



# Central nervous system (CNS) neuroblastoma. A case-based update

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## Abstract

**Background** Primary central nervous system (CNS) neuroblastoma is a rare intracranial tumor affecting children mainly in the first years of life. It is usually a supratentorial tumor with a wide spectrum of clinical presentation, seizures, and focal neurological deficits being the most common presenting signs.

**Case description** A 2-year-old child was admitted to our ward after a generalized seizure. Neurological examination was normal. Radiological studies showed a small DWI hyperintense lesion of the right rectus gyri. Follow-up brain MRI 8 months later showed a huge growth of the tumor (90 × 80 × 65 mm) with polycyclic and apparently defined margins, cystic components, and diffuse contrast enhancement. Complete tumor removal was performed in two planned surgical steps. Histological diagnosis was CNS neuroblastoma. At a follow-up of 8 months, the child is in good clinical and neurological condition and is completing chemotherapy treatment according to the SIOP PNET 4 protocol.

**Discussion and conclusion** A thorough review of the literature confirms that primary CNS neuroblastoma has to be considered a distinct entity. The disease related mortality is 12.5%, lower than the one usually reported for other previously described as PNETs tumors. The most relevant factors influencing prognosis are the possibility of obtaining a complete tumor removal and age more than 3 years, which allows to include radiotherapy among treatment options.

**Keywords** Neuroblastoma · Infant · Surgery · Tumor

## Introduction

In the 2016 WHO classification of the CNS tumors, among embryonal tumors primary CNS neuroblastoma is defined as an embryonal tumor characterized by poorly differentiated neuroepithelial cells, groups of neurocytic cells, and variable neuropil-rich stroma [1]. The tumor is relatively rare, and only a limited number of cases have been in detail reported in the literature. Due to its rarity, little is known also about treatment regimens and patients risk stratification; the low age at diagnosis of the majority of the patients represent in this context a limit in the choice of the management protocols and represent a factor which might condition the prognosis.

## Background

### General epidemiological considerations

From the analysis of the literature primary, CNS neuroblastomas tend to involve preferentially the supratentorial space, with a prevalence of the frontal and the parietal region. The mean age of the reported patients is 5 years confirming that neuroblastoma is substantially a tumor of early infancy. A slight female prevalence has been reported.

### Genetic considerations

In the new WHO 2016 classification, CNS-PNET is no longer regarded a single disease but encompassed many distinct molecular entities. A recent study demonstrated that a large number of previously diagnosed CNS-PNETs display molecular profiles indistinguishable from those of various other well-recognized CNS tumors (such as ATRT, ETMR, and H3.3G34-mutated glioma) or other systemic mesenchymal tumors (such as Ewing sarcoma). However, among the remaining putatively “true” CNS-PNETs, the molecular

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**Table 1** Primary CNS neuroblastoma. Review of the literature

Author	Number of cases	Mean age at diagnosis (min/max)	Sex (M/F)	Localization	Treatment	Follow-up duration (mean)	Clinical conditions at latest follow-up
Ahdeevara et al. 1977	13	9.17 years (2.5 months–17-years)	4 M/9-F	Temporal (4), frontal (2), parietal (5), III ventricle (1), PCF (1)	Surgery alone (7), surgery + RT (2), surgery + RT + CT (1), None (3)	45 months	Alive at 2 years
Latchaw et al. 1982	1	7 years	1F	Parieto-occipital	Biopsy + RT + CT	29 months	Dead
Berger et al. 1983	10	8.25 years (17 months–13-years)	4 M/6-F	Parietal (4), occipital (3), frontal (2), basal ganglia (1)	Surgery + RT (9 + 1 with additional CT),	59 months	–
Torres et al. 1985	1	3 years	–	Intracerebral	–	108 months	–
Davis et al. 1990	5	3.2 years (15 days–4 years)	3 M/2-F	frontal (2), parietal (2), ventricle (1)	Surgery + RT + CT (4), Surgery + RT (1)	32,5 months	2 (dead), 3 (stable)
McLendon et al. 1997	1	5 years	1F	Parietal	–	–	–
Yaris et al. 2004	1	5 years	1F	Fronto-parietal	Surgery + RT + CT	34 months	Alive without recurrence
Author's case	1	2 years	1 M	Frontal	Surgery+ future CT	8 months (at this moment)	No neurological deficits

