Child's Nervous System
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CASE-BASED REVIEW

Central nervous system high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)—case-based reviews

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Abstract

Introduction High-grade neuroepithelial tumor with BCOR alteration (HGNET BCOR) has been recently classified as a new category of tumors among those previously known as PNET. They are molecularly characterized by the mutation of the BCOR gene, a corepressor of BCL6 a gene (which has an important role in immune responses). Only case reports and very small series have been published so far; therefore, their behavior and management are still under investigation. The goal of the present case-based review is to provide a summary about the state of the art on these tumors.

Methods and results The pertinent review has been reviewed, and an exemplary case has been reported (15-month-old boy with large HGNET BCOR of the left cerebellopontine angle). So far, 24 cases have been described, with a 5.5 mean age at diagnosis and a 1.4 male/female ratio. The cerebellar hemisphere is the more frequently involved region. No metastases are usually detected at diagnosis, though they are common in case of tumor recurrence. There are no specific radiological or pathological features to differentiate HGNET BCOR from other brain malignant neuroepithelial tumors so that the differential diagnosis is obtained by DNA methylation profiling. The management possibly relies on surgery and (high dose) chemotherapy and radiotherapy but without a dedicated protocol yet. The overall survival after 48-month follow-up is 50%. A gross total resection, which is mandatory for a better outcome, is achievable in the majority of cases.

Conclusions The clinical research on HGNET BCOR is just at the beginning. New targets and wide-ranging clinical trials are needed to get an optimal management.

Keywords HGNET · BCOR · Brain tumor · Methylation profiling

Introduction and background

In 2016, the WHO classification of the embryonal tumors other than medulloblastoma has undergone a substantial revision, with removal of the term primitive neuroectodermal tumor or PNET from the diagnostic lexicon [8]. Afterwards, the molecular genetic analysis led to the identification of specific subtypes, the CNS high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR) being among them. They were actually described in 2016 as frequently affecting the pediatric age, being localized in the cerebral and cerebellar hemispheres and often burdened by a poor prognosis [15]. Most of the patients are less than 5-year-old, with no clear sex prevalence [5, 15].

The BCOR gene is an epigenetic regulator, localized in the short arm of the X11.4 chromosome, first described in 2000 as interacting corepressor of BCL6, a gene with an important role in immune responses, which can either promote or inhibit apoptosis, depending on the situation and cell type. It operates by increasing the BCL-6-mediated transcriptional repression and its name derives from its function (BCOR = BCL-6 corepressor) [3, 6]. BCOR performs an integral role in embryological development by epigenetically silencing regions of the

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genome through its interactions with histone deacetylases and polycomb repressive complex 1. Constitutional mutations in the BCOR gene have been linked with organogenesis disorders during the development, such as oculofaciocardiodental syndrome; somatic alterations in BCOR have been implicated as recurrent genetic drivers in a wide spectrum of human tumor types [3].

Herein, we present a review of the literature and a case of a child with HGNET BCOR with the goal to update the main clinical, pathological, and management aspects of this new, rare, and highly aggressive tumor.

Genetic classification

A large series of tumors diagnosed as CNS PNET have been investigated and re-classified after detailed molecular analyses. Four new entities have been identified and differentiated as follows: CNS NB-FOXR2 (CNS neuroblastoma with FOXR2 activation), CNS EFT-CIC (CNS Ewing sarcoma family tumor with CIC alteration), CNS HGNET-MN1 (CNS high-grade neuroepithelial tumor with MN1 alteration), and CNS HGNET-BCOR (CNS high-grade neuroepithelial tumor with BCOR alteration) [15].

In the CNS HGNET-BCOR, somatic internal tandem duplications (ITD) in the 3rd end (exon 15) of the BCOR gene have been identified, with a subsequent remarkable overexpression of BCOR [15, 17].

Clinical presentation

So far, 23 cases have been reported in the literature, usually as case/cases reports, except for two small series including 6 and 10 cases, respectively [5, 17]. Overall (including the present case), the mean age at diagnosis was 5.5 years (median 4 years), ranging from 7 months to 22 years. The male/female ratio was 1.4 (14 boys, 10 girls). The infratentorial compartment was more frequently involved (16 cases, 71%) than the supratentorial one (7 cases, 29%). The cerebellar hemisphere was the predominant location in the infratentorial compartment, the cerebellopontine angle being involved only in 2 cases. Similarly, the brain hemisphere was the usual location in the supratentorial compartment (mainly frontal or front-parietal lobe), the basal ganglia being involved only in one case.

As expected, the symptoms occurred according to the location of the tumor [1, 2, 5, 7, 11, 12, 17]. Children harboring infratentorial tumors frequently presented with headache and vomiting, as result of the raised intracranial pressure possibly due to the associated hydrocephalus (obstruction of the CSF flow caused by the compression of the IV ventricle). Less commonly, signs/symptoms of cerebellar (ataxia, imbalance and inability of fine motor movements) or brainstem impairment (cranial nerve palsy, sensory-motor dysfunction, neck pain) were observed. On the other hand, children with supratentorial tumors typically showed epileptic seizures, headache, and motor deficits.

