

Case Presentation

Primary Infratentorial Central Nervous System Neuroblastoma: Case Report and Review from Paediatric Population

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Abstract

Background: Neuroblastomas of the central nervous system are rare malignant neoplasms that predominantly affect children. The neoplasia can present a wide variety of symptoms depending on its location and size. It has been documented predominantly in the supratentorial and spinal regions. The objective is to report an infratentorial pediatric neuroblastoma case and review of the literature.

Methods: The case of a patient diagnosed with neuroblastoma was reported. In addition, an exhaustive review of the literature between the years 1966 to 2024 was carried out.

Results: From our cohort study, we found 197 patients, including our patient. Of the total number of cases, 195 were supratentorial; 49 frontal, 14 fronto-parietal, 7 fronto-temporal, 2 fronto-temporo-parietal, 9 temporal, 6 temporo-parietal, 3 temporo-parieto-occipital, 23 parietal, 13 parieto-occipital, and 6 occipital cases.

Conclusion: Neuroblastoma is a high-grade neoplasm (WHO grade 4) with predominantly supratentorial involvement. We present a pediatric case of infratentorial neuroblastoma and a review of the literature.

Introduction

According to the World Health Organization (WHO) 2021 on Central Nervous System (CNS) tumors, neuroblastoma is considered an embryonal neoplasm, characterized by the activity of the transcription factor FOXR2 with chromosomal structural rearrangement [1]. Gains in chromosome 1q have been found more frequently in about 83% - 100% of cases [2-4]. Others are in 3q, 8p, 8q, 17q and losses in 3p, 6q, 10q and 16q [5]. Histologically characterized by poorly differentiated cells with round, hyperchromatic nuclei with scant cytoplasm, Homer Wright rosettes, and areas of necrosis. Neurocytic differentiation and mature ganglion cells may be present, and intense mitotic activity may be present. Immunohistochemistry (IHC) studies show immunoreactivity to Olig2, and some embryonic cells may show positivity to synaptophysin, and

Ki67 is usually high [1]. Clinical manifestations present a varied spectrum due to the predominantly supratentorial location of the neoplasm, from focal neurological deficits, irritative signs such as seizures, to neurological deterioration [6]. We submit a case of neuroblastoma (NBs) located in the cerebellum and a review of the literature.

We can find studies on neuroblastoma; however, this work presents an exhaustive review on neuroblastoma, where we were able to collect 197 patients, which allowed us to perform a better data analysis and a better presentation of cases.

Case presentation

A 9-year-old male, admitted with the complaint of headache, nausea, vomiting, and ataxia, was previously treated for vertigo. After a month and clinical deterioration, a head tomography

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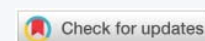
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was performed, and evidence of a cerebellum tumour was found, involving the fourth ventricle with dimensions of 1.2 x 0.6 x 0.4 cm in the rostrocaudal, ventrolateral and transverse planes and cerebral edema, for which a ventricle-peritoneal bypass valve was placed. A mid-suboccipital craniotomy was performed with partial resection of 50% of the tumour. He was sent to the HPCMNSXXI for chemotherapy treatment (ifosfamide, carboplatin, and etoposide) and radiotherapy. The Pathology service received slides that included routine stains and IHC (synaptophysin, GFAP, CD99, Ki67) without paraffin blocks; therefore, it was not possible to perform other IHC markers or the identification of the transcription factor FOXR2 (forkhead box R2).

An embryonic, hypercellular tumor, consisting of undifferentiated, small and hyperchromatic cells, densely packed with Homer Wright rosettes, which alternated with well-differentiated areas with multiple ganglion cells in different stages of maturation on a fibrillar background was identified. With areas of palisade necrosis and dystrophic calcifications. IHC was positive for synaptophysin in tumor cells, GFAP positive in neuropil, and Ki67 positive 95% in neoplastic cells. The diagnosis of NB grade 4 (WHO 2021) was issued (Figure 1).

Magnetic resonance imaging was performed in April 2023 with the presence of a residual lesion in the fourth ventricle that caused a volume effect on the ventricle and adjacent structures (Figure 2). She was followed for 17 months with chemotherapy and radiotherapy treatment, with a torpid evolution followed by death.

