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CASE-BASED UPDATE

Pediatric intracranial primary anaplastic ganglioglioma

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Abstract
Background Primary intracranial anaplastic gangliogliomas are rare tumors in the pediatric patient group. Most of them present with symptoms of elevated pressure or symptomatic epilepsy. Extraaxial location is far more common than axial location. On MRI examination, they mimic pilocytic astrocytomas. The outcome after surgery depends mainly on the possible amount of surgical resection, and oncological therapy is necessary to prevent recurrence of the disease.
Case report An 11-year-old boy presented with headache and double vision due to obstructive hydrocephalus. MRI of the brain revealed an axial partially contrast enhancing lesion in the quadrigeminal plate extending from the cerebellum to the pineal gland and causing hydrocephalus. Subtotal removal of the lesion was performed, and the diagnosis of an anaplastic ganglioglioma was established and confirmed by the reference center. At the latest follow up (3 months), the boy is without any neurological symptoms and scheduled for radiation therapy as well as chemotherapy

Keywords Brain · Child · Primary anaplastic ganglioglioma · Intracranial · Magnetic resonance imaging; surgical treatment

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Introduction

Gangliogliomas are tumors of the central nervous system suspected to derive from common precursor cells in a hamartomatous glioneural lesion [19]. Histopathologically, these tumors consist of ganglionic and glial cells. They compromise up to 4% of all pediatric central nervous system neoplasms and are thus rare [11]. Anaplastic intracranial gangliogliomas are an aggressive subtype of gangliogliomas featuring mitotic figures, hypercellularity, vascular proliferation, and necrosis mainly in the glial compartement of the lesions [11]. BRAF V600E mutation is reported to be more frequent in intracranial anaplastic gangliogliomas than in spinal intramedullary lesions [5, 15]. Secondary malignant transformation of primary benign gangliogliomas is reported [9].

Historical background

Gangliogliomas were first described in 1926 as a distinct type of intracranial neoplasm [19]. The largest series of anaplastic gangliogliomas was reported in 2011 with 85 cases and a median age of 25.5 years, most frequent temporal location (27%), and a median overall survival of 28.5 months [19]. The first case report from a child dates back to 1986 [7].

Clinical presentation

Gangliogliomas are highly epileptogenic lesions, especially with the most frequent location of the temporal lobe [13]. Primary anaplastic ganglioglioma can furthermore present with symptoms of elevated intracranial pressure as well as diplopia, hemiplegia, and other neurological symptoms. Symptomatic epilepsy was as frequent (8/19 = 42%) as the

Table 1 A comparison of 19 reported cases of an intracranial primary anaplastic ganglioglioma in pediatric patients (0–21 years) in chronological order. The mean age is 11 years

Age/gender	Symptoms	Location	Therapy	Course	Follow up	Year/author
6 m/f	ICP elevation	Right frontal	Surgical total resection	Complete remission	20 mo	1986/[7]
21y/f	Seizures	Temporal	Surgical total resection	Complete remission	54 mo	1991/[20]
10y/m	Diplopia ataxia respiratory problems	Brainstem	Surgical partial resection radiotherapy	Death	18 mo	1992/[6]
12y/f	Headache, hemiplegia	Brainstem cerebellar, spinal cord	Surgical partial resection radiotherapy	Death	8 mo	1992/[8]
13y/m	Seizures	Left temporal	Surgical total resection	Complete remission	mo	1994/[2]
20y/f	seizures	Temporal	Surgical partial resection radiotherapy	Death	69 mo	1996/[3]
3y/m	ICP elevation	Suprasellar	Surgical partial resection radiotherapy carboplatin	Partial remission	42 mo	1996/[3]
6y/m	Seizures	Parietal	Surgical partial resection radiotherapy	Complete remission	93 mo	1996/[3]
11y/m	Headache	Fronto-parietal	Surgical partial resection radiotherapy PVI	Death	nk	2006/[20]
20y/f	ICP elevation	Right fronto-parietal	Surgical partial resection radiotherapy	Death	18 mo	2007/[14]
16y/f	Focal seizures	Right temporo-mesial	Surgical total resection radiotherapy	Stable disease after local progression	25 mo	2009/[11]
10y/f	Tremor, ICP elevation	Right fronto-temporo-parietal	Surgical total resection radiotherapy HIT GBM D	Complete remission	42 mo	2009/[11]
2y/m	Seizures	Left frontal	Surgical total resection	Complete remission	31 mo	2009/[11]
10y/m	Psychomotor slowing, diplopia, ICP elevation	Right parieto-occipital	Surgical partial resection radiotherapy HIT GBM C	Death	6 mo	2009/[11]
3y/m	Focal seizures	Right frontal	Surgical total resection HIT GBM	Complete remission	54 mo	2009/[11]
14y/m	ICP elevation	Brain stem and fourth ventricle	Surgical subtotal resection radiotherapy	Stable disease	8 mo	2009/[11]
14y/m	Focal seizures	Left frontal	Surgical total resection radiotherapy	Complete remission	72 mo	2012/[16]
12y/m	ICP elevation	Left temporo-parietal	Surgical partial resection radiotherapy chemotherapy	Death	23 mo	2015/[13]
11y/m	ICP elevation diplopia	Quadrigeminal plate	Surgical partial removal radiotherapy temozolamide	Asymptomatic	3 mo	2016/presented case