PCF posterior cranial fossa, RT radiotherapy, CT chemotherapy

investigation revealed a group of lesion with FOXR2 activation. This group encompassed tumors that would be classified as CNS neuroblastoma or CNS ganglioneuroblastoma in the 2007 WHO classification scheme and have been therefore defined as FOXR2 CNS-neuroblastoma (CNS NB-FOXR2) [2].

## Clinical presentation

Primary CNS neuroblastomas may present with a wide spectrum of symptoms due to the variety of possible location of the mass as well as of the size of the lesion.

In line with the preferential supratentorial location, clinical presentation has been reported to vary from focal signs and symptoms due to focal mass effect (focal neurological deficits), to irritative signs (seizures), chronic signs of CNS functions disturbance (neurocognitive impairment), up to signs of increased intracranial pressure due to CSF pathways impairment (headache, vomiting, abnormal head circumference

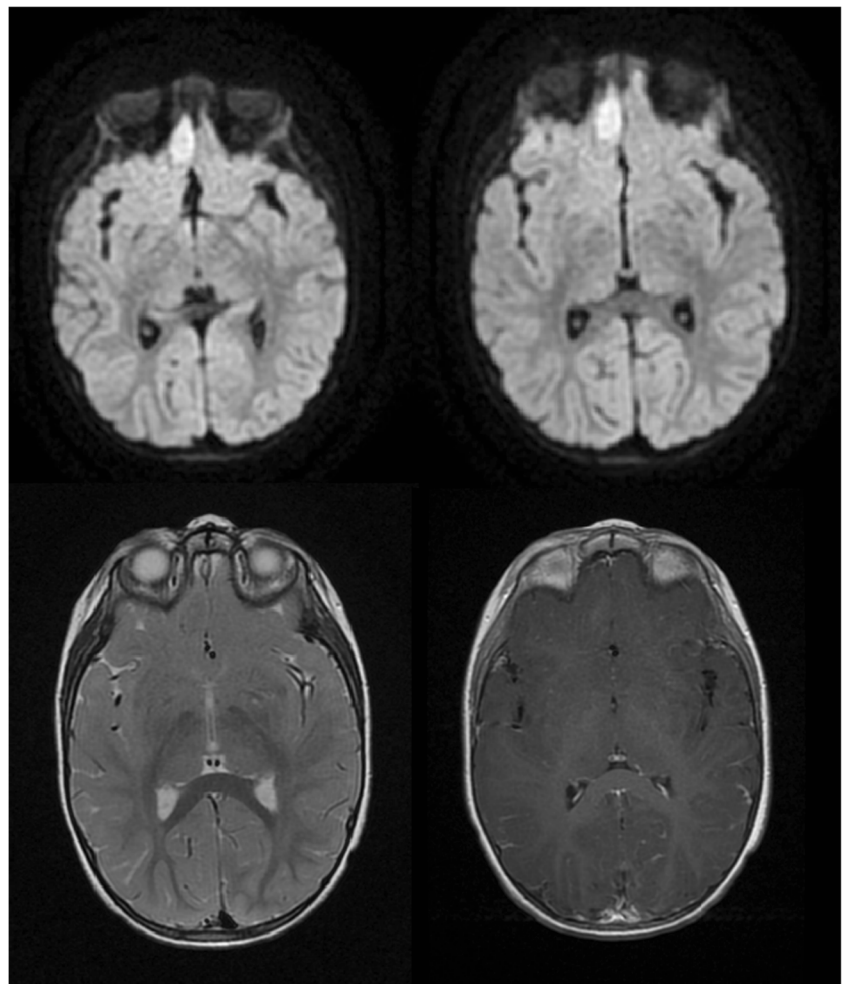
growth) (Table 1) [3–10]. In infants on the other hand, even though the tumor reaches a huge size, no clear sign or symptom might be present, due to compensatory and adaptation mechanisms of the surrounding brain structures.