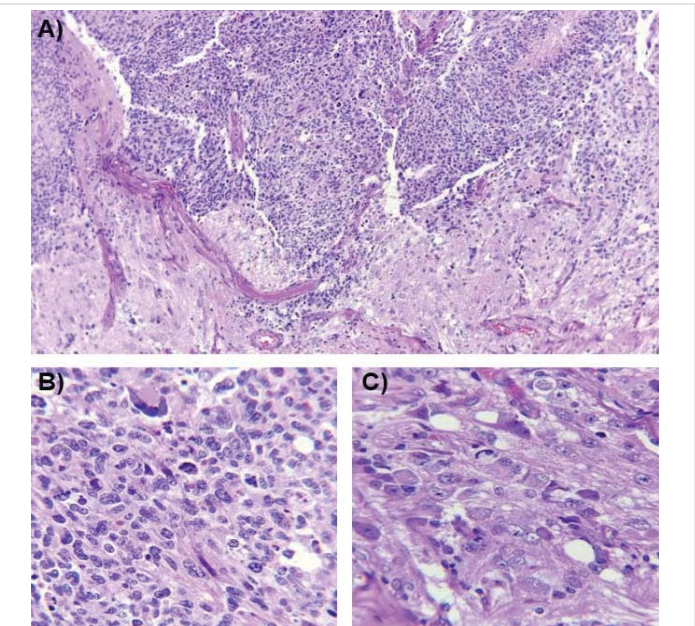


Figure 1: Histopathological diagnosis. A) HE, Photomicrograph showing a neoplasm consisting of two differentiation components with evidence of embryonic neoplasia alternating with differentiated hypocellular areas 10X. B) Presence of embryonic component with apoptosis and mitosis, as well as evidence of multinucleated cells with neuronal differentiation. C) Close-ups in which a fibrillar background is observed with the presence of multiple cells with neuroblastic or neuronal differentiation. (HE, 40x).

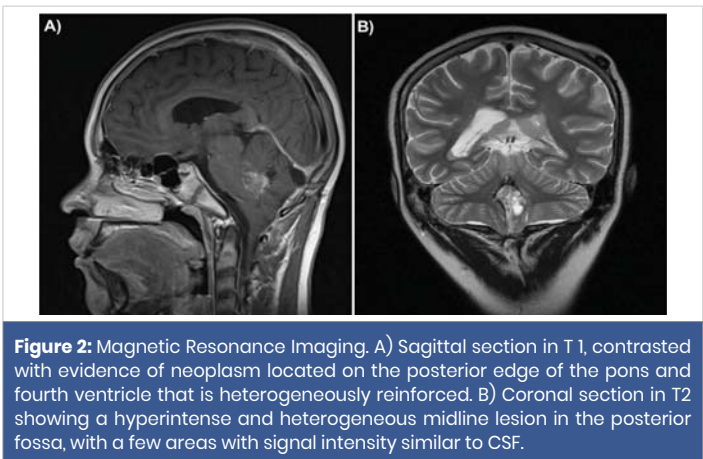


Figure 2: Magnetic Resonance Imaging. A) Sagittal section in T1, contrasted with evidence of neoplasm located on the posterior edge of the pons and fourth ventricle that is heterogeneously reinforced. B) Coronal section in T2 showing a hyperintense and heterogeneous midline lesion in the posterior fossa, with a few areas with signal intensity similar to CSF.

Material and methods

A comprehensive review of published cases in the Web of Science (WOS), SCOPUS, Google Scholar, TripDatabase, Science Direct, and PubMed was carried out without using language restrictions, and the search strategy included all known descriptors on CNS neuroblastoma and FOXR2, with no date limit.

The main parameters that were considered eligible for the study were: primary location in the CNS and paediatric population. Other criteria that were included: sex, clinical presentation, surgical treatment, medical treatment, and survival time. The exclusion parameters that were considered for the study were: duplicate cases, CNS metastasis, non-paediatric population, case report, and cases without clinical data of the patients.

