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Atypical presentation of paediatric giant intraventricular cavernoma with familial cavernomatosis: Case report and literature review

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Abstract

Introduction: A giant cavernous malformation (GCMs) occurring during childhood is different to smaller cavernous malformations in clinical and imaging presentations and, at presentation, giant lesions are often mistaken for tumour lesion.

Observations: We report the case of a 2-year-old girl presenting a giant intraventricular cavernoma (63x52mm) with a family history of cavernous malformations. The lesion radiologically mimics a tumor arising from the choroid plexus, intensely enhancing after injection of gadolinium. The magnetic resonance imaging also revealed the presence of multiple micro cavernomas. The diagnosis of giant cavernous malformation was confirmed by histopathologic analysis. Trio exome sequencing identified a heterozygous pathogenic variant in KRIT1 and a heterozygous variant of unknown significance in PDCD10, both inherited from her symptomatic mother.

Conclusion: Our article describes for the first time a pediatric giant cavernoma presenting with a family history, a positive genetic testing and multiple cavernous malformations at diagnosis. There are not many case reports nor literature about those rare lesions. The diagnosis of GCMs should be always considered in both diagnostic and preoperative assessments in case of positive family history.

Abbreviations

CT: computer tomography

MRI: magnetic resonance imaging

EEG: electroencephalogram

GCM: giant cavernous malformation

CM: cavernous malformation

CCM: cerebral cavernous malformation

FCCM: familial cerebral cavernous malformations

gnomAD: Genoma Aggregation Database

RNA: RiboNucleic Acid

WI: weighted imaging

Gd: Gadolinium

TSE: Turbo Spin Echo

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Introduction

Giant Cavernous Malformations (GCMs) differ significantly from smaller cavernous malformations both clinically and on imaging. Due to their size and radiologic appearance, they are frequently misdiagnosed as tumors, potentially leading to inappropriate treatment plans. This case highlights the importance of considering GCMs in differential diagnoses, especially in pediatric patients with a positive family history. Here, we present a rare case of giant cavernoma presenting with a family history, a positive genetic testing and multiple cavernous malformations at diagnosis. The article aims to raise awareness of the importance of reporting these rare lesions, accompanied by comprehensive genetic data. Such thorough reporting helps clinicians in making accurate diagnoses and managing the condition, ultimately contributing to better patient outcomes and a clearer understanding of the genetic basis of cavernous malformations.

Material and Methods

Clinical, radiological, surgical and genetic features were retrieved from the electronical patient management system with the agreement of the parents. Additionally, a scoping literature review on cavernous malformations occurring during childhood was performed.

Observations: We describe the case of a 2-year-old girl who was reported to have a recent balance disorder. This appeared under form of repeated sudden falls without loss of contact, without loss of urine, without associated abnormal movements. After each episode, she got up spontaneously and started her activities again. The falls were more oriented towards the right side and parents also noticed stereotypical tilting movements of the head towards the same side. The frequency and duration of these falls had increased, alarming parents who referred to the emergency pediatric department.

Furthermore, she was in excellent general condition, with no vomiting, headache or fever.

She has no past medical or surgical history, but a family history of cavernous malformations (first and second-degree relatives). A complete and full neurological examination showed no abnormalities with an adequate psychomotor development for age.

A computer tomography (CT) scan of the brain revealed a large lobulated hyperdense mass of the right lateral ventricle, with an oedema of the peri-ventricular white matter and a significant mass effect. The observed magnetic resonance imaging (MRI) features, which are described in detail in figure 1, confirmed a large right intraventricular lesion (63x52mm) corresponding in the first hypothesis to a tumor of the choroid plexus.

The lesion appeared polilobulated, displaying high signal heterogeneity, with cystic and hemorrhagic components, intensely enhancing after injection of gadolinium. MRI also revealed the presence of multiple foci of magnetic susceptibility artifacts at the infra and supra-tentorial level which could suggest micro cavernomas (Figure 2).

The hypothesis of a giant cavernoma was then considered.