No metastases were detected at diagnosis. Nevertheless, metastasis occurred in large amount of patients mainly as recurrence or tumor spreading during the course of the disease (25%, 6 out 24 cases), the surgical field being the most common location, followed by the cerebellar hemispheres, spinal cord and column, bones, lung, and liver [2, 5, 7, 11, 12, 17].

Diagnosis

Pathological features

The pathological features of these tumors are not highly characterized, so that the differential diagnosis with embryonal and glial tumors may be difficult to establish. HGNET BCOR is relatively well-circumscribed tumors characterized by a combination of spindle to oval cells with fine chromatin. They may show microcystic features and perivascular pseudorosettes, sometimes with an ependymoma-like appearance. Moreover, they may exhibit fibrillary cytoplasmic processes that suggest a glial differentiation [5, 15, 17].

HGNET BCOR is mostly GFAP, synaptophysin, and EMA negative but may be positive staining for OLIG2 and NeuN. A strong nuclear BCOR protein expression is often present. The Ki-67 labeling index is variably increased, ranging from 15 to 60% in the most actively proliferating areas [5].

Radiologic aspects

On magnetic resonance image (MRI), the tumor appears as a solid and well-circumscribed mass, usually occupying the superficial layer of the cerebral or cerebellar hemisphere. Hypointensity on T1-weighted images, hyper-intensity on T2-weighted images (with clear hypo-intensity compared with CSF), and hyper-intensity on diffusion-weighted images (as in high cellularity neoplasms) are the main findings on standard MRI. Gadolinium administration exhibits variable degrees of heterogeneous contrast enhancement without a clear ring-enhancing. In some cases, cystic components, intratumoral necrosis, and/or hemorrhages (evidenced by T2 star) can be appreciated [5, 17]. Spectroscopy was reported only in one child in the literature [1] and in the present case: as expected, it showed the typical signs of an aggressive tumor, like high choline peak, reduction of N-acetyl-aspartate, and lactate/lipid doublet. No cases of significant tumor bleeding were reported. The problem of associated hydrocephalus was not addressed specifically in the literature.

Management

Surgery was the first step of treatment in all cases. No specific aspects concerning the neurosurgical management were reported. A subtotal surgical resection (STR) was achieved in 3 out of 24 cases; it was invariably associated with an early local progression, which occurred in all cases with an average of 3 months from surgery, independently from the adjuvant treatment [7, 17]. Considering the gross total resection (GTR), which was obtained in the remaining 21 cases, a local recurrence was reported in 50% of case patients, with an average time of 20 months from surgery. In these last 20 patients (information about one case is missing), it was observed a considerable difference between those who underwent radiotherapy (RT) and chemotherapy (CT) (mean time of recurrence 36 months) and those who received only partial (RT or KT) or no adjuvant treatment (mean time of recurrence 7.5 months) (Fig. 1). In case of local recurrence, GTR followed by adjuvant treatment (mainly CT and/or RT including the region of the recurrence) was the most used option (Table 1), although a standard protocol for this tumor is not available yet. Similarly, in case of metastasis along the surgical bed, GTR was performed together with CT and RT (involving all the surgical bed, skin included). Paret and coworkers proposed a craniospinal irradiation plus a boost on the tumor bed after the removal of the primary tumor to prevent local progression and metastasis [12].

RT was performed in 50% of cases, the overall dose ranging from 51.2 to 60 Gy (mean dose 56 Gy). In 4 cases, it was specified that a cranial or craniospinal irradiation with focal boost was used; in these instances, no recurrences were observed after a 20-month mean follow-up (range 13–26 months).

Several CT regimens were utilized, changing even in the same series. These included the use of a multi-agent treatment (vincristine, cisplatin, cyclophosphamide, and etoposide), bevacizumab, and the use of intrathecal chemotherapy (methotrexate and topotecan). IGF-1 receptor is being investigated as a potential new therapeutic target for BCOR HGNET [14, 16]. However, to date, it is not possible to establish a superiority of a given scheme. High dose (HD) CT with hematopoietic stem cell rescue (SCT) was performed in 25% of cases (6 patients) during the management of the primary tumor. HD CT was associated also with RT in 2/3 of cases. No recurrence was observed in these 6 cases (mean follow-up 14 months; range 7–26 months).

When all treatments are considered together: (1) all patients undergoing GTR + RT only or CT only (or no adjuvant treatment), finally developed a local recurrence; (2) patients undergoing GTR + RT + CT did not show local recurrence in 63% of cases (7 out of 11 patients) after a 17-month mean follow-up (range 4–26 months). The remaining 3 cases presented the local recurrence after a 36-month mean period (the remaining patient had an extracranial metastasis). In this group, 4 patients received HD CT and did not show relapses (mean follow-up 17.5 months); (3) two patients underwent GTR +