The selection process was carried out using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 (Figure 3). The studies in this comprehensive review were carried out between 1966 and 2024.

Results

From our cohort study, we found 197 patients, including our patient. Table 1 shows the summary of the cases found.

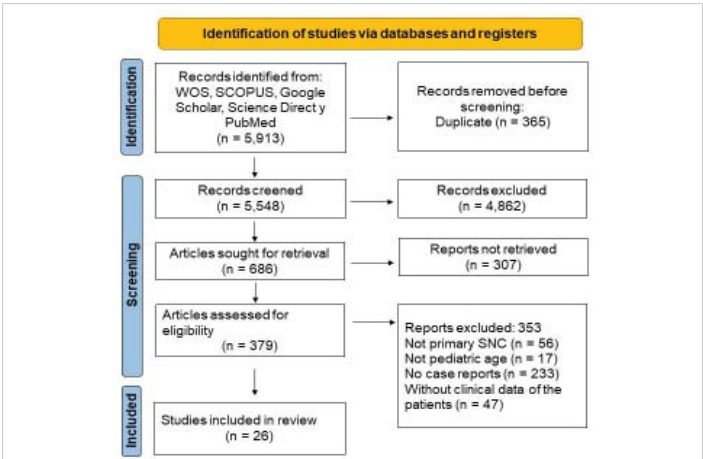


Figure 3: Flow diagram of study identification.

**Table 1:** Literature review of reported cases of primary CNS neuroblastoma.

Author	No. case	Sex M/F	Mean age at diagnosis (min - max)	Symptoms	Location	Resection Yes / No Partial / Total	Chemotherapy Yes/no	Radiotherapy Yes/no	Survival time Average (min - max)
Schmincke 1914*	1	M	17 yr	ND	Temporal	ND	ND	ND	ND
Doyle and Kernohan 1931*	1	F	11 yr	ND	Third ventricle	Yes	No	No	Alive (30 m)
Kernohan, et al. 1932*	1	F	16 yr	ND	Temporo-parietal	Yes	No	No	Alive (72 m)
Tönnis and Zurich 1939 *	3	M	3,10,14 yr	ND	Temporo-parietal, parieto-occipital 2	Yes	No	No	ND
Miller and Ramsden 1966 [19]	1	M	3 m	Distal cyanosis	Fronto-parietal	Yes, total	No	No	Alive (37 m)
Durity, et al. 1967 [20]	1	F	3 yr	Headache, vomiting, hyperreflexia, bilateral positive Babinski and papilledema	Right cerebellar hemisphere	Yes, total	No	Yes	Alive (1 yr)
Russell and Rubinstein 1971*	16	8 M 8 F	2.5 m – 9 yr	ND	Hemispheres	Yes	No	Yes	ND
Henríquez, et al. 1973 [21]	1	M	7 yr	Headache, vomiting and papilledema	Fronto-parietal	Biopsy	Yes	No	Dead (15 m)
Rubinstein and Treel 1974*	1	F	9 yr	ND	Parieto-occipital	Yes	No	No	Alive (24 m)
Horten and Rubinstein 1976 [8]	31	17 M 14 F	4 m – 11 yr Average 4.1 yr	Nausea, vomiting, seizures and headache,	Frontal 10, parietal 6, temporal 2, fronto-parietal 5, fronto-temporal 4, parieto-occipital 2, parieto-temporal 1 and parieto-temporo-occipital 1	ND	Yes (1 case)	Yes (8 cases)	Alive 10 (3m - 13yr) Dead 20 (3s – 10yr) ND 1
Ahdevaara, et al. 1977 [7]	1	F	13 yr	Headache, vomiting and syncope	Frontal	Yes, Partial	No	Yes	Alive (25 m)
Latchaw, et al. 1982 [22]	1 (case 1)	F	7 yr	Papilledema	Nodule in skull	No	Yes	Yes	Dead (29 m)
Bennett and Rubinstein 1983 [9]	40	14 M 26 F	5 m - 18 yr Average 5.7 yr	Increased intracranial pressure 13, seizures 13, hemiparesis 7, headache 2, aphasia 2, macrocephaly 1, hydrocephalus 1 and irritability 1	Frontal 14, parietal 4, temporal 2, occipital 2, parieto-occipital 5, fronto-parietal 4, temporo-parietal 1, fronto temporo-parietal 2, middle fossa 1, ventricles 2, hemispherical 2 and gyrus rectus 1	ND	ND	ND	Alive 21 (18 m – 13 yr) Dead 12 (0.5 m – 14 yr) ND 7
Berger, et al. 1983 [23]	10	4 M 6 F	17 m – 13 yr Average 8.2 yr	Headache 4, nausea and vomiting 4, paresthesia of the extremities 4, seizures 2 and decreased memory 2	Parietal 3, occipital 3, frontal 2, basal ganglia 1 and temporo-parietal 1	Yes, partial 8, total 2	Yes (case 3, 4)	Yes	Alive 1 (52m) Dead 2 (23 and 29 m.) ND 7
Torres, et al. 1985 [24]	1	F	3 yr	Papilledema and syncope	Temporal	Yes, partial	No	Yes	Alive (9 years)
PC Davis, et al. 1988 [25]	4 (Case 6, 7, 8, 12)	2 M 2 F	4, 1, 2 a 2 s	Increased intracranial pressure, seizures, vomiting, macrocephaly and ataxia	Case 6: fronto-parietal Case 7: parietal Case 8: fronto-temporal Case 12: parieto-temporo-occipital	Yes, Partial	Yes	Yes	Alive 3 (28 - 36 m) Dead 1 (2.5 yr.)
Volkan Etus, et al. 2002 [26]	1	F	9 a	Headache, nausea, papilledema and hemiplegia	Fronto-parietal	Yes, Total	Yes	Yes	Alive (8m)
Yarýp, et al. 2004 [27]	1	F	5 to	Headache, vomiting, papilledema and hyperreflexia	Fronto-parietal	Yes, partial	Yes	Yes	Alive (34 m)
Ren, et al. 2014 [28]	1	M	7 a	Dizziness, nausea and vomiting	Thalamus	Biopsy	Yes	Yes	Alive (16 m)