An electroencephalogram (EEG) confirmed the presence of a structural lesion, highly epileptogenic, in the right hemispherical region. Antiepileptic therapy with Levetiracetam was started at a dose of 40 mg/kg/day.

Maximal safe resection of the lesion was achieved. Intraoperatively, the lesion presented typical signs of cavernoma: a multi-loculated and well-defined dark-bluish mass surrounded by edema. The adjacent parenchyma showed some bleeding stigmata recognizable as yellow-coloured hemosiderin deposits.

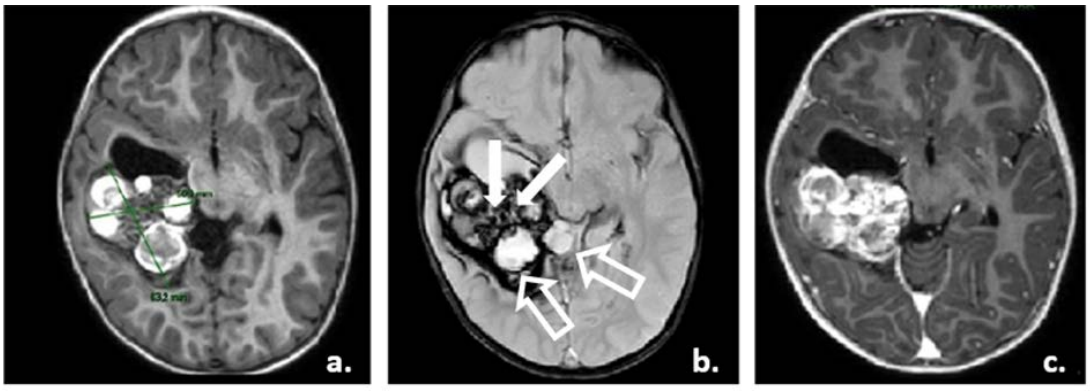

Figure 1: T1WI before gadolinium (Gd) shows a large intraventricular lesion (right lateral ventricle), polilobulated, heterogeneous, with numerous cystic and haemorrhagic components (a).

T2*WI shows heterogeneity of the lesion with "larges bubbles of blood" (→) associated with "pepper and salt" areas (⇨) (b.).

T1WI shows an intense enhancement of the lesion after Gd injection (c).

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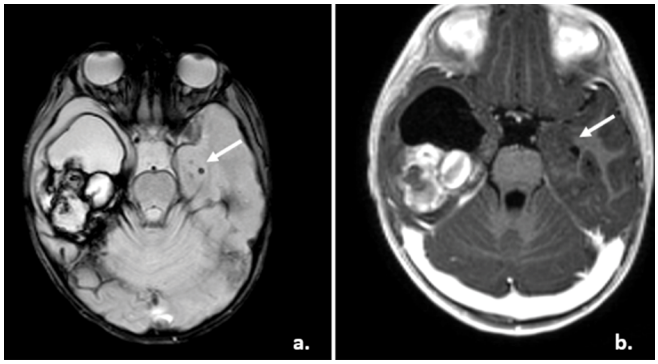

Figure 2: T2*WI shows the presence of multiple smalls foci of magnetic susceptibility artefacts evoking a diagnostic of microcavernomas (a). No enhancement is observed (b).

The diagnosis of cavernous malformation was confirmed by histopathologic analysis. Trio-exome sequencing identified a heterozygous pathogenic variant in KRIT1 and a heterozygous variant of unknown significance in PDCD10, both inherited from her symptomatic mother presenting a spinal cord cavernoma.

Postoperative brain MRI performed 1 month after surgery showed a small right parietal residue without signs of haemorrhagic complications (Figure 3).

The patient progressed with complete regression of preoperative symptoms and a normal EEG profile at 5-month follow-up.

