CASE REPORT



Fatal intracranial hemorrhage from brain AVM in a 7-week-old infant: case report and recent literature review

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Abstract

Brain arteriovenous malformations (AVMs) are vascular abnormalities that typically present with spontaneous hemorrhage, seizure, or as a mass lesion. Pediatric brain AVMs are rarely diagnosed but carry a higher rate of rupture. We report a 7-weekold infant with rapid fatal intracranial hemorrhage from an undiagnosed brain. AVM confirmed at autopsy. Literature review on pediatric patients who had acute death caused by previously undiagnosed brain AVM from 1992 to 2018 revealed that cerebellum is the most frequent location of such AVMs, followed by thalamus. All the children had extensive intracranial hemorrhage that led to their deterioration despite surgical intervention.

Keywords Arteriovenous malformation · Intracranial hemorrhage · Death · Infant · Autopsy

Introduction

Cerebral arteriovenous malformations (AVMs) are lesions composed of disorganized arrays of thick- and thin-walled vessels penetrating the brain parenchyma and often extending into the leptomeninges, associated with gliosis, inflammation, and hemosiderin-laden macrophages in the intervening brain. They typically present with spontaneous hemorrhage, mass effect, or seizure [1]. They are considered as congenital vascular abnormalities, although rare identification of brain AVMs in infants have challenged this view [2–5]. The pathophysiology of brain AVM is not well-understood. A

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combination of genetic, molecular, and environmental factors contribute to their formation, growth, and rupture [6]. It is well-recognized that a higher prevalence of brain AVM is associated with syndromic diseases including hereditary hemorrhagic telangiectasia (HHT), cerebrofacial arteriovenous metameric syndrome (CAMS), and hereditary neurocutaneous angiomatous malformations [7]. The peak incidence of AVMs is between 20 and 40 years of age. Pediatric brain AVMs are rarely diagnosed, but carry a higher rate of rupture than in adults, due to the fact that most of them are only detected after rupture [8]. AVM is the most common cause of intracranial hemorrhage in pediatric patients, although germinal matrix hemorrhage is the most common cause in preterm neonates.

We report a 7-week-old female infant with a previously undiagnosed sporadic form of brain AVM, who had catastrophic intracranial hemorrhage and rapid death. A literature review on pediatric patients who had rapid death caused by previously undiagnosed intracranial AVM from 1992 to 2018 revealed 16 cases.

Case presentation

A 7-week old previously healthy female infant experienced respiratory distress following a feeding. Cardiopulmonary resuscitation was initiated immediately by the patient's father and then by paramedics. In the local hospital, she was





emergently intubated for agonal breathing. MRI showed left cerebellar bleeding with acute hydrocephalus. An external ventricular drain was placed, and the patient was transferred to UCLA. Head CT and MRI showed large bilateral cerebellar hematomas with extensive intraventricular rupture and regional mass effect with hydrocephalus (Fig. 1A and 1A'). The differential diagnosis included ruptured AVM, hemorrhagic brain tumor, or dural sinus thrombosis. The size of the ventricular system decreased following successful interval placement of a ventriculostomy catheter. However, persistent findings of cerebral edema with decreased density of the brain and loss of gray-white matter differentiation were noted. CT angiography did not reveal evidence of vascular malformation or patent intracranial aneurysm (Fig. 1B). Despite aggressive intracranial pressure management, the patient remained unresponsive off sedation, showed lack of brain stem reflexes with fixed, dilated pupils, no cough or gag, and no response to pain stimuli. The patient expired 40 h after the initial onset of symptoms.

Neuropathologic findings

The unfixed brain at the time of autopsy weighed 700 g (expected normal weight for age is 560 g) [9]. There was no fracture in the base of the skull. There was yellow-green

discoloration on the inferior surface of both temporal lobes (Fig. 2A). The cerebellum and brainstem were friable, and there was extensive clotted blood apparently originating from the cerebellum. The volume of hematoma was difficult to evaluate. Sections of the brain showed a large hematoma within the cerebellum, with blood extending into the entire ventricular system, causing extensive dilatation of the lateral ventricles (Fig. 2B). The gyral pattern appeared symmetrical and unremarkable.

Microscopic examination revealed a large vascular lesion within the cerebellum, consisting of disorganized arrays of dilated vessels penetrating through and separated by the cerebellar parenchyma, which showed significant gliosis (Fig. 3C). The vessels varied in caliber and wall thickness, and some vascular channels showed focal loss and fragmentation of the elastica (Fig. 3E-H). The extensive altered blood pigment throughout the subarachnoid space and adjacent to the AVM suggest prior "leakage" of blood from it (Fig. 3D). There was also dense subarachnoid neutrophil infiltration, but GMS and Gram stains were negative for infectious agents (Fig. 3A-B). This was interpreted as an inflammatory meningeal reaction secondary to remote hemorrhage. Within the AVM, we identified an abnormal artery with potential rupture sites (Figs. Fig. 4AA", B-B' and C-C'). EVG and Trichome staining highlighted discontinuous elastica in the vessel walls (Fig. 4B" and C").

Fig. 2 Brain Autopsy gross findings. (A) Ventral view of brain showed disrupted cerebellum covered with fresh blood clot. There is yellow-green discoloration on the ventral surface of bilateral frontal and temporal lobes, indicating chronic prior hemorrhage. (B) Coronal section revealed a large hematoma extending from cerebellum throughout the ventricular system





Fig. 3 Microscopic findings. (A) Dense subarachnoid neutrophil infiltration on the cerebral surface. (B) Magnified view of neutrophils and hemosiderin-laden macrophages. (C) AVM in the cerebellar parenchyma. (D) Abundant hemosiderin-laden macrophages adjacent to AVM. (E-H) Disorganized and dilated vessels within AVM, showing damaged



Fig. 4 Microscopic finding of AVM A-A'': H&E staining of the AVM displays abnormal vessels (A, dotted square). A' highlights an abnormal artery and the putative rupture sites (A''-A'''). B-B'' and C-C'': EVG (B, B') and Trichrome (C, C') staining of the putative rupture site and discontinuous elastica within arterial wall (B'' and C'', black arrowheads). Elastica is absent in the vascular segment shown in B' and C'. Scale bar, 5mm

dilated and fragmented vessel wall by Hematoxylin and eosin (H&E) staining (E), Verhoeff-van Gieson (EVG) staining for elastic fibers (F), Masson's Trichrome staining for blood vessels (G), and anti-smooth muscle actin (SMA) antibody staining (H)

Discussion

We describe a 7-week-old-infant who experienced a sudden onset of cardiopulmonary arrest. Imaging revealed a large hemorrhage in the cerebellum with dilated blood-filled ventricles. Autopsy confirmed rupture of a large AVM in the deep cerebellum, with intraventricular extension, causing hydrocephalus. Altered blood pigment throughout the subarachnoid space, suggested that recurrent minor hemorrhages had occurred prior to this catastrophic event.

Intracranial hemorrhage in childhood is a rare event. The most frequent causes for pediatric intracranial hemorrhage are vascular