Y years, *f* female, *nk* not known, *mo* months

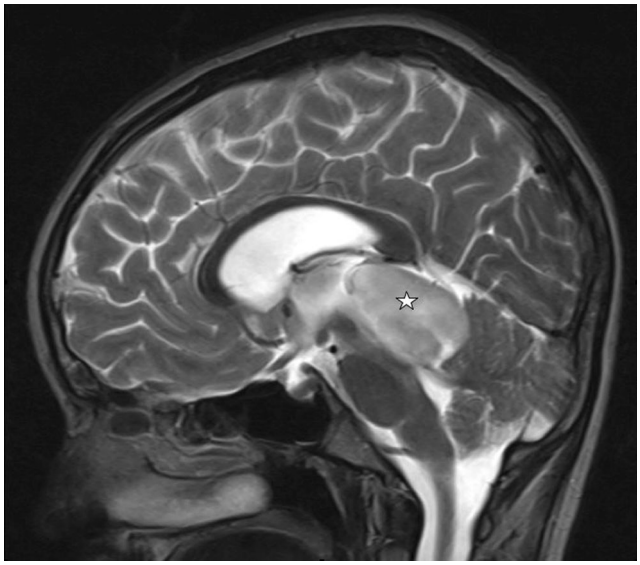

Fig. 1 Preoperative sagittal T2-weighted MR-image showing the hyperintense lesion (*star*) of the quadrigeminal plate extending from the cerebellum to the thalamus

symptoms of elevated intracranial pressure as a presenting sign in the described cases of an intracranial primary anaplastic ganglioglioma in children (Table 1).

Diagnosis

Areas of histologically mitotic activity, pronounced hypercellularity, vascular proliferation, and necrosis are typical for the diagnosis of anaplasia [10]. These anaplastic changes are most frequent in the glial part of the tissue, while an occurrence in the neuronal part is also reported [12].

Gangliogliomas with anaplastic features in histology are reported to have a wide variation in a radiological appearance: solid and cystic components as well as contrast uptake and calcification [13]. In the pediatric group, contrast enhancement is frequently described [2, 13]. In T1-weighted magnetic resonance imaging, the tumors are hypointense and on T2-weighted imaging hyperintense (Figs. 1 and 2). MR spectroscopy may reveal distinct but nonspecific choline peaks that might differentiate from a benign ganglioglioma but not from other primary brain tumors [12].

Only a few cases of primary anaplastic intracranial gangliogliomas are reported in children (Table 1), whereas the gangliogliomas in general are reported to be frequent in children and young adults [13]. Nineteen cases of intracranial primary anaplastic gangliogliomas were found including the presented one. Mean age was 11 years with a range from 0 to 21 years. Most lesions were similar to pilocytic gliomas and involving the temporal lobe. Rare lesions as desmoplastic infantile ganglioglioma or anaplastic gliomas must also be considered in the differential diagnosis [21].

Treatment and results

Seven deaths (37%) are reported (Table 1), thus oncological therapy including radiotherapy seems necessary, if possible. But clinical studies on prognosis of anaplastic gangliogliomas were unsure about the role of adjuvant radiotherapy, as they found no survival advantage with radiotherapy [18].

Contradictory reports about a devastating course for pediatric anaplastic gangliogliomas and relatively good survival rates in other studies are to be found in the literature [18].