Metastatic spread of primary CNS neuroblastoma at diagnosis has been reported in only two cases. In one of them, the spreading route was through the CSF pathways and in the other case through the cervical lymph nodes [3].

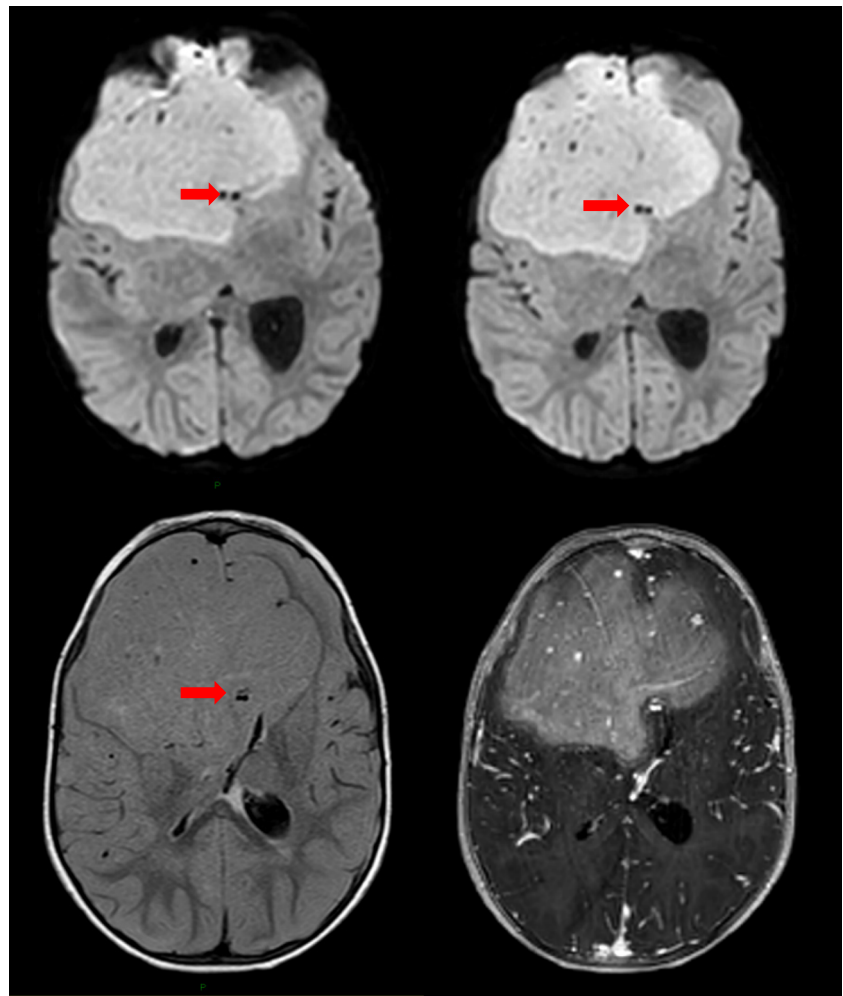
## Diagnosis

The diagnosis of a primary CNS neuroblastoma is most commonly performed on the removed tumor tissue at the time of the histological examination. The basic MR sequences appearance is, indeed, not unique of the disease. In most cases, the tumor appears as heterogeneous due to the common coexistence of solid and cystic components and is apparently separated from the normal CNS tissue. However, pure solid tumors have been described. The solid part is usually isointense

