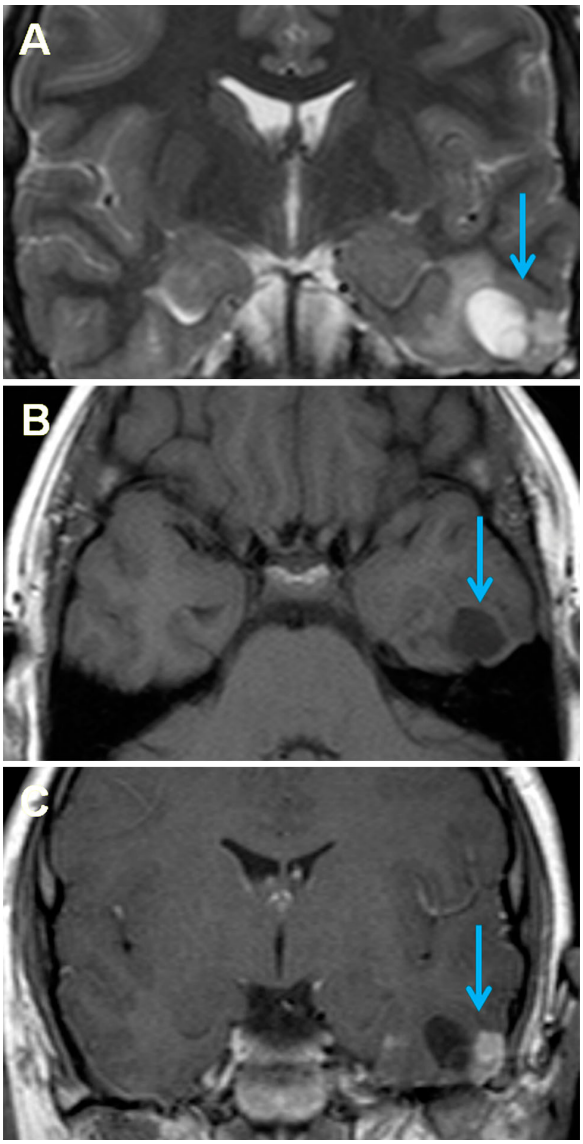


Fig. 1 ST GG in a 13 year old boy with seizures. **a** T2-weighted coronal image shows a well-circumscribed hyperintense *left* temporal lobe mass with adjacent edema. **b** T1-weighted axial image shows a hypointense mass. **c** T1-weighted post contrast coronal image shows heterogeneous enhancement with both solid and cystic components (mass marked by *blue arrows*)

Imaging characteristics of ST and PF GGs differed (Table 1). Most ST GGs were well circumscribed (10 of 20), mixed solid and cystic intra-axial masses (12 of 20) with variable enhancement (Fig. 1). In contrast, PF GGs were infiltrative and/or expansile solid masses, with dorsal predominant enhancement in a linear distribution which we have termed "paintbrush" type enhancement (6 of 11; Figs. 2, 3, 4). Most PF GGs were infiltrative: 5 of 11 involved the cerebellum, brainstem and upper cervical