Bianchi, et al. 2018 [6]	1	M	2 to	Seizures	Frontal	Yes, total	Yes	No	Alive (8m)
Mishra, et al. 2018 [29]	2	1 M 1 F	7 and 12 a.m.	Headache, vomiting and seizures	Both lateral ventricles and Parieto-occipital	Yes, total	ND	ND	ND
Furuta, et al. 2020 [30]	1	F	3 to	Anorexia and vomiting	Frontal	Yes, partial	Yes	Yes	Alive (24 m)
Lastowska, et al. 2020 [16]	3	2 M 1 F	5, 4.5, 7 to	ND	Parietal, parieto-occipital, frontal	Yes, total	Yes	Yeah	ND
Holsten, et al. 2021 [10]	8	4 M 4 F	1 to – 9 to Average 5 to	ND	Frontal 3, occipital 1, parieto-occipital 1, parieto-temporo-occipital 1, fronto-temporal 1 and intraventricular 1	ND	ND	ND	Alive 4 (139, 12, 31, 8 m.) Dead 2 (18, 26 m) ND 2
Borni, et al. 2021 [18]	1	M	6 a	Headache, vomiting and papilledema	Fronto-temporal	Yes, total	No	No	ND
Taschner, et al. 2021 [31]	1	F	6 a	Vomiting and facial paralysis	Temporo-parietal	Yes, partial	Yes	No	Alive (4 s)
Korshunov, et al. 2021 [4]	20	5 M 15 F	4 a – 16 a Average 8 to	ND	Hemispherical	Yes, partial 10, total 10	Yes	Yes	ND
Shimazaki, et al. 2022 [17]	3	1 M 2 F	6.7, 1.6, 2.6 a	Nausea, vomiting and convulsions	Frontal 2, Parietal 1	Yes	Yes (case 1)	Yes (case 1)	Alive (7, 66, 1 m)
Tietze, et al. 2022 [11]	25	12 M 13 F	1.4 a – 16 a Average 4.5 to	A case with seizures	Frontal 13 Parietal 7 Temporal 3 Basal ganglia 2	ND	ND	ND	ND
Liu, et al. 2022 [3]	6	3 M 3 F	0.91 a - 11.9 a Average: 1.7 a	ND	Hemispheres	Yes, partial 2, total 5	Yes	Yes (4 cases)	ND
Schepke, et al. 2023 [2]	7	3 M 4 F	3 a – 15.7 a Average 5.3 a	ND	Hemispherical	Yes, partial 2, total 5	Yes	Yeah	Alive (5 to)
Sharkey, et al. 2024 [32]	1	M	2 to	Seizures	Frontal	Yes, partial	Yes	Yeah	ND
Villalobos and Sordia 2024	1	M	9 a	Headache, nausea, vomiting and ataxic gait	Cerebellum	Yes, partial	Yes	Yes	Dead (17m)