**Fig. 1** DWI, T2, and enhanced T1 MR scans showing a small DWI hyperintense, slight T1 contrast enhancing oval-shaped lesion of the right frontal gyrus



**Fig. 2** DWI, T2 inversion recovery, and enhanced T1 MR images after 8 months, showing a huge growth of the tumor. The lesion appears highly vascularized, encasing both anterior cerebral arteries (arrows)



in T1 and T2 sequences, slightly hyperintense in DWI and might also not partially enhance after Gadolinium administration. When present that cystic components are usually hyperintense in T2 sequences due to their hyperproteic content. Surrounding edema is inconstant, whereas vascular structures crossing the tumor are not uncommon. Spectroscopy shows an increase in the Choline peak and an inversion of the Cho/NAA rate, indicating an aggressive brain tumor, but again not a unique feature of primary CNS neuroblastomas. Perfusion sequences show elevated values of relative cerebral blood volume (rCBV) with a tendency to a recover of the slope [5].

As for any suspected malignant brain tumor, an enhanced scan of all the neuraxis should be performed and CSF samples should be obtained to search for CSF tumor spreading.

Two are the aspects that need to be respected to define a CNS tumor as a primary neuroblastoma: first of all, the histological findings and second, the exclusion of the presence of a systemic neuroblastoma. There are no tumor blood markers or radiological signs that are pathognomonic and/or might help in the definition of a primary neuroblastoma.

