Child's Nervous System
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CASE REPORT

A case of medulloblastoma in a patient with fetal ventricular enlargement

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Abstract

Medulloblastoma is the second-most common malignant tumor in children. Medulloblastoma has been categorized into four distinct molecular subgroups: WNT, sonic hedgehog (SHH), group 3, and group 4. We report on a male child with medulloblastoma, in whom an enlarged ventricle was diagnosed in utero. Magnetic resonance imaging showed cyst formation in the cerebellar hemisphere initially, with tumor growth being indicated later. Tumor resection was performed when the boy was 12 months old. The histological findings showed extensive nodularity. Further genetic analysis revealed the tumor to be SHH type. This is the first description of a medulloblastoma observed from the fetal stage. Our findings in this case indicate that cyst formation may be the pre-neoplastic lesion of SHH-subtype medulloblastomas.

Keywords Medulloblastoma · Cyst formation · Sonic hedgehog subtype

Introduction

Medulloblastoma is the second-most common pediatric brain tumor, accounting for 10–20% of primary CNS neoplasms and approximately 40% of all posterior fossa tumors [1, 2]. Adjuvant therapies, including radio- and chemotherapy, have improved the outcome for patients with these tumors, with the 5-year survival rate being 50–80% [3–6].

There is also evidence that medulloblastomas should be classified into 4 distinct molecular subgroups (WNT, sonic hedgehog [SHH], group 3, and group 4), and that the subgroup classification is a significant prognostic factor [7–11]. Owing to the malignant nature of this tumor, immediate excision is required, thus limiting the ability to study its natural history. We present the case of a male child with medulloblastoma in whom ventricular enlargement was detected in utero at 30 weeks gestation.

Case report

A male fetus, screened by routine fetal ultrasound, was found to have an enlarged ventricle. Magnetic resonance imaging (MRI) of the brain was performed at 30 weeks gestation. Brain MRI showed an enlarged ventricle, but no tumor or obstructive hydrocephalus was observed (Fig. 1).

A follow-up MRI was performed when the boy was two months old, which showed no change in ventricle

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size, but cyst formation was found in the cerebellum (Fig. 2c). This patient also had outpatient visits every 1–2 months thereafter. His neurological examination was normal, including the patient's head circumference. Because there were no obvious abnormalities, imaging studies were not performed until the boy was 12 months old. A follow-up MRI revealed that the volume of the cyst had increased and a nodular lesion within the cyst enhanced at a T1-weighted post-gadolinium sequence (Figs. 2 and 3).

Due to rapid progression of the tumor, it was subtotally resected by surgery when the boy was 13 months old (Fig. 3c). The operation was performed in the left lateral position and an L-shaped skin incision was made in the right occipital region (Fig. 4e). After incising the dura mater, a fence post was inserted into the left side of the mass by a surgical navigation system. A cortical incision was then made in order to approach the cyst under a microscope. Tumor identification was not particularly difficult due to the fact that the mass existed in the deep part of the cyst. The tumor was pale red and not hemorrhagic (Fig. 4f), and in the end it was subtotally resected.

Pathological findings showed desmoplastic/nodular medulloblastoma, and immunohistochemistry showed the MIB-1 labeling index was 40%, and p53 protein was negative (Fig. 4a–d). Genetic analysis, using both the gene expression profile determined by NanoString and DNA methylation array, revealed the tumor to be SHH type [12]. Sanger sequencing and next-generation