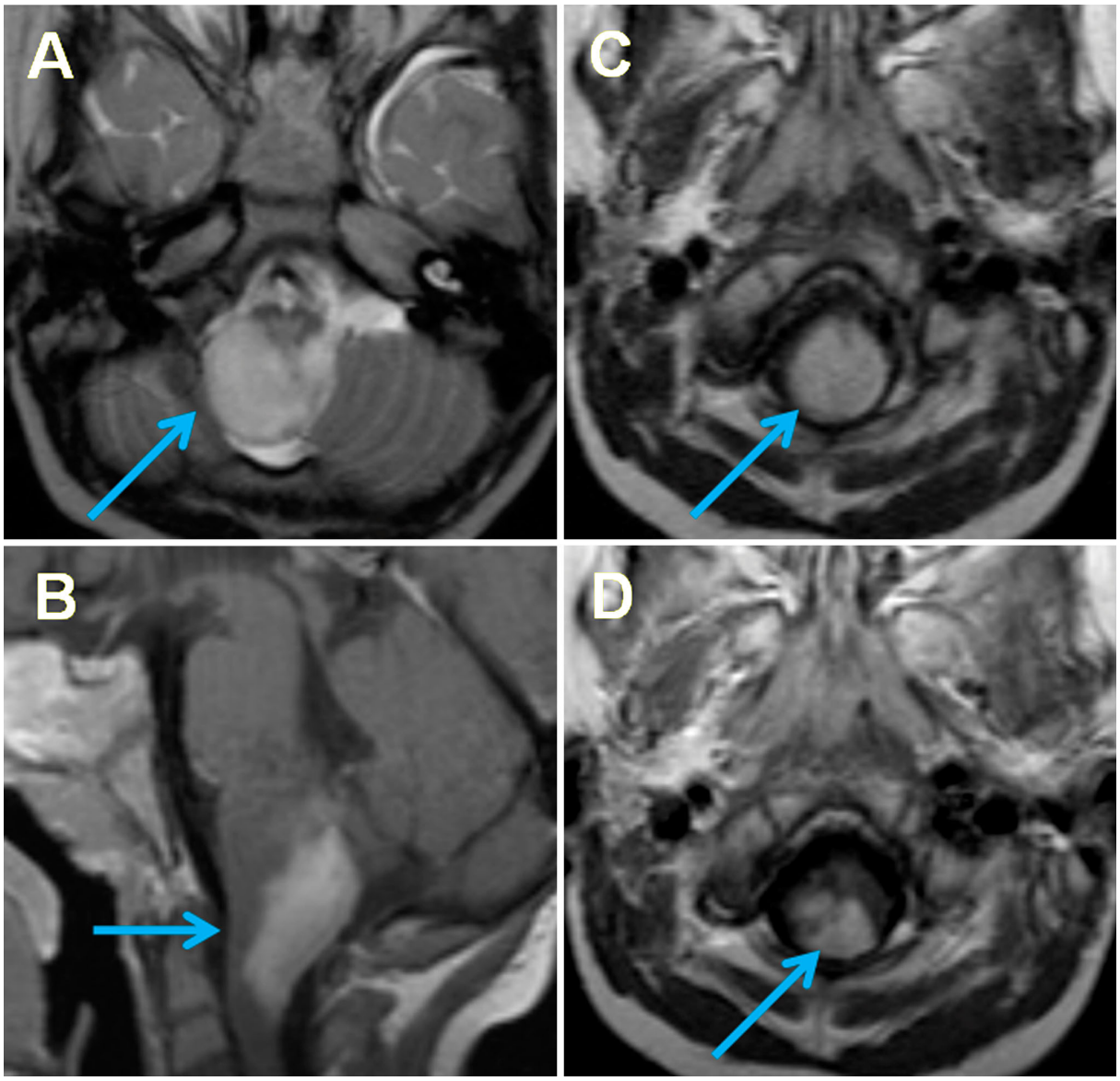


Fig. 2 PF GG in a 3 year old boy with soft voice and dysphagia. **a** T2-weighted axial image demonstrates a hyperintense expansile mass at the pontomedullary junction. **b** T1-weighted post contrast sagittal image shows characteristic dorsal predominant "paintbrush" enhancement. **c** FLAIR axial image demonstrates the full extent of the mass in an axial plane. **d** T1-weighted post contrast axial image at the same level as the image in **c** demonstrates dorsal predominant enhancement (mass marked by *blue arrows*)

spinal cord, 1 both the cerebellum and brainstem and 1 both the brainstem and upper cervical spinal cord. Two PF GGs involved the cerebellum only and two the brainstem only. None had extra-axial extension through the foramina of Magendie or Luschka. Diffusion-weighted imaging was available for 8 of 11 PF GGs and 8 of 20 ST GGs. No ST or PF GG demonstrated restricted diffusion. No tumor calcification was identified in the two PF GG or four ST GG patients who had preoperative brain CT.

MRI of the spine was performed in 9 of 11 PF GGs and 5 of 20 ST GGs. With the exception of local extension into the upper cervical cord (6 of 11 PF GGs), there were no spinal leptomeningeal metastases.