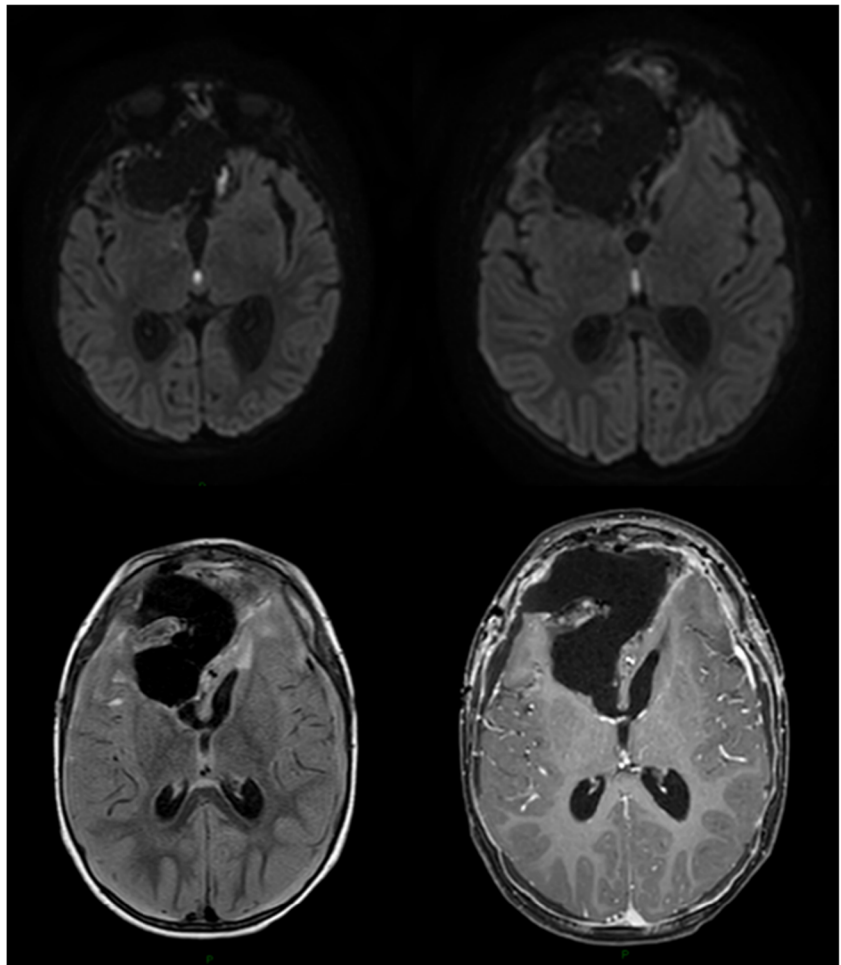
## Histology

CNS neuroblastomas are neuro-epithelial/neurocytic tumors with high cellularity and relatively monomorphic cells with a round nucleus that might be irregular or enlarged. Cytoplasm is not abundant and PAS negative. A high number of mitosis is usually present. The cells are Vimentin, GFAP, S-100, and EMA negative while positivity might be found for MAP2, synaptophysin, Olig2, and Neu-N. Homer-Wright rosettes and ganglionic differentiation may occur [10]. The tumor is usually LIN28A negative and expresses INI1.

## Management

First line of treatment is represented by surgery which is aimed to a complete tumor resection whenever possible. Surgical treatment for larger sized tumors should take into account a provisional elevated volume of blood loss, which, especially in younger children, should lead the surgeon to a planned staged tumor resection.

**Fig. 3** DWI, FLAIR, and enhanced T1 MR images after second surgery showing a complete tumor removal



Chemotherapy has been the most frequently performed adjuvant treatment. Due to their histological aggressiveness and their “niche” brain location, CNS neuroblastomas are treated according to the supratentorial PNET protocols [6]. According to the presence or absence of metastasis at diagnosis, different regimens have been proposed. For non-metastatic tumors, a therapy with a combination of multiple chemotherapeutic agents is considered. The most common ones are vincristine (1.5 mg/m<sup>2</sup> (maximum, 2 mg)), lomustine (75 mg/m<sup>2</sup>), cisplatin (70 mg/m<sup>2</sup>), and etoposide. On the other hand, metastatic neuroblastomas are treated with single high-dose chemotherapeutic agents in sequence such as the sequence of cisplatin, methotrexate, etoposide, temozolomide, and steroids.

Radiotherapy has had a limited role as the usual age of primary CNS neuroblastoma patients is less than 3 years old.

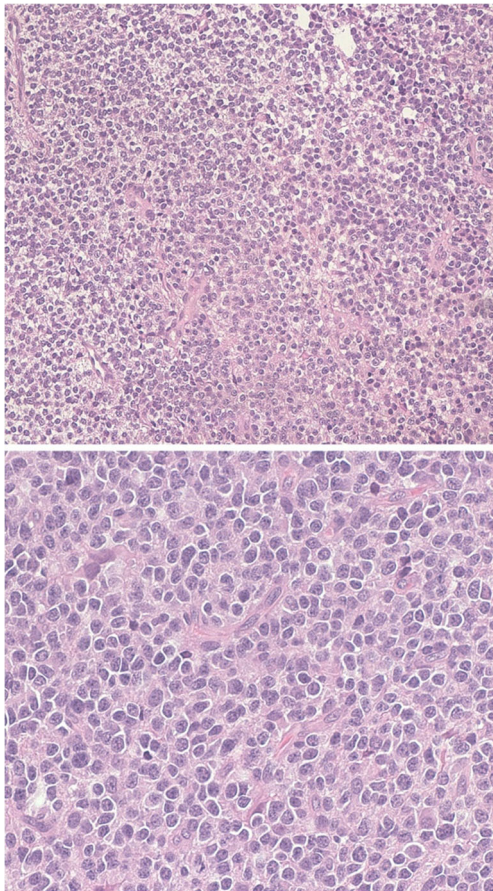
It is difficult to compare primary and systemic neuroblastoma from a prognostic point of view as no paper is clearly focused on such a matter. The younger than 3 years age at presentation of most children with primary neuroblastoma exclude in principle the possibility to perform adjunctive radiotherapy, which also is the only reliable combined treatment

option after 3 years, leading to a higher rate of possibilities for tumor recurrence and hence for a worse prognosis.