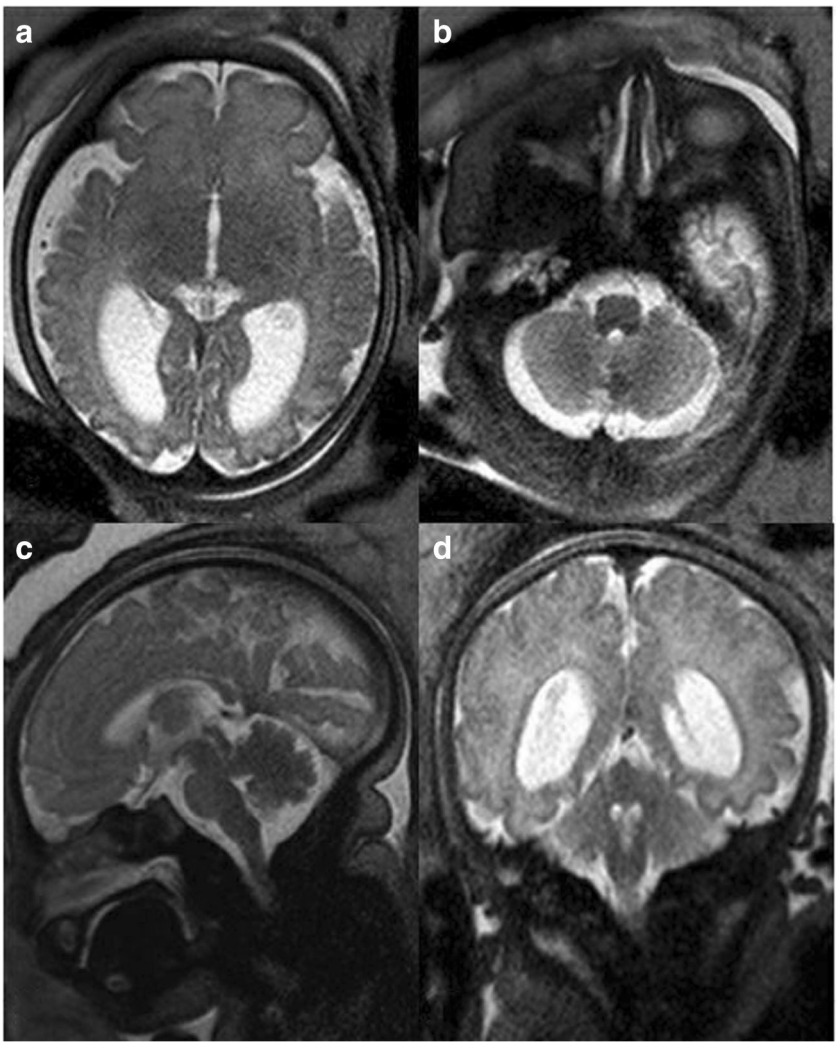

Fig. 1 Brain MRI at 30 weeks gestation showed enlargement of the posterior horn of the lateral ventricle, but no tumor or obstructive hydrocephalus was observed (**a**, **b** axial plane, T2-weighted image; **c** sagittal plane, T2-weighted image; **d** coronal plane, T2-weighted image)

sequencing showed 2 mutations in *PTCH1* (c.3478_3486delACCATCCTC, p.Thr1160_Leu1162del, and c.1405delG, p.Val469fs), but no mutation in *TP53*, *SUFU*, or *SMO*.

Adjuvant treatment with chemotherapy according to the HIT-SKK 92 protocol was performed [4]. Follow-up MRI obtained at age10 years revealed no regrowth.

Discussion

According to the molecular classification system, medulloblastomas can be categorized into 4 distinct subtypes—WNT, SHH, group 3, and group 4. Each subtype is independent and there is no overlap among subtypes based on genetic analysis [8].

The SHH-subtype medulloblastoma is characterized by aberrant SHH signaling that is often driven by inactivating mutations in PTCH1. These medulloblastomas tend to arise in very young children, and display a "large cell-anaplastic" or "desmoplastic" character. The PTCH1 germline mutation is a well-known gene in nevoid basal cell carcinoma syndrome (NBCCS) where 5% of patients go on to develop medulloblastoma [13]. Germline genetic screening was not performed, and therefore NBCCS could not be confirmed, although there was no family history and the diagnostic criteria for NBCCS were not fulfilled.

Mouse models have shown that WNT-subtype tumors infiltrate the dorsal brainstem, while SHH-subtype tumors are localized within the cerebellar hemispheres. Mouse experiments have shown the upper rhombic lip (URL) at embryonic day E11.5 and E15.5 and the cerebellum to be the most common sites of the SHH-subtype signature gene expression [14, 15]. These results suggest that gene expression occurs in the early days of embryonic development. The tumor in our patient was found at a very early stage of development. Since we did not observe tumor formation in the fetal MRI, it is suggested that gene expression occurred earlier than morphological change.