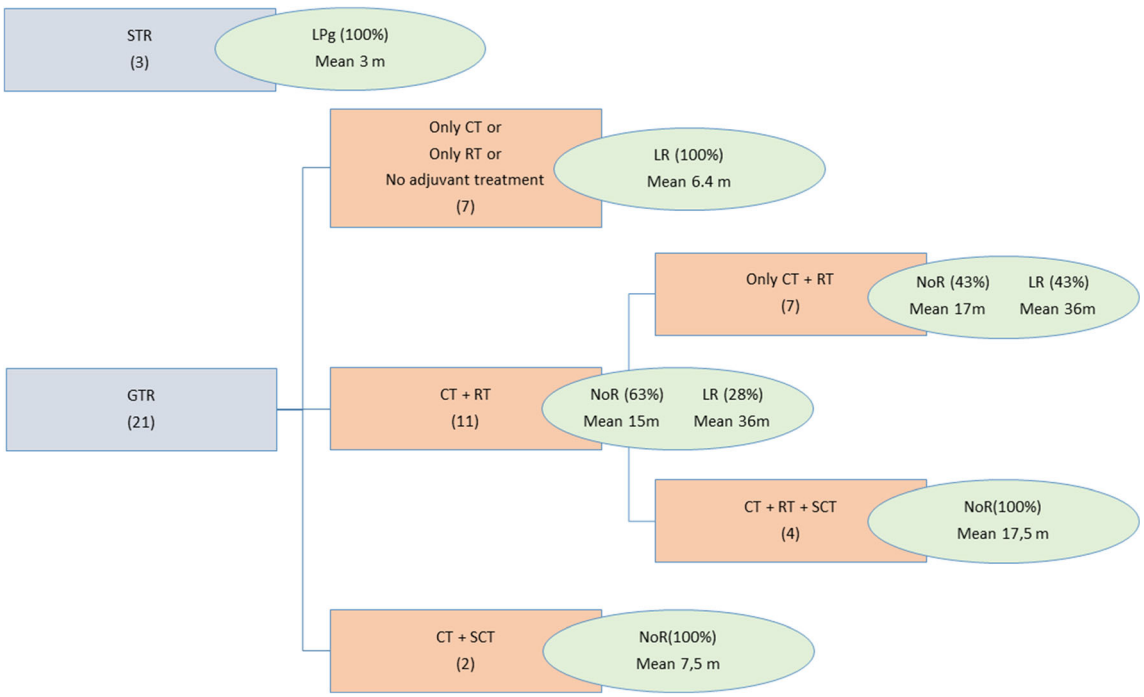

Fig. 1 Combination of primary treatments and their outcomes. (STR, subtotal resection; GTR, gross total resection; CT, chemotherapy; RT, radiotherapy; SCT, stem cell transplantation; LPg, local progression; LR, local recurrence; NoR, without recurrence)

Table 1 Cases and the step-by-step treatment of the primary tumor and its relapses in all patients reported in the literature and in our case

Articles	Case	Age Sex	Location	Surgery	Adjuvant treatment	Recurrence LR; LPg; MT; SD	Recurrence Treatment	Outcome
Kirkman et al. (2018)	1.	5 years M	Right cerebellar hemisphere	STR	No	LPg (5 months)MT in surgical bed (12 months)	GTR (8 months) RT: post fossa—54 Gy–30 cy GTR (25 months) RT: Pt fossa, cervical incision—54 Gy–30 cy CT: VCR, CPT11, TMZ	Alive (3 years)
Al-Battashi et al. (2019)	1.	2 years M	Right cerebellar hemisphere	GTR	Until 3 years CT: VCR, CPA, CDDP, VP16–4 cy after 3 years RT: 54 Gy–30 cy CT: TMZ	LR (2 years 5 months)LR (2 years 11 months)	GTR CT: TMZ, BEV—6 cy After 4 tandem autologous bone marrow transplants Palliative	Dead (3 years)
Paret et al. (2016) Paret et al. (2017)	1.	6 years M	Right parietooccipital lobe	GTR	RT: 59.4 Gy–30 cy CT: TMZ (during RT) VCR, CDDP, CCNU (after RT)	MT in surgical bed (10 months) SD (17 months)	GTR (10 months) RT: skull lesions—44 Gy (5 × 2/w) CT: ICE, I^2VAd, DOX TT: ATO (IV) TT: ATO (VO)	Dead (1 year 10 months)
	2.	4 years F	Posterior fossa	GTR	RT: craniospinal—18 Gy–10 cy focal boost (36 Gy–20 cy) to 54 Gy CT: CPA, VP16, CDDP, MTX, CBDCA, Thp SCT	No		Alive (1 year 8 months)
Appay et al. (2017)	1.	3 years M	Cerebellar hemisphere	GTR	No	LR (6 months) LR, MT hemispheric and leptomeningeal (12 months)	GTR (6 months) RT RT: spinal CT	Dead (1.5 years)
	2.	4 years M	Left Cerebellar hemisphere	GTR	CT: VP16, CBDCA	LR (6 months) LR (8 months) LR, MT bones (18 months)	GTR (6 months) CT GTR (9 m) RT: local CT	Dead (1 year 8 months)
	3.	7 years F	Right Cerebellar hemisphere	GTR	RT: craniospinal CT: CPT11, TMZ, Itz–metronomic	No		Alive (1 year 2 months)
Yoshida et al. (2017)	1.	11 months M	Cerebellar hemisphere	STR	No	LPg	No*	Dead (2 months)
	2.	6 years M	Cerebellar hemisphere	GTR	RT: focal—55.8 Gy–31 cy	LR, MT in surgical bed LR LR	GTR RT: IMRT—59.4 Gy–33 cy CT: CDDP, VP16, CPA GTR RT: electron—54 Gy RT: SRT—40 Gy–10 cy CT: BEV	Dead (3 years)
	3.	6 years		GTR		No		Alive (2 years 2 months)