### Exemplary case description

A 2-year-old child was admitted in our ward after a generalized tonic-clonic seizure. On admission, the patient was neurologically intact. A CT scan showed an area of spontaneous hyperdensity on the right rectus gyrus (15 × 10 mm). The brain MRI before and after Gadolinium injection confirmed the alteration seen on the CT scan, only visible on DWI sequences and not enhancing after Gadolinium injection (Fig. 1). Considering the high signal in the DWI sequence, surgery was proposed to the family in order to obtain a histological diagnosis. The family refused surgery. Eight months later, the patient came back to our ward again in good neurological conditions, without any neurological deficit and a negative anamnestic history since the previous admission. A control MR was performed, showing a huge growth of the tumor (90 × 80 × 65 mm) with polycyclic and defined margins, cystic components, and heterogeneous contrast enhancement (Fig. 2). Spectroscopy documented an increase of choline





**Fig. 4** Case sample histological study.

and inversion of the choline/N-acetyl aspartate ratio. Perfusion was clearly increased (2.5:1). This radiological progression is unusual for primary CNS neuroblastomas, none of the previous papers having reported such a fast and clinically asymptomatic tumor growth. A staged tumor removal was planned. The aim of the first surgery was to grossly devascularize the tumor and to remove its front mesial component.

Due to brain parenchyma herniation and the planned second stage of surgery, at the end of this first operation the bone flap was not re-positioned.

The postoperative course was uneventful, the patient remaining in good clinical and neurological conditions. The postoperative MR scan showed a subtotal tumor resection. Few days later, after a good clinical recovery, a second-step surgery was performed completing the tumor removal with back positioning of the bone flap.

The patient had a prompt clinical recovery and did not show any postoperative neurological deficit. The control MRI scan confirmed a complete tumor removal in the absence of complications (Fig. 3). The histological diagnosis was: embryonal neoplasm with neuronal differentiation characteristic of a CNS primary neuroblastoma (WHO 2016 grade IV) [1]. The tumor, which was well demarcated from the surrounding brain parenchyma, showed high cellularity and consisted of

proliferation of medium-sized rounded cells which were mostly MAP2+/OLIG+/GFAP– and partially positive for neuronal markers synaptophysin and Neu-N, features that are the most relevant to direct the histological diagnosis to the one of a primary neuroblastoma. Part of the cells cytologically showed neurocytic and ganglionic differentiation. The tumor cells did not display positivity for LIN28A. The expression of INI1 was retained. The tumor showed a high proliferation (MIB1: 20%) and high mitotic index (Fig. 4). The baby was scheduled for chemotherapy. A total body CT scan excluded a systemic involvement. The brain MR before the start of chemotherapy showed the presence of a bilateral subdural hygroma.

Because of its asymptomatic occurrence, the subdural hygroma was initially treated conservatively. Two months later, the child started to complain headache. A CT scan showed an increase in size of the bilateral subdural hygroma; for this reason, a subduro-peritoneal shunt was implanted (programmable valve set at 10 cm H<sub>2</sub>O).

## Discussion and conclusions

Primary CNS neuroblastomas are a rare condition in the pediatric neurosurgical practice. The histological features and clinical behavior lead to consider them as highly malignant tumors. However, the disease-related mortality reported in the literature is 12.5%, lower than the one usually reported for other embryonal tumors. A dedicated treatment protocol has not been established yet; even if surgery remains the first step of treatment, adjuvant strategies are not specifically tailored to neuroblastomas. A further limiting clue is represented by the fact that radiotherapy is not an option in most cases due to the age lower than 3 years of the majority of the affected children; analyzing data from the literature (1), it is possible to see how, in children older than 3 years, in which radiotherapy is a treatment option, the survival rate and the length of the survival is higher. The rarity of the pathology further contributes to render the task of establishing a uniform treatment regimen is not easy though.

## Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

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