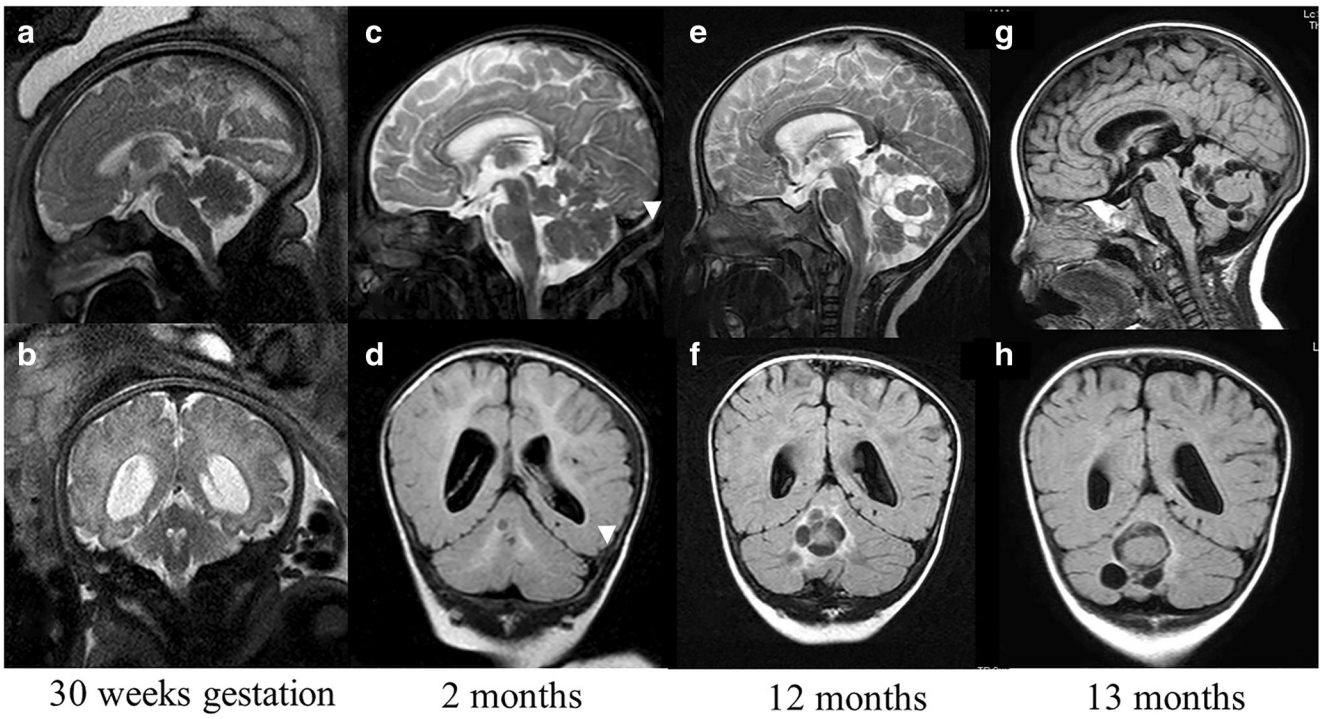

Fig. 2 Brain MRI at 30 weeks gestation (**a**, **b**), 2 months old (**c**, **d**), and 1 year old (**e**, **f**) showed that cyst formation is observed in the cerebellar hemisphere at 2 months old (white arrow) and tumor is observed at 12 months old. Enlargement in tumor size was observed pre-operatively at 13 months old (**g**, **h**). (**a** sagittal plane, T2-weighted image; **b** coronal plane, T2-weighted image; **c** sagittal plane, T2-weighted image; **d** coronal plane, fluid-attenuated inversion recovery; **e** sagittal plane, T2-weighted image; **f** coronal plane, fluid-attenuated inversion recovery; **g** sagittal plane, T1-weighted image; **h** coronal plane, T1-weighted image)

Although medulloblastoma usually causes obstructive hydrocephalus, we observed an enlarged ventricle at the fetal stage, prior to tumor development. This patient did not have any structures obstructing the cerebrospinal fluid pathway on fetal MRI. Therefore, we speculate that this patient's ventricular enlargement occurred for the same reason as communicating hydrocephalus, which is entirely coincidental with the tumor. Interestingly, there have been reports of cases of medulloblastoma after treatment of arachnoid cyst [16], so some cases of medulloblastoma may be accompanied by abnormalities in cerebrospinal fluid circulation.