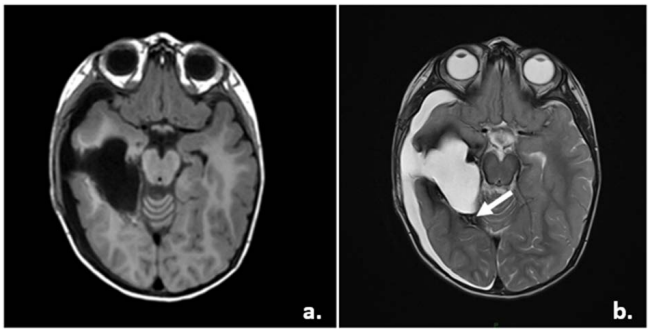

Figure 3: T1WI post operative status of a large right hemispherical cavernoma satisfactory without evidence of haemorrhagic complications (a). T2TSEWI shows the persistence of a small right parietal residue (b).

Discussion

A cavernoma is a cluster of abnormal blood vessels, usually found in the brain and, rarely, in the spinal cord. It is filled with blood that flows slowly through vessels that are like "caverns" and represent 1.7 to 18% of all vascular malformations in children [1,2]. The most frequent localization is supratentorial brain area (76,3%), with a preponderance for frontal region [2]. A cavernoma can vary in size, from a few millimetres to several centimetres with a reported mean size of 1,4 cm [3,4]. Lawton et al [5] in 2004 defined a giant cavernous malformation (GCM) as one that has a diameter of more than 6 cm. However, Kan et al [6]. in 2008, proposed the most accepted definition, based on the radiographic features: a lesion larger than 4 cm in at least one dimension (this represents the threshold for the characteristic multicystic MRI appearance of GCM). The biggest described lesion was 14 cm [7] with a mean size ranged between 4 and 6 cm (50.81%; 40.98% >6 cm; 8.19% >10 cm) [8].

GCM is a rare lesion and no data on its prevalence among all cavernomas are reported in the literature.

A giant cavernous malformation occurring during childhood is different to smaller cavernous malformations (CMs) in clinical and imaging presentations and, at presentation, giant lesions are often mistaken for tumour lesion. In this clinical case, the unusual appearance, localisation, and the intense enhancement after injection of gadolinium, led the clinician to this differential diagnosis as well.

Clinically, all GCM are symptomatic and characteristics of increased intracranial pressure and local mass effect are observed more frequently. In small cavernoma 13,8% of patients are asymptomatic, and the main clinical manifestation is seizure [2].

A male predominance was observed and not reported in small cavernoma. In a recent paediatric large systematic review of 61 GCM [8], 55.73% of patients were male, data which confirms the male predominance already described by Ozgen et all. [9] and Shroff et al [10].

Most patients with a GCM were diagnosed under 2 years of age (40-44%) [8-10], when the mean age of diagnosis for the smallest cavernoma is 9,1-10,2 years of age [2].

The most common MRI presentation of cerebral cavernous malformations (CCMs) in children is a large, well-delineated acute or subacute hematoma with a spherical shape, sharp and regular margins and no or limited perilesional oedema. Mass effect is rare [11]. On the contrary, mass effect and oedema were reported in 100% of cases of GCM with no contrast enhancement in 89% of cases. The typical MRI presentation is a large cavernoma with “bubbles of blood” appearance in T1 and hemosiderin rim with central signal of heterogeneous intensity in T2 [9,10].

Among children with CCMs, CM multiplicity was reported in 12,6-15% of cases [2,12]. In a 2022 study included 129 paediatric patients diagnosed with CCM admitted between 2003 and 2020 in the University Hospital of Essen (Germany): 42,1% of patients had multiple CCM [13]. In the same study, CM family history was reported in 27,1% of patients (10% according to Gross et al. in 2015). CCMs can manifest sporadically or follow an autosomal dominant

pattern with varying penetrance. Approximately 80% of familial CCM cases are linked to three genetic loci: CCM1/Krit1, CCM2/MGC4607, and CCM3/PDCD10 [14-16].

In the most recent systematic review about GCM [8] (61 cases of GCM), all patients presented a single cavernous malformation and cavernoma multiplicity was not reported. A total of 4.91% cases showed a confirmed or suspected familiar cavernomatosis, but only one patient was genetically tested and genetic testing did not reveal mutations.