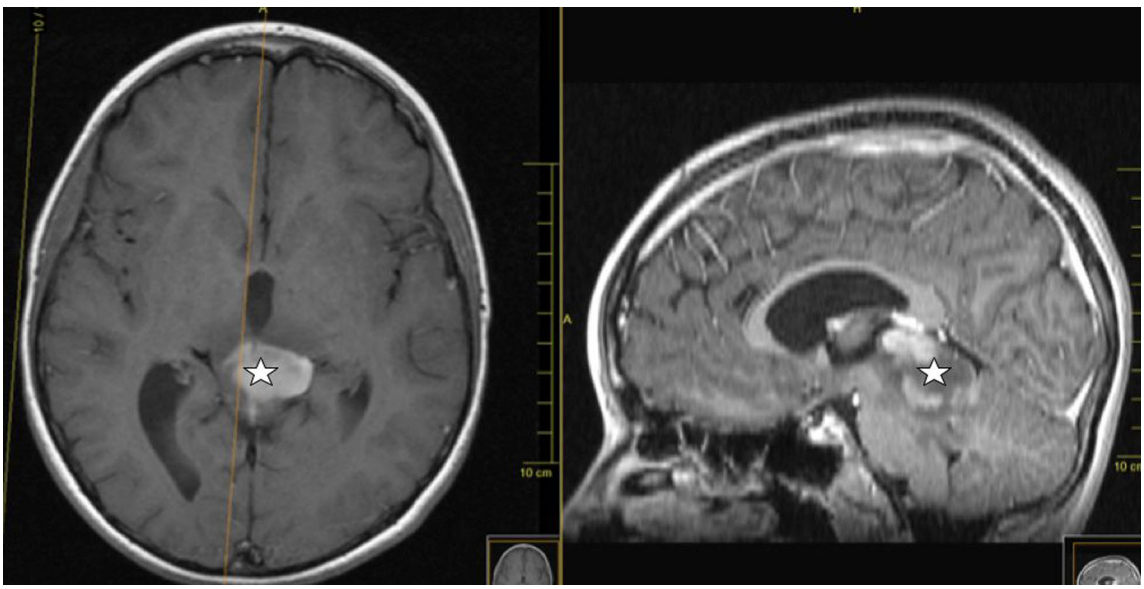

Fig. 2 Preoperative axial and sagittal T1-weighted MR-image with contrast showing the partly contrast enhancing hypointense lesion (*star*) of the quadrigeminal plate and bilateral thalamic involvement

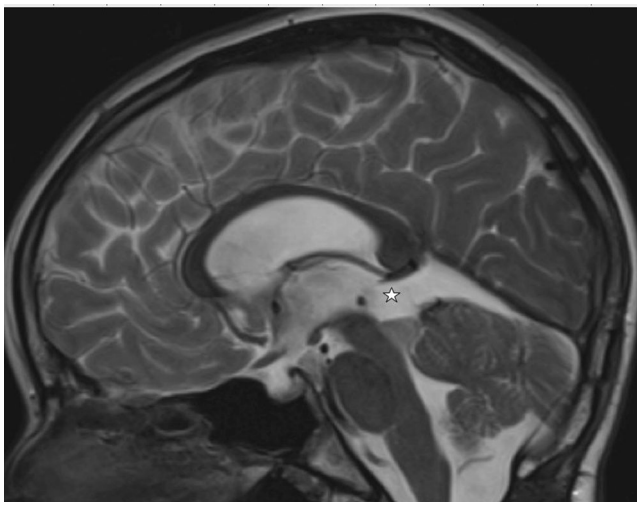

Fig. 3 Postoperative sagittal T2-weighted MR-image showing resection cavity of the tumor (*star*) and a small residual tumor below

The course of AGG is characterized by a local recurrence or leptomeningeal spread [13]. The five-year overall survival was reported to be 88% with a superior outcome in patients, who underwent a gross total tumor resection, when compared with a partial resection [11]. In the presented series, fatal outcome was only to be seen in partially resected tumors (7/8 = 88%).

Treatment with vemurafenib, selectively inhibiting the oncogen BRAF could be an interesting option in lesions with BRAF V600E mutation as in the presented case [1, 17]. In brain metastasis of BRAF V600E mutation-positive melanoma vemurafenib showed considerable success rates with side effects [4]. In the view of the described prognosis of anaplastic gangliogliomas, other therapeutic options derived from genetic histological examinations should be considered.

Exemplary case

An 11-year old boy came to the admission with the diagnosis of a midline tumor at the quadrigeminal plate symptomatic with headache and double vision due to bilateral abducent nerve palsy. Examination revealed bilateral papilledema.