Several studies have reported that distinctive MRI features are associated with the medulloblastoma histologic subtypes. The presence of focal cysts was positively correlated with classic medulloblastoma and desmoplastic medulloblastoma [17]. Furthermore, Taylor has indicated that the SHH-type medulloblastoma often shows the desmoplastic/nodular histologic subtype [9]. During follow-up of the present patient, cyst formation was noted at an early stage before the tumor was identified. In other words, the tumor existed but it could not be detected, at least not by plain MRI, at that stage. There may be an unexplored link between cyst formation and medulloblastoma, as there are other case reports of medulloblastoma after treatment with quadrigeminal arachnoid cyst [16] besides our case. Thus, a cystic lesion of the posterior cranial fossa in a pediatric case may need to be followed with care after treatment.

This is the first description of a medulloblastoma observed by serial MRI from the fetal stage. During the observation period, cyst formation and tumorigenesis were observed in time sequences. This case may provide insight into the possible natural history of SHH-subtype medulloblastomas.

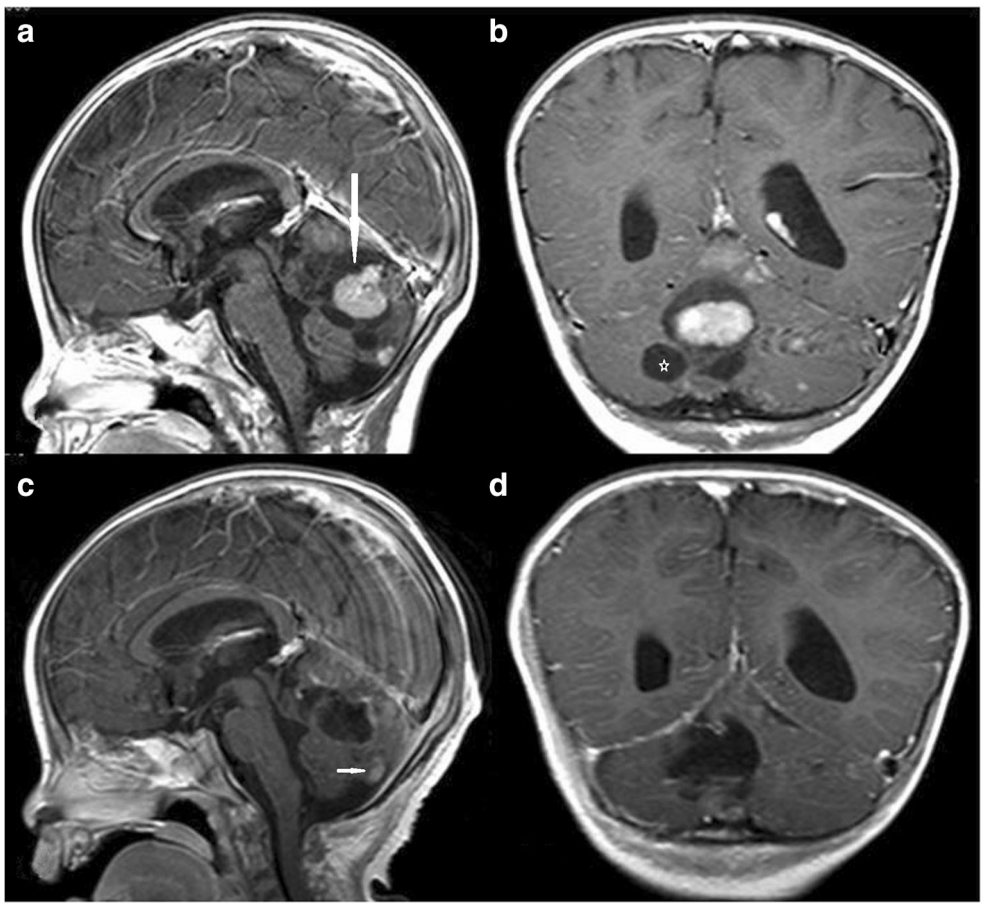

Fig. 3 MRI T1 with Gd before operation showed a round, enhancing lesion (long arrow) with a cyst (star) in the cerebellar hemisphere (**a**, **b**). Postoperative MRI showed that the tumor is partially resected and shows the residual tumor (short arrow) (**c**, **d**)