Table 1 (continued)

Articles	Case	Age Sex	Location	Surgery	Adjuvant treatment	Recurrence LR; LPg; MT; SD	Recurrence Treatment	Outcome
		M	Left temporal lobe		RT: craniospinal, 24 Gy–16 cy, focal—27.2 Gy–17 cy CT: CDDP, CPA, VP16 SCT			
	4.	3 years F	Cerebellar hemisphere	GTR	Not reported	Not reported		Not reported
	5.	7 months M	Cerebellar hemisphere	GTR	No	LR LR	GTR CT: IT-MTX GTR RT: post fossa, focal—50.4 Gy–28 cy CT: IT-MTX, IT-TPT, HD-CT SCT	Alive (3 years 1 month)
	6.	22 years M	Cerebellopontine angle	STR	CT: CDDP, VP16	LPg	No*	Dead (2 months)
Ferris et al. (2019)	1.	1 years F	Frontoparietal lobe	GTR	CT: VCR, CDDP, CPA, VP16–4 cy	LR (14 months)LR (21 months)	GTR CT: TMZ CT: LEN GTR RT: focal CT: CCNU, CRA	Alive (14 years)
	2.	4 years F	Cerebellum	GTR	RT: craniospinal–18 Gy, local boost to 54 Gy CT: VCR, CDDP, CPA, VP16–4cy, CBDCA, Thio - 3 cy SCT	No		Alive (1 years 8 months)
	3.	3 years F	Frontal lobe	GTR	RT: cranial—54 Gy CT: CBDCA, VP16–4 cy, CBDCA, VP16, CPA, Thio—3cy SCT	No		Alive (4 months)
	4.	3 years M	Cerebellum	GTR	No	LR (4 months) LR (16 months)MT spinal cord (20 months)	GTR RT: cranial CT: CDDP, CPA, VP16 GTR RT: craniospinal CT: D1MT, TMZ	Alive (2 years) *with disseminate disease in the brain and spinal cord
	5.	2 years F	Cerebellum	GTR	CT: VCR, MTX, LV, CDDP, VP16, CDA—4cy, CBDCA, Thio—3cy SCT	No		Alive (7 months)
	6.	2 years F	Frontoparietal lobe	GTR	CT: VCR, CDDP, VP16, CDA—4 cy, CBDCA, Thio—3cy SCT	No		Alive (8 months)
	7.	9 years	Basal ganglia	GTR	RT: cranial—60 Gy	No		Alive (2 years)

Table 1 (continued)

Articles	Case	Age Sex	Location	Surgery	Adjuvant treatment	Recurrence LR; LPg; MT; SD	Recurrence Treatment	Outcome
		F			CT: TMZ, BEV—12 cy			
	8.	13 years M	Frontal lobe	GTR	RT: cranial—60 Gy CT: TpMZ, BEV—12 cy	LR (49 months)	GTR CT: CPT11, BEV	Alive (4.5 years)
	9.	2 years M	Cerebellum	GTR	RT: cranial—60 Gy CT: TMZ, BEV—4 cy	LR (31 months)	GTR CT SCT	Alive (3 years)
	10.	12 yeaars F	Frontoparietal lobe	GTR	RT: craniospinal—36 Gy, local boost to 54 Gy CT: VCR, CDDP, CPA—6 cy	No		Alive (1 years 1 months)
Our case	1.	1 years M	Cerebellopontine angle	GTR		LR (2 months)LR (23 months) LR, MT cerebellar hemisphere (49 months) MT leptomeningeal (53 months)	GTR CT: MTX, VCR, VP16, CPA—3 cy, Thio—2 cy SCT GTR* GTR*	Alive (4 years 6 months)

(Time after initial diagnose) year, month

M male, *F* female, *LPg* local progression, *LR* local recurrence, *MT* Metastases, *SD* systemic disease

Treatments: *RT* radiotherapy, *CT* Chemotherapy, *cy* cycles, *SCT* stem cell transplantation, *STR* subtotal resection, *GTR* gross total resection, *TT* target therapy, *IT* intrathecal; *HD* high-dose, *IMRT* intensity modulated radiation therapy, *SRT*: stereotactic radiotherapy

Drugs: *ATO* arsenic trioxide; *BEV* Bevacizumab; *CBDCA* carboplatin; *CCNU* lomustine; *CDDP* cisplatin; *CPA* cyclophosphamide; *CPT11* irinotecan; *CRA* cis-retinoic acid; *D1MT* indoximod; *DOX* doxorubicin; I^2 *VAd* ifosfamide, vincristine, dactinomycin C; *ICE* ifosfamide, carboplatin, etoposide; *LEN* lenalidomide; *LV* leucovorin; *MTX* methotrexate; *Thio* thiotepa; *TMZ* temozolomide; *TPT* topotecan; *VCR* vincristine; *VP16* etoposide