Treatment for patients with ST and PF GGs differed considerably. ST GGs were most often treated with surgery alone (19 of 20) whereas all PF GGs required adjuvant chemotherapy and/or radiation in addition to surgery. GTR was achieved in 15 of 20 ST GGs and 0 of 11 PF GGs. One

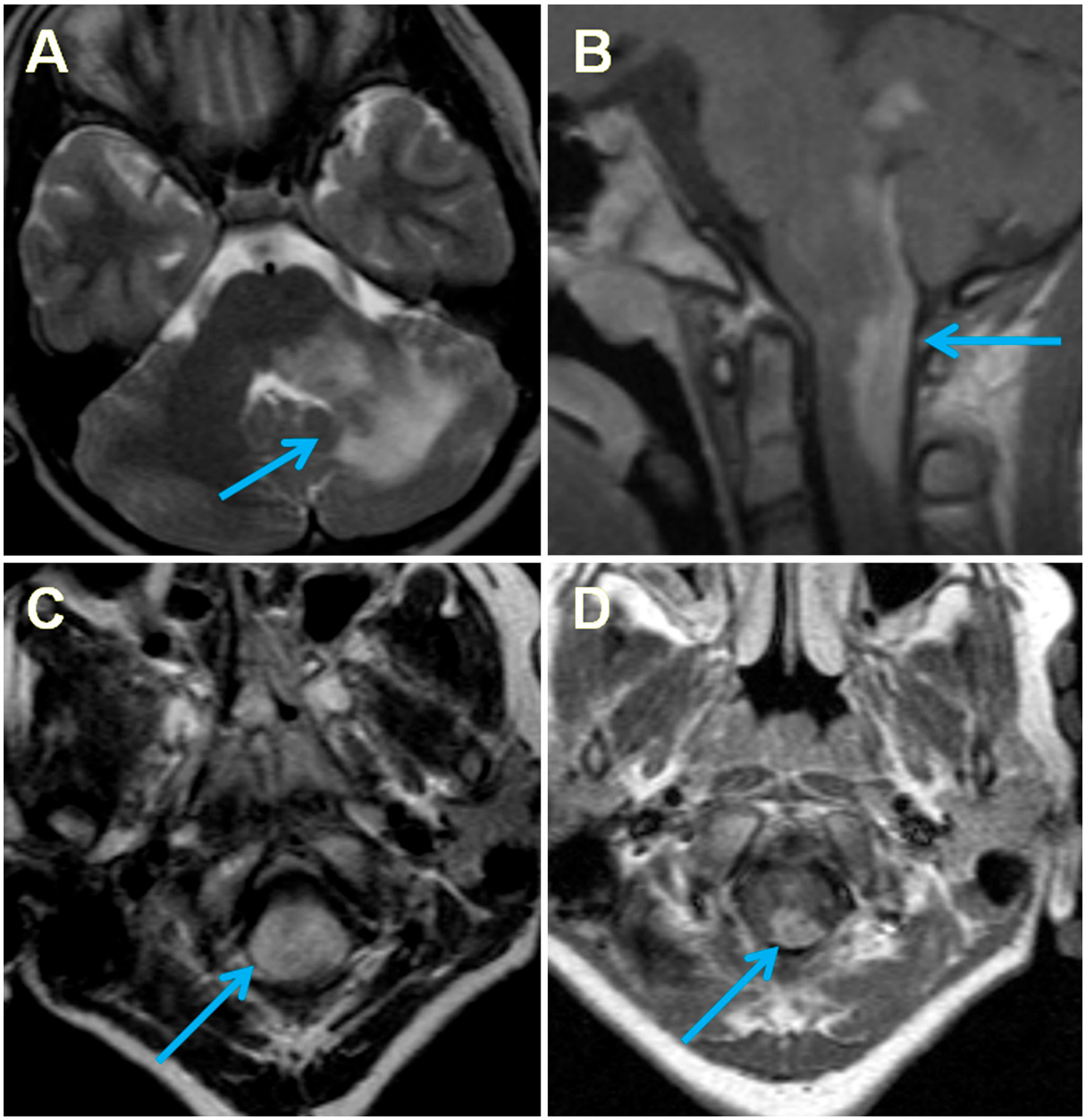
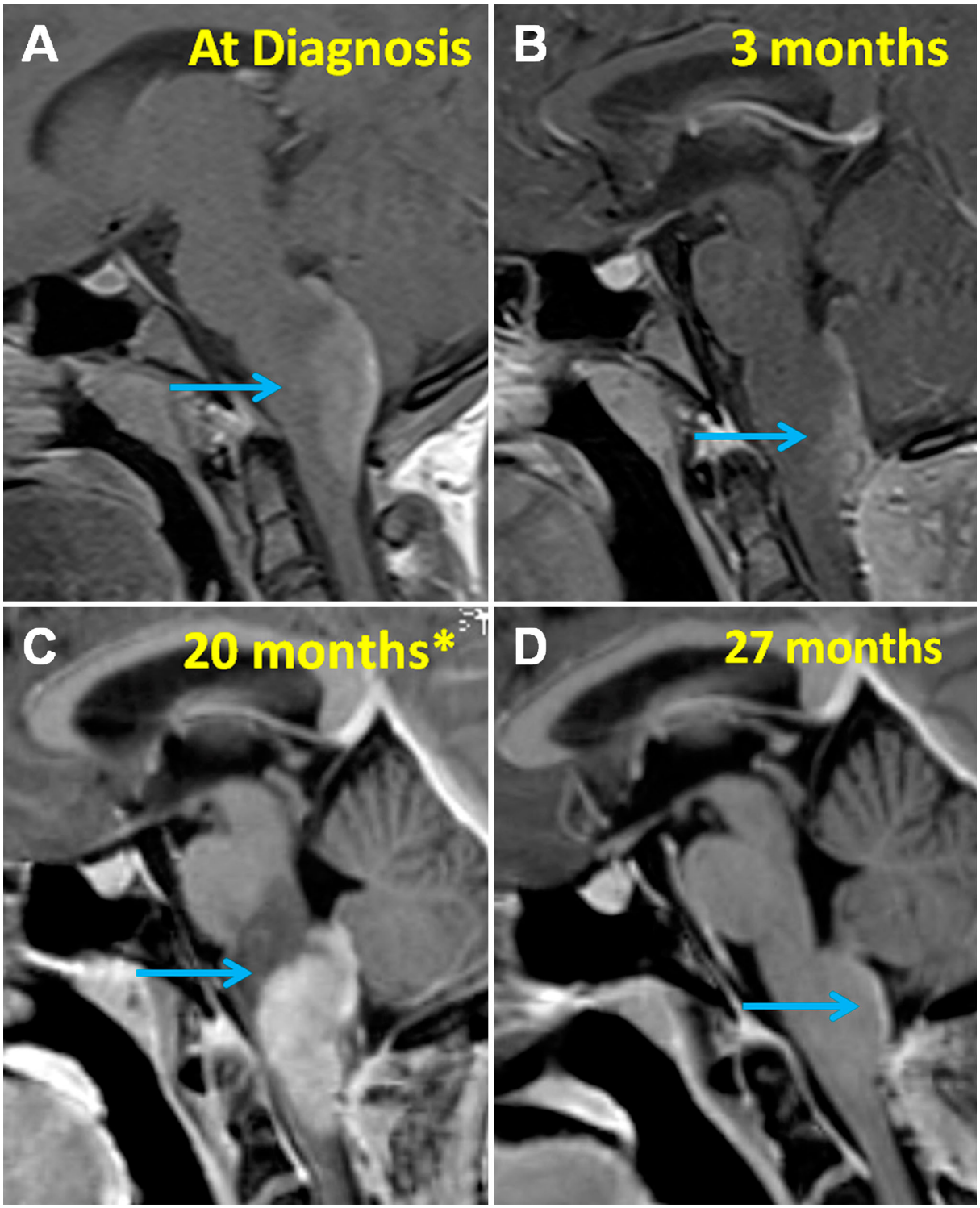