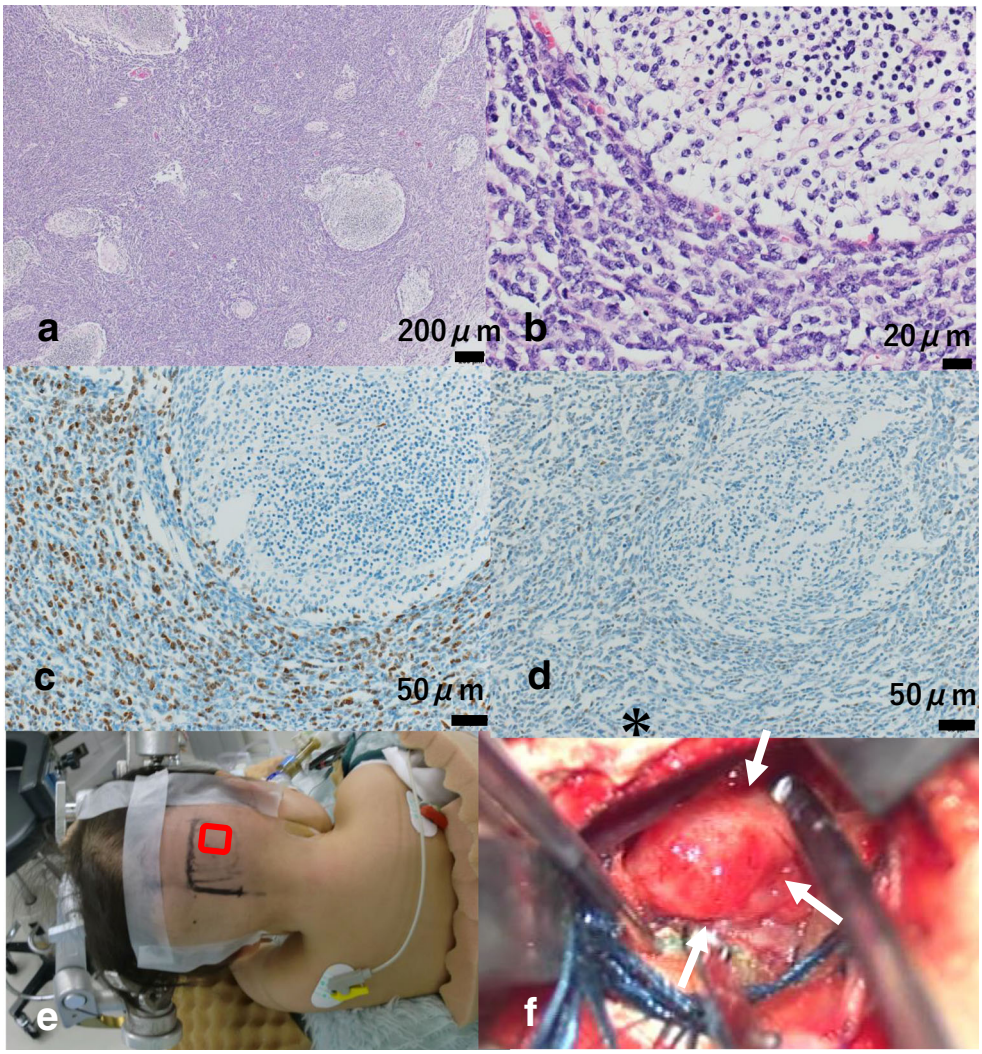

Fig. 4 Hematoxylin and eosin staining shows desmoplastic/nodular type (**a** × 10, **b** × 100), immunohistochemistry shows MIB-1 proliferation index was 40% (**c** × 50), and p53 protein was negative (**d** × 50). **e**, **f** Intraoperative images. **e** Surgical position and skin incision (black line), craniotomy site (red line) are shown. **f** Tumor (white arrow) detached from the surrounding brain just before removal. The single asterisk indicates rostral side

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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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