*Incomplete treatment due to the patient or parent refusal

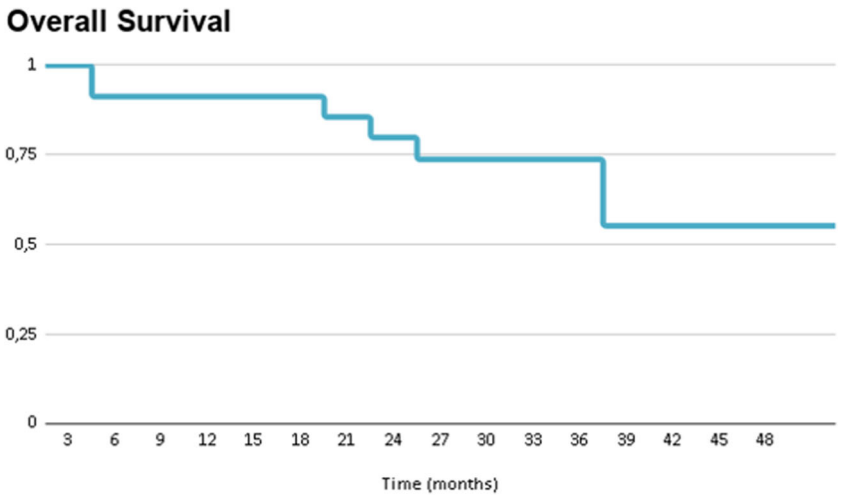

Fig. 2 Survival Kaplan-Meier curve

HDCT + SCT, with no recurrence observed, although the follow-up is too short to have conclusions (mean follow-up 7.5 months). Figure 1 summarizes the results of the combination of adjuvant treatments. Table 1 details the cases and the step-by-step treatment of the primary tumor and its relapses in all patients reported in the literature and in our case [1, 2, 5, 7, 11, 12, 17].

Outcomes

The prognosis of BCOR HGNET may be dismal. There is no clear relationship between the patient characteristics or the tumor localization and the recurrences or the survival time (the heterogeneity of the treatments and the small sample of patients represent a bias for this analysis) [1, 2, 5, 7, 11, 12, 17].