Fig. 3 PF GG in a 13 year old girl with left sided hearing loss. **a** T2-weighted axial image demonstrates a hyperintense infiltrative mass centered at the *left* pontomedullary junction extending into the *left middle* cerebellar peduncle and cerebellar hemisphere. **b** T1-weighted post contrast sagittal image shows characteristic dorsal predominant "paintbrush" enhancement. **c** FLAIR axial image demonstrates the full extent of the mass in an axial plane. **d** T1-weighted post contrast axial image at the same level as the image in **c** demonstrates dorsal predominant enhancement (mass marked by *blue arrows*)

ST GG patient received adjuvant chemotherapy and no ST GG patient received radiation therapy. In contrast, 8 of 11 patients with PF GGs received chemotherapy and 6 of 11 received radiation therapy. Five patients with PF GGs received both chemotherapy and radiation.

Five of 11 (45 %) PF GGs expressed the BRAF V600E mutation and 6 of 9 (67 %) ST GGs expressed this mutation. BRAF V600E mutation status was not available for the remaining 11 ST GGs. Comparison in frequency of the BRAF V600E mutation with regards to tumor location was


A
At Diagnosis
B
3 months
C
20 months*
D
27 months

◀**Fig. 4** PF GG in a 12 year old girl with right hand sensory changes progressing to difficulty with fine motor skills. Sequential post gadolinium sagittal T1-weighted images **a** at diagnosis, **b** 3 months, **c** 20 months, and **d** 27 months after diagnosis. Subtotal resection was performed between **a** and **b**. **b**, **c** Mass increasing in size and enhancement despite ongoing combined chemoradiation. Vemurafenib (BRAF inhibitor), was initiated after 20 months (indicated by * in **c**). Note decrease in volume and enhancement of the mass in **d** (mass marked by *blue arrows*)

avoided given the limited number of ST GGs tested for the mutation. No unique imaging characteristic was identified in those PF or ST GGs with or without the BRAF V600E mutation. The dorsal "paintbrush" enhancement pattern was present in three PF GGs with and three without the BRAF V600E mutation.

Compared to patients with ST GGs, patients with PF GGs had shorter progression-free survival by imaging [mean 1.2 years (±0.71 years 95 % CI) vs. 5 years (±1.6 years 95 % CI); $p = 0.004$], shorter progression-free survival by clinical assessment [mean 1.7 years (±0.76 years 95 % CI) vs. 5.6 years (±2.1 years 95 % CI); $p = 0.02$] and higher mortality (4 deaths versus 0; $p = 0.003$). Median follow up was 3.5 years for the PF GG cohort and 5 years for the ST GG cohort. Compared to PF GGs without the BRAF mutation, BRAF V600E positive PF GGs demonstrated shorter progression free survival determined by imaging [mean 0.4 years (±0.2 years 95 % CI) vs. 2.1 years (±0.7 years 95 % CI); $p = 0.009$] and clinical assessment [0.9 years (±0.3 years 95 % CI) vs. 2.61 years (±0.8 years 95 % CI); $p = 0.016$] but no change in mortality (two deaths in each group). When comparing ST GGs with and without the BRAF V600E mutation, no difference in progression free survival by imaging [mean 4.4 years (±1.95 years 95 % CI) vs. 7.3 years (±0.1 years 95 % CI); $p = 0.4$], progression free survival by clinical assessment [mean 4.4 years (±1.95 years 95 % CI) vs. 6 years (±0.9 years 95 % CI); $p = 0.67$] or mortality (zero deaths in each group) was observed; however analysis is limited by the small size of the BRAF V600E negative ST GG cohort.

One BRAF V600E positive PF GG patient received a novel BRAF inhibitor, vemurafenib, after failing traditional therapy [29]. This child's PF GG involved the brainstem and upper cervical cord and typified the dorsal predominant "paintbrush" pattern of enhancement. There was a dramatic decrease in tumor volume and enhancement over a 12 month period (Fig. 4) following initiation of vemurafenib.