MRI studies of the head revealed a midline lesion, around the tectal area with an extension from the cerebellum to the pineal gland invading the diencephalon (Figs. 1 and 2). The lesion was homogenously in contrast enhancing and hyperintense in T-2 weighted imaging. Spinal MRI was uneventful. β-HCG as well as α-fetoprotein were within normal limits. An endoscopic ventriculostomy was performed. A median suboccipital craniotomy was performed with a supracerebellar approach, and a near total excision of the lesion was performed (Fig. 3). Fresh frozen section suggested pilocytic astrocytoma. Dysplastic ganglionic cells with multiple nuclei as well as mitotic activity in the glial and ganglionic part could be demonstrated in the further histological slides (Fig. 4). Final histology confirmed by the reference center, showed KI-67 positivity in 2–10% of the areas and staining for

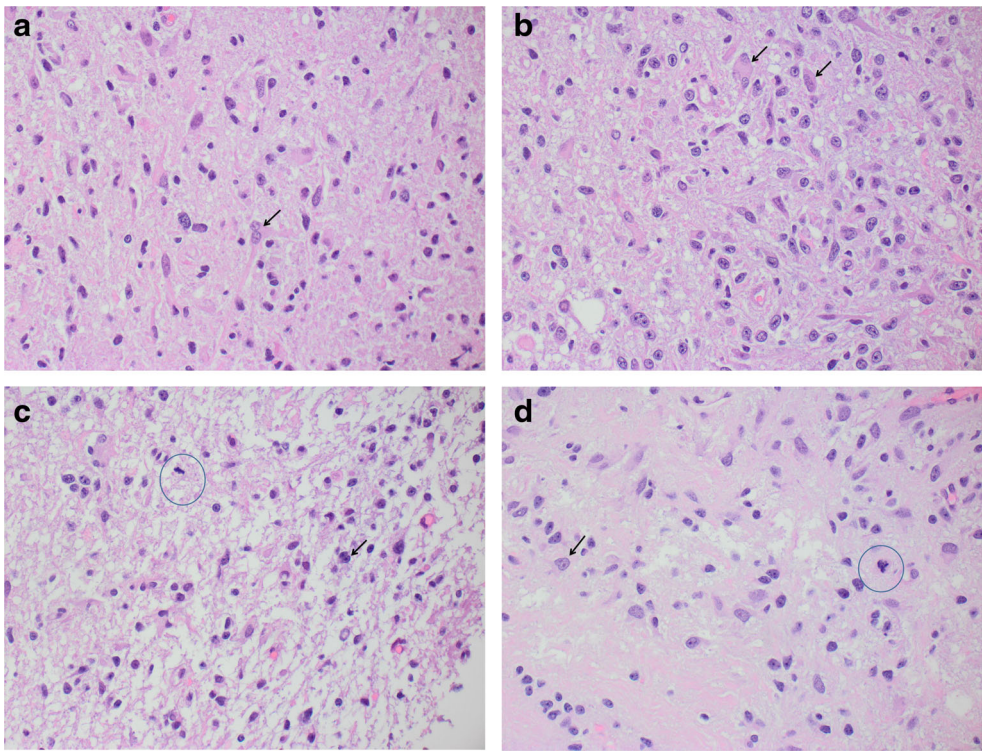

Fig. 4 **a** Histological slide of the tumor composed of astrocytes and ganglion cells with dysplastic, binucleated neurons (*arrow*) (H & E) 400×. **b** Histological slide of the tumor showing ganglion cells with dysplastic, binucleated, and trinucleated neurons (*arrows*) (H & E) 400×. **c** Histological slide showing mitotic activity (*open circle*) in the glial part of the tumor and ganglion cells with dysplastic binucleated neurons (*arrow*) (H & E) 320×. **d** Histological slide showing mitotic activity (*open circle*) in the neural part of the tumor and ganglion cells with dysplastic binucleated neurons (*arrow*) (H & E) 400×

synaptophysin, as well as the mitotic marker pHH3. BRAF (V600E) mutation was detected. Thus, the diagnosis of an anaplastic ganglioglioma WHO grade III was stated.

In the postoperative course, the boy showed a vertical gaze palsy that completely recovered within 14 days after the surgery. Proton beam radiation therapy and temozolamide therapy were initiated after obtaining the final diagnosis (Table 1).

Summary and management recommendation

AGG is as rare as an intracranial lesion in children and was described to be radiologically similar to pilcyotic astrocytomas.

Histological examination is mandatory in the establishment of the diagnosis of AGG.

Postoperative oncological treatment should be initiated.

AGG must be considered as a differential diagnosis in supratentorial lesions especially with rapidly developing symptoms.

Compliance with ethical standards

Conflict of interest No conflict of interest.