M: male F: female ND: not available a: years m: months s: weeks

*The papers were not gotten and the cases were referenced in Ahdevaara, et al. 1976.

The criteria were met in 26 publications, plus 6 articles that were not obtained, but the case information was obtained from the publication of Ahdevaara, et al. 1976 [7], with a total of 197 cases of NBs from CNS, of which 111 (56.34%) cases were female, and 86 (43.65%) cases were male, with a male:female ratio of 1:1.2.

Only 66 cases (33.5%) documented the most frequent clinical symptoms, those secondary to increased intracranial pressure (headache, nausea, vomiting, convulsions, papilledema), with only ataxia being added in the identified cerebellar case [5].

Of the total number of cases, 195 were supratentorial; 49 frontal, 14 fronto-parietal, 7 fronto-temporal, 2 fronto-temporo-parietal, 9 temporal, 6 temporo-parietal, 3 temporo-parieto-occipital, 23 parietal, 13 parieto-occipital and 6 occipital cases. In the basal nuclei and thalamus, 4 cases, intraventricular with 5 cases and 3 cases were in other locations. A total of 51 cases were identified as supratentorial lesions, without specifying the affected area. In infratentorial location, a single case was identified located in the right cerebellar lobe and our case, with intraventricular presentation, both cases of the same age at diagnosis and with similar histopathological findings. Treatment was reported in 92/197 cases (46.7%); 65/92 cases had surgery, 33 cases with partial resection, and

32 cases with total resection. Chemotherapy was received in 52 cases, and 80 cases received radiotherapy.

The authors Schmincke 1914*, Horten and Rubinstein 1976, Bennett and Rubinstein 1983, Holsten, et al. 2021, and Tietze, et al. 2022, with more than 50% (105 patients) of cases included, do not report information on surgical, chemotherapeutic, and/or radiotherapy treatment [8-11].

Of the total number of cases, 62 were reported alive at the time of publication, and the rest were lost and dead as our case. In 102/165 cases, the mean survival was 3 years (0.5 months-14 years), and surgical resection could not be correlated with survival.

Discussion

NB, FOXR2-activated is a rare, recently described tumor that presents in children. They correspond to 10% of all neoplasms previously referred to as primitive neuroectodermal tumors of the CNS [1,12]. There are cases of FOXR2 NB in the literature, diagnosed as ependymomas or glioblastomas before the WHO 2021 classification, and even after this classification, a case diagnosed as meningioma [13].

NB originates from neuroectodermal cells, although the exact cell that gives rise to it is not clear. Histologically, it is



characterized by a poorly differentiated pattern, many of them being previously diagnosed as primitive neuroectodermal tumor of the CNS due to the embryonic characteristics constituted by small, round hyperchromatic nucleus cells with scant cytoplasm, alternating with areas with clear cells with the appearance of neurocytic differentiation. The differentiated areas show ganglion cells on a histologically fibrillar background, like a ganglioneuroblastoma; the presence of both differentiation patterns is suggestive of CNS FOXR2 NBs similar histological appearance that is observed in the present case. Necrosis, high mitotic index, the presence of Homer-Wright rosettes, as well as infiltration into adjacent parenchyma, are evident as in any other embryonal tumor. IHC markers [1,6] are nonspecific, usually positive for Olig2, synaptophysin, NeuN, MAP2C, SOX10 and 1q gain by FISH with sensitivity and specificity of 100% [4,10,13,14]. Fibrillar glial acid protein staining is occasionally identified, although there are publications that report that it is not expressed in this type of tumor. The Ki67 proliferation index is high. Holsten et al., reported in eight cases, range from 12 to 50% with an average of 26% positive cells [1,10].