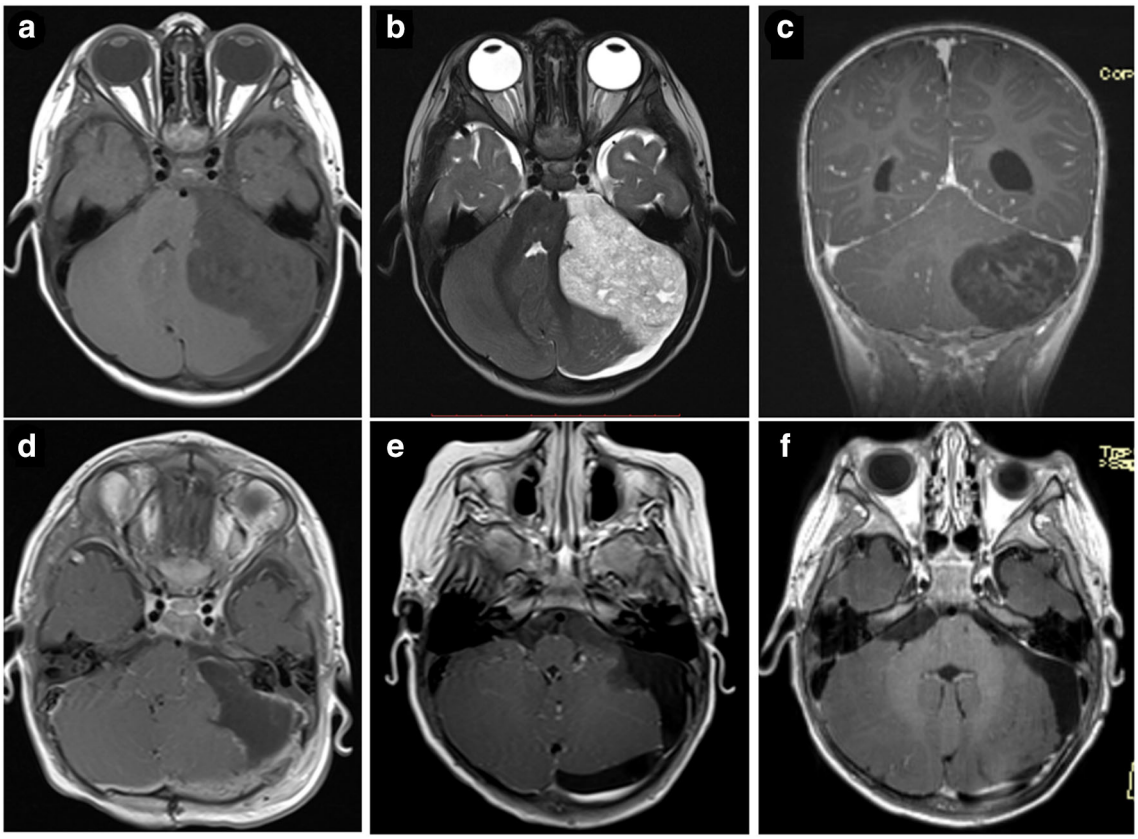

Fig. 3 The MRI at clinical onset shows a large well-demarcated tumor of the left cerebellopontine angle, with mass effect and involvement of the ventral cisternal space up to the midline, hypointense on T1 (axial, **a**), and heterogeneously hyperintense on T2 (axial, **b**) with poor and heterogeneous contrast enhancement (coronal, **c**). No tumor remnants were detected after tumor excision (**d**). After 2 months, a small tumor recurrence occurred in the inferior aspect of the prepontine cistern and in the surgical field (**e**); a new radical excision was performed (**f**)

The overall survival rate after a 34-month mean follow-up (range 5–170 months) is 70% (16 out of 23 cases). Such a rate decreases to 50% in patients with relapse (7 out of 14 cases, mean follow-up 58 months, range 28–170 months) and to 33% in patients with metastasis. It is worth noting that the rate of patients without relapse after a 15-month follow-up is 39% (9 out of 23, range 4–26 months). The mean time to relapse is 20 months (range 4–49 months). Figure 2 shows the Kaplan-Meier curve elaborated on the cases reported so far.

Exemplary case description

The clinical history of this young boy started when he was 15-month-old with gait and balance disturbances, left lateral deviation of head and neck, and left VI cranial nerve palsy with convergent strabismus (November 2015). Brain MRI showed a huge mass ($70 \times 51 \times 44$ mm) occupying the left cerebellopontine angle with a cisternal growth that reach up to the midline (Fig. 3a–c). The patient underwent a GTR of the tumor at another hospital through a retrosigmoid approach (November 2015) (Fig. 3d). The postoperative course was uneventful. A histopathological diagnosis of low grade glioneuronal tumor was provided so that no adjuvant treatment was planned. A small tumor recurrence was detected by MRI 2 months later (Fig. 3e). Therefore, the child was admitted to our Institution (Pediatric neurosurgery, A. Gemelli Hospital, January 2016): the neurological picture was improved compared with the beginning of the clinical history, only the VI nerve palsy persisting. The tumor recurrence was completely removed by following the previous surgical corridor (Fig. 3f). The postoperative course was uneventful. The histopathological analysis showed a tumor with moderate cellularity, composed of glial-appearing cells with hyperchromatic oval or rounded nuclei. Several mitoses and apoptosis were found. The tumor did not display significant GFAP expression but showed partial staining for synaptophysin. The proliferation index (Ki67) reached 30%, and p53 was positive in 5% of tumors cell nuclei. The histopathological features were consistent with the diagnosis of a high grade glioma. Chemotherapy was started according to the AIEOP (*Associazione Italiana di Ematologia e Oncologia Pediatrica*) PNET infant indications [9]. Three courses of induction chemotherapy were administered (methotrexate 8 g/m2 plus vincristine 1.5 mg/m2 week 0; etoposide 2.4 g/m2 week 1;