References

1. Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, Varlet P, Valteau-Couanet D, Geoerger B (2014) Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer 61:1101–1103
2. Campos MG, Zentner J, Ostertun B, Wolf HK, Schramm J (1994) Anaplastic ganglioglioma: case report and review of the literature. Neurol Res 16:317–320
3. Chintagumpala MM, Armstrong D, Miki S, Nelson T, Cheek W, Laurent J, Woo SY, Mahoney DH Jr (1996) Mixed neuronal-glial tumors (gangliogliomas) in children. Pediatr Neurosurg 24:306–313
4. Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, Veronese L, Hilfiker PR, Felderer L, Rinderknecht JD (2014) Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. Eur J Cancer 50:611–621
5. Gessi M, Dorner E, Dreschmann V, Antonelli M, Waha A, Giangaspero F, Gnekow A, Pietsch T (2016) Intramedullary gangliogliomas: histopathologic and molecular features of 25 cases. Hum Pathol 49:107–113
6. Haddad SF, Moore SA, Menezes AH, VanGilder JC (1992) Ganglioglioma: 13 years of experience. Neurosurgery 31:171–178
7. Hall WA, Yunis EJ, Albright AL (1986) Anaplastic ganglioglioma in an infant: case report and review of the literature. Neurosurgery 19:1016–1020
8. Hirose T, Kannuki S, Nishida K, Matsumoto K, Sano T, Hizawa K (1992) Anaplastic ganglioglioma of the brain stem demonstrating active neurosecretory features of neoplastic neuronal cells. Acta Neuropathol 83:365–370
9. Jay V, Squire J, Becker LE, Humphreys R (1994) Malignant transformation in a ganglioglioma with anaplastic neuronal and astrocytic components. Report of a case with flow cytometric and cytogenetic analysis Cancer. 73: 2862–2868
10. Karabekir HS, Balci C, Tokyol C (2006) Primary spinal anaplastic ganglioglioma. Pediatr Neurosurg 42:374–378
11. Karremann M, Pietsch T, Janssen G, Kramm CM, Wolff JE (2009) Anaplastic ganglioglioma in children. J Neuro-Oncol 92:157–163
12. Kawataki T, Sato E, Sato T, Kinouchi H (2010) Anaplastic ganglioglioma with malignant features in both neuronal and glial components—case report. Neurol Med Chir (Tokyo) 50:228–231
13. Lucas JT Jr, Huang AJ, Mott RT, Lesser GJ, Tatter SB, Chan MD (2015) Anaplastic ganglioglioma: a report of three cases and review of the literature. J Neuro-Oncol 123:171–177
14. Pandita A, Balasubramaniam A, Perrin R, Shannon P, Guha A, Sarkaria JN, Carlson BL, Schroeder MA, Grogan P, Brown PD, Giannini C, Ballman KV, Kitange GJ, James CD, Aldape KD, Zadeh G (2007) Malignant and benign ganglioglioma: a pathological and molecular study use of an orthotopic xenograft model for assessing the effect of epidermal growth factor receptor amplification on glioblastoma radiation response contrasting in vivo and in vitro fates of glioblastoma cell subpopulations with amplified EGFR. Neuro-Oncology 9:124–134
15. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, Schmieder K, Wesseling P, Mawrin C, Hasselblatt M, Louis DN, Korshunov A, Pfister S, Hartmann C, Paulus W, Reifenberger G, von Deimling A (2011) Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol 121:397–405
16. Scoccianti S, Giordano F, Agresti B, Detti B, Cipressi S, Franceschini D, Greto D, Mussa F, Sardi I, Buccoliero A, Arico M, Genitori L, Biti G (2012) Pediatric primary anaplastic ganglioglioma: a case report and review of the literature. Pediatr Neurosurg 48:35–41
17. Selvanathan SK, Hammouche S, Salminen HJ, Jenkinson MD (2011) Outcome and prognostic features in anaplastic ganglioglioma: analysis of cases from the SEER database. J Neuro-Oncol 105:539–545
18. Silver JM, Rawlings CE 3rd, Rossitch E Jr, Zeidman SM, Friedman AH (1991) Ganglioglioma: a clinical study with long-term follow-up. Surg Neurol 35:261–266
19. Tamburrini G, Colosimo C Jr, Giangaspero F, Riccardi R, Di Rocco C (2003) Desmoplastic infantile ganglioglioma. Childs Nerv Syst 19:292–297
20. Zorlu F, Selek U, Onal C, Soylemezoglu F, Gurkaynak M (2006) Postoperative radiotherapy in cranial ganglioglioma. J Neuro-Oncol 77:321–324