Discussion

Clinical presentation

Symptoms at presentation differ for ST and PF GGs. Most patients with ST GGs present with seizures [5, 13], reflecting their temporal lobe predilection. In contrast, PF GGs present with symptoms of raised intracranial pressure, ataxia, long tract signs, and cranial nerve deficits, related to tumor location [11]. This was confirmed in our series; notably all PF GG patients presented with multiple symptoms, most commonly ataxia, weakness, and soft voice.

Imaging

Imaging characteristics differ between ST and PF GGs. ST GGs were well-circumscribed, mixed cystic and solid, and demonstrated variable enhancement, findings that are concordant with that reported in the literature [5, 8, 13]. In contrast, the PF GGs in our series were infiltrative and expansile, solid without cystic component, and demonstrated characteristic dorsal predominant "paintbrush" pattern of enhancement, observed in 6 of 11 patients. This pattern of enhancement has not been previously described and may be a useful differentiating imaging characteristic of PF GGs relative to other PF tumors. Limited previous reports on PF GG imaging characteristics demonstrate a tendency for these tumors to be solid and show patchy enhancement [11, 15, 30], confirmed in our series. No ST or PF GG showed restricted diffusion or spinal leptomeningeal dissemination.

Compared to PF GG, pilocytic astrocytoma, medulloblastoma and ependymoma are more commonly encountered pediatric PF tumors. Unlike PF GG, pilocytic astrocytoma typically has cystic components, medulloblastoma is typically hypointense on T2-weighted sequences and demonstrates restricted diffusion and ependymoma is an extra-axial mass with characteristic extent through the foramina of Luschka and/or Magendie. In contrast, PF GGs are solid intra-axial infiltrative and expansile masses without cystic component, are hyperintense on T2-weighted sequences, do not restrict diffusion and do not have extra-axial extent through skull base foramina. The typical dorsal predominant "paintbrush" pattern of enhancement may be a helpful differentiating imaging feature of PF GGs from the other more common pediatric PF tumors.

Differentiating a PF GG confined to the brainstem from a brainstem glioma can be challenging. Both are typically T1 hypointense, T2 hyperintense solid, expansile masses without restricted diffusion. Brainstem gliomas typically have little early enhancement and heterogeneous late enhancement [31]. A dorsal predominant "paintbrush" pattern of enhancement has not been described in brainstem gliomas and therefore may be a differentiating feature favoring PF GG.

Treatment and prognosis

Treatment differs for ST and PF GGs. The best prognostic indicator for ST GGs is GTR [5, 10, 12, 13], achieved in 15

of 20 of our ST GG patients. Adjuvant chemotherapy and radiation therapy have occasionally been used in patients with residual or recurrent disease [30]. ST GGs have an impressive 7.5 year survival of 98 % [6]. In contrast, GTR is rarely achieved in PF GGs, predominantly due to tumor location [10, 11], and was not achieved in any of our 11 PF GG patients. Treatment for residual PF GG includes adjuvant chemotherapy and radiation [10, 11]. Concern of radiation therapy potentiating malignant degeneration of GGs has been raised, hence it is recommended only in patients with residual or recurrent disease [7]. In our series, one PF GG patient was treated with surgery alone then lost to follow up. All other PF GG patients received adjuvant chemotherapy and/or radiation therapy. At least in part due to the inability to achieve GTR, patients with PF GGs had worse progression-free survival and mortality than ST GGs. These prognostic results (including detailed Kaplan–Meier progression-free and overall survival) containing a majority of the same patients have recently been published by Donson et al. [23].

BRAF V600E mutation

BRAF, short for v-raf murine sarcoma viral oncogene homolog B1 (where v-raf stands for virus-induced rapidly accelerated fibrosarcoma), is a member of the serine/threonine kinase family and plays an instrumental role in the RAS–RAF–MEK–ERK–MAP kinase signaling pathway. More than 36 mutations in the BRAF gene have been associated with human cancers [18–20]. The BRAF V600E mutation is the most common mutation and results in constitutive activity of BRAF.