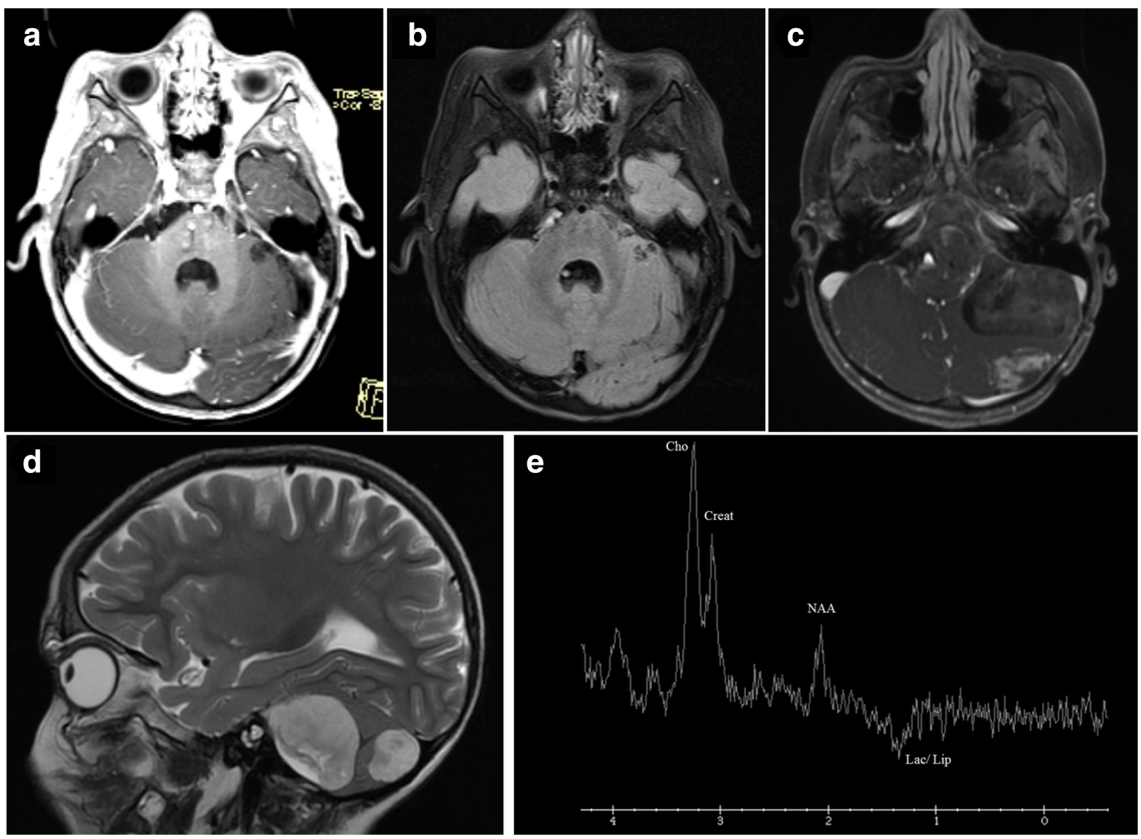

Fig. 4 Axial T1 (**a**) and FLAIR MRI (**b**) showing the absence of recurrence at 19-month follow-up. The MRI performed 2 years later shows the last tumor relapse (**c**, axial T1 after gadolinium administration; **d**, sagittal T2), which appears as two apparently separate lesions, the largest one involving the surgical field in the cerebellopontine angle and the prepontine cistern, the smallest one involving the left cerebellar hemisphere. Both lesions are heterogeneously and poorly contrasted. The spectroscopic analysis (**e**) demonstrates a peak of choline (Cho), reduction in N-acetylaspartate (NAA), and a lactate/lipid doublet (Lac/Lip)

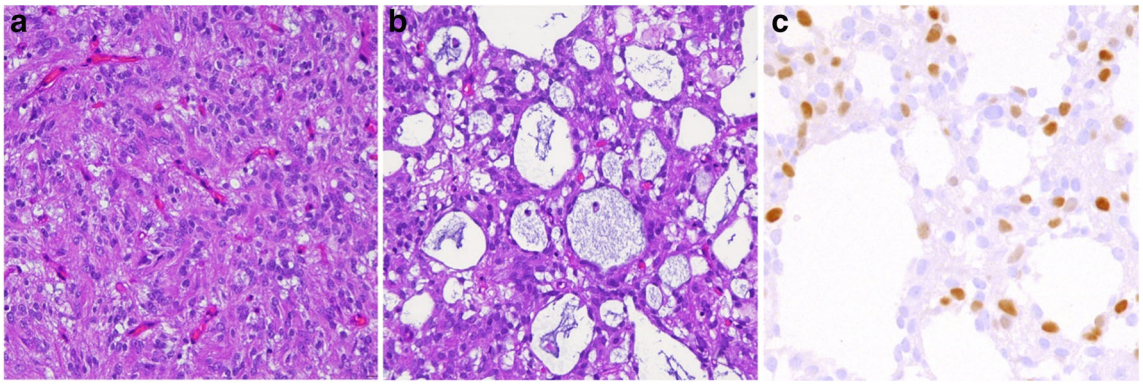

Fig. 5 The tumor showed solid (**a**) and micro-cystic areas (**b**), being composed of cells with round nuclei scant eosinophilic cytoplasm. The tumor was GFAP negative but showed OLIG2 expression in a subpopulation of cells (**c**)

cyclophosphamide 4 g/m2 plus vincristine 1.5 mg/m2 week 4). Then, the child received two courses of high-dose thiotepa (300 mg/m2 for 3 days, week 7) followed by autologous hematopoietic stem cell transplantation. MRIs performed 6 (July 2016) and 14 months (May 2017) after surgery did not point out recurrences, while the exam realized 19 months after surgery disclosed a new local recurrence (October 2017) (Fig. 4a, b). A further GTR was carried out through the same approach. The postoperative course was uneventful, and the child was in good neurological condition. The pathological analysis once again revealed a tumor composed of rounded cells: they did not express GFAP, synaptophysin, and S100 but were partially OLIG2 positive. The parents refused further standard oncological treatments, and the child was lost at follow-up until December 2019 when he was readmitted because of dysphagia and dysphonia. The physical examination revealed a left 7th and 8th cranial nerve palsy as well as a bilateral palsy of the 6th cranial nerve; moreover, a left cerebellar syndrome was evident. MRI showed two lesions in the posterior fossa: a bigger one, presenting a diameter of approximately 5 × 5 × 7 cm and involving the left cerebellopontine angle, and a smaller one, probably a metastatic tumor, invading the left cerebellar hemisphere (size 2 × 2 × 1 cm) (Fig. 4c–e). Once again, the child underwent a left retrosigmoid approach with GTR of both tumor masses. No additional problems were observed in the postoperative period. Cytological examination of the cerebrospinal fluid revealed lymphocytic cells, but no malignant cells were detected. The neuropathological examination revealed a highly cellular tumor