FOXR2 is a transcription factor located on the X chromosome, and its activation is associated with hypomethylation. The expression is absent in almost all normal postnatal human tissues and has been related as an oncogene in a large number of neoplasms of different types of cancer that represent 71% of the most frequent neoplasms (melanoma, endometrial cancer, non-small cell lung cancer) in adults and in pediatrics in NB, sarcomas and diffuse midline glioma with different epigenetic and genetic mechanisms of their expression. In NBs, the detection of FOXR2 has been studied only in supratentorial tumors, and they have not been described in the infratentorial region, which can be expected due to the rarity of the presentation. To date, 70 cases of the entire review had FOXR2 detected [10,11,14,15].

In the literature, it is reported that 85% of cases of CNS neuroblastoma occur in the first decade and 65% in the first 5 years of age. The mean age was 5.5 years with a range of 2 weeks to 18 years of age [6,13].

The clinical manifestations are nonspecific, although due to their mainly supratentorial presentation, signs associated with intracranial hypertension (vomiting and headache), neurocognitive impairment, and seizures predominate; in infants, the signs and symptoms are not so evident, because the sutures have not fused. The two cases of infratentorial presentation were characterized by cerebellar signs such as ataxic gait [16].

Dissemination at diagnosis has only been reported in the literature in two cases of CNS NBs; one of them to the neuroaxis by seeding through the CSF and extracranial metastasis (lymph node) in another case, in the present case, they were not documented [6].

Radiographically, CNS NBs are characterized by being heterogeneous with solid and cystic components or pure solids, and the findings of tomography (T1 and T2) and magnetic resonance imaging are nonspecific for this entity. In a systematic review conducted by Shimazaki, et al. in 34 cases, the frontal lobe was reported to be more frequent in 67.6%, cortical involvement in 85.3%, deep white matter in 97.1%, and in the ventricular system in 61.8%. Spectroscopy is expected to indicate the accentuated choline peak, indicating synthesis and degradation of the membrane, which is an indicator of hypercellularity [16,17]. A finding documented in the literature and observed in our experience is the fact that embryonal tumors of the CNS, including in NBs, are characterized by producing little or no peritumoral edema [11,17].

The survival reported by Von Hoff, et al. 2021 [5] mentions that the 5-year Progression-Free Survival (PFS) is $63\% \pm 8\%$ and the 5-year overall survival (OS) of $85\% \pm 5\%$, is very similar with Liu, et al. 2022 [3] with 5-year PFS of $66.7\% \pm 19.2\%$ and 5-year OS of $83.3\% \pm 15.2\%$, on the other hand, Schepke, et al. 2023 report that in their cases PFS and OS at 5 years was 100% in both and refers to the fact that all their patients received treatment with high-dose radiotherapy in the CNS and neuraxis, which for them was the factor that favored their patients. [2]

Surgical resection is one of the prognostic factors of great importance for the survival of CNS neoplasms, and treatment is based on American, European or Japanese protocols, in which they all have the same chemo agents, but with different application schemes. Although radiation therapy is the treatment of choice, its usefulness is limited in children younger than 3 years of age. The review that was conducted did not specify survival related to the type of resection (partial or total) in most of the cases reported. The present case survived 17 months to a partial resection of 50% coupled with chemotherapy and radiotherapy, well below than previously reported [18].

Conclusion

Neuroblastoma is a WHO grade 4 embryonal neoplasm that preferentially affects the pediatric group. Its location is predominantly supratentorial, most frequently affecting the frontal lobe. Only two cases are infratentorial, including the case to be reported.

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