A multicenter retrospective cohort study [18] involving four tertiary paediatric institutions including all children with a diagnosis of familial cerebral cavernous malformations (FCCM) (presence of ≥ 1 CCM associated with either a positive family history and/or a confirmed pathogenic variant in the CCM1-3 genes in the affected patient or in a first-degree relative) found five giant lesions out of 587 cavernomas (41 children, all children except one with multiple CCM at diagnosis). Unfortunately, no further information on these GCMs is reported (size, location, genetics).

In our study, genetic testing identified a heterozygous mutation in the KRIT1 gene (c.2026-12A>G variant) and in the PCD10 gene (c.151-3T>C variant) in both the patient and her mother.

Monoallelic abnormalities in KRIT1 lead to familial cerebral cavernomatosis type 1 (OMIM 116860) and monoallelic PDCD10 abnormalities lead to familial cerebral cavernomatosis type 3 (OMIM 603285), both through autosomal dominant transmission.

The c.2026-12A>G variant is extensively documented in cerebral cavernomatosis patients [18-22], and it is present in the Genome Aggregation Database (gnomAD). Functional studies showed that the variant had an effect on the splicing of KRIT1 [20,21]. The ClinVar database (https://clinvarminer.genetics.utah.edu/variants-by-gene/KRIT1/condition/not%20provided/pathogenic) classifies this variant as pathogenic.

The c.151-3T>C variant in the PDC10 gene is not documented in the literature and is absent in the gnomAD. Positioned outside the splice consensus site, its neighboring variant, c.151-1G>C, at the consensus splicing site, is reported as a pathological variant in cerebral cavernomatosis [22]. However the SpliceAI (a deep learning-based tool to identify splice variants) [23] peadiatrician does not foresee a pathological impact of the c.151-3T>C variant on PDCD10 RiboNucleic Acid (RNA) splicing, leading us to classify this variant as a variant of unknown clinical significance (class III).

The natural history of familial giant cavernoma has not yet been studied.

Conclusion

Giant cavernoma are uncommon lesions, and giant familial cavernoma are even more rare. There are not many case reports nor literature about those lesions. Giant cavernous malformations in children are different to smaller CMs in clinical and imaging presentations and represent a diagnostic challenge.

Our article presents, for the first time, a paediatric giant cavernoma presenting with a family history, a positive genetic testing and multiple cavernous malformations at diagnosis

The diagnosis of GCMs should be always considered in both diagnostic and preoperative assessments in case of positive family history.

The clinical impact of the KRIT1 variant is confirmed in both the patient and her mother, while the effect of the PDCD10 variant remains uncertain. Variants of uncertain significance use in the clinical context is challenging and literature often omit this kind of data.

This article highlights the importance of systematic reporting of these unusual lesions, accompanied by comprehensive genetic data. Such reporting aids clinicians in accurate diagnosis and management, while also contributing to the groundwork for future systematic reviews of such lesions.

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Statements

Statement of Ethics: The parents of the patient provided their written informed consent for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/ national guidelines.

Conflict of interest statement

The authors declare no conflicts of interest to declare.

Author contributions

FIORESE Elena: First author, wrote the article based on the current literature and applied revisions from the other authors, approved the final version to be published

RODESCH Marine: Substantial contribution to the conception and design of the work. Critically revising it thoroughly. Approved the final version to be published.

DAVID Philippe: Substantial contribution to the conception of the work and critically revising it, in particular for the radiological points. Choice and comments on the appropriate pictures. Approved the final version to be published.

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COPPENS Sandra: Substantial contribution to the conception of the work, drafted some part of the work and reviewed literature. Approved the final version to be published.

SCULIER Claudine: Critical review of the article and approval of the final version to be published.

LEBRUN Laetitia: Critical review of the article and approval of the final version to be published.

DE WITTE Olivier: Critical review of the article and approval of the final version to be published.

FRICX Christophe: Critical review of the article and approval of the final version to be published.

GILIS Nathalie: Last author, Substantial contribution to the conception and design of the work and critically revising it thoroughly. Approved the final version to be published.

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