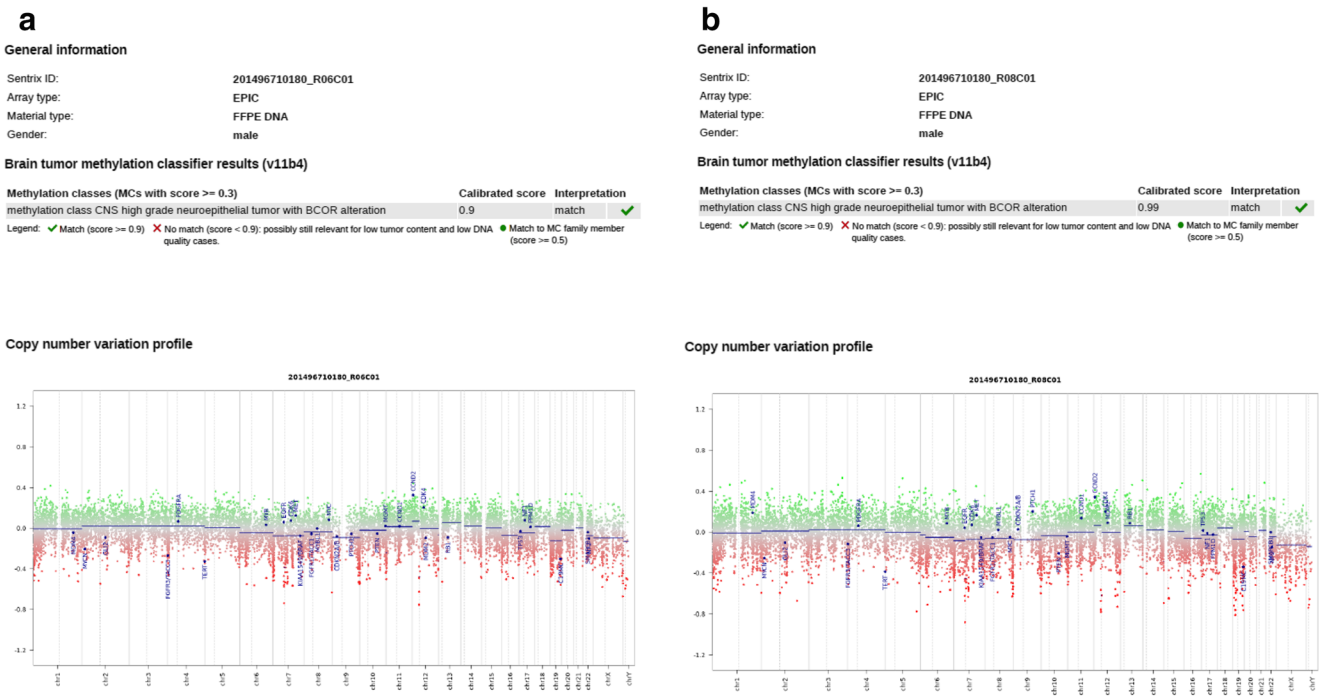

Fig. 6 DNA Methylation profiling report, including copy number variation plots of both primary (**a**) and first relapse (**b**) of the present case, according to brain tumor classifier v11b4

alternating solid and micro-cystic areas (Fig. 5a–b). The tumor cells showed rounded nuclei and eosinophilic cytoplasm. The cells were negative for GFAP, synaptophysin, and CD34 and showed a strong vimentin expression. Notably, scattered OLIG-2 positive cells were present (Fig. 5c). The proliferation index (Ki67) was up to 20–25%. The final diagnosis of BCOR HGNET was formulated using methylation profiling analysis [4] at Bambino Gesù Children's Hospital, as previously reported [10, 13]. More in details, tumor areas with highest tumor cell content (≥ 70%) were selected for DNA extraction from the formalin-fixed paraffin-embedded tumor specimens coming from both the primary tumor and the first relapse. DNA methylation profiling was performed, following protocols approved by the institutional review board. Samples were analyzed using Illumina Infinium HumanMethylationEPIC BeadChip (EPIC) arrays according to the manufacturer's instructions, on Illumina iScan Platform. Two hundred and fifty nanograms of DNA was used as input material from formalin-fixed paraffin-embedded tissues. Generated methylation data were compared with the Heidelberg brain tumor classifier [4] to assign a subgroup score for the tumor compared to 91 different brain tumor entities. Both tumors had a score of > 0.9 in the methylation class: "Methylation class CNS high grade neuroepithelial tumor with BCOR alteration" (Fig. 6). The child is experiencing tumor progression with leptomeningeal dissemination.

Conclusions

The goal of this review was to summarize and update the information emerging about this rare subset of brain tumors characterized by an aggressive behavior and still missing a dedicated treatment algorithm. GTR should be obtained whenever possible. Moreover, both adjuvant treatments are mandatory, as demonstrated by the course of our patient and the similar cases in the literature. Indeed, isolated RT or CT is invariably associated to relapse, while their association has shown the best results, especially in case of RT plus HD CT with hematopoietic stem cell rescue. New targets and wide-ranging clinical trials are needed for an optimal treatment.

Compliance with ethical standards

Conflict of interest No conflict of interest to disclose.

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