BRAF V600E mutations occur in approximately 50–60 % of melanomas [18, 32], 40–70 % of papillary thyroid cancers [33–35], and to a lesser extent in other cancer types [18, 28]. BRAF V600E mutations also occur in 8–16 % of glial and mixed glial origin CNS tumors [27, 28] including, 9–16 % of pilocytic astrocytomas [27, 28], 2–10 % of malignant astrocytomas [27, 28, 36, 37], 66 % of pleomorphic xanthoastrocytomas [27, 28], and 18–58 % of GGs [21–28]. BRAF V600E mutations have been associated with a worse prognosis in patients with colorectal cancer and melanoma [38]; extrathyroid extension, lymph node metastases, advanced stage, and increased risk of persistent disease or recurrence in papillary thyroid cancer [33–35]; and higher grade astrocytomas [37].

BRAF V600E incidence and GGs

PF GGs have been shown to differentially express certain genes compared to ST GGs [14] suggesting a different genetic makeup may play a role in the differences observed in tumor behavior. Several recent studies regarding GGs demonstrate BRAF V600E positivity rates of 18 % (14 of 77 adult and pediatric patients) [28], 57 % (8 of 14 pediatric patients) [26], 50 % (9 of 18 pediatric patients) [24], 23.5 % (12 of 51 adult and pediatric patients) [27], 38 % (18 of 47 pediatric patients) [22], 45 % (14 of 31 pediatric patients) [21], and 58 % (41 of 71 adult and pediatric patients) [25]. Schindler et al. [28] demonstrated a slight increase in BRAF V600E incidence in adults (21 %) versus pediatric patients (13 %) whereas Myung et al. [27] demonstrated an increase in incidence in pediatric patients (34.5 %) compared to adults (14.3 %). Increased incidence of the BRAF V600E mutation in pediatric patients was also recently demonstrated in a study published by Koelsche et al. [25]. The incidence of the BRAF V600E mutation in pediatric patients with ST and PF GGs in our study is 55 %, more closely matching that reported by Dougherty et al. [24] (50 %), MacConaill et al. [26] (57 %), and Koelsche et al. [25] (58 %). In our series of five BRAF V600E positive PF GGs, three involved the brainstem without the cerebellum and two involved the cerebellum and brainstem. A table with detailed information regarding the PF GGs included in this study can be found in Table 1 in the recent study by Donson et al. [23].

BRAF V600E prognosis and GGs

A recent study by Chappe et al. [21] showed that the BRAF V600E mutation in GGs is not predictive of survival whereas another study by Dahiya et al. [22] showed that the mutation is associated with shorter progression-free survival. In our small series, patients with BRAF V600E PF GGs demonstrated statistically significant worse progression free survival and no difference in mortality compared to patients with PF GGs without the BRAF V600E mutation. The small size of the PF GG patient cohorts compared (five patients compared to six patients) limits drawing too strong of a conclusion from this data. No statistically significant difference was observed in BRAF V600E ST GGs. These prognostic results have previously been published by Donson et al. [23].

BRAF V600E and imaging

No unique imaging characteristic was identified in PF or ST GGs with or without the BRAF V600E mutation. The typical dorsal "paintbrush" enhancement and infiltrative and expansile appearance of PF GGs was equally observed in PF GGs with and without the mutation.

Limitations of this study include the small sample size of the patient cohorts, particularly the patients with PF GGs (11). This increases the likelihood of not detecting some statistically significant differences (type II error) and detecting perceived differences by chance alone (type I

error). Another limitation is that only 9 of 20 ST GGs were tested for BRAF V600E. An attempt to compare the frequency of the BRAF V600E mutation to tumor location in this study was avoided given the limited number of ST GGs tested for the mutation.

Conclusion

PF GGs and ST GGs differ in presenting symptoms, imaging, treatment, and prognosis. Compared to ST GGs, PF GGs present with ataxia, long tract signs and cranial nerve deficits; by imaging are expansile, infiltrative, and show dorsal predominant "paintbrush" enhancement; are not amenable to GTR and have worse progression-free survival and mortality. BRAF V600E mutation positive PF GGs exhibit no unique imaging features, are associated with shorter progression-free survival, and carry promising treatment implications by BRAF inhibitors.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study complies with the current laws of the country in which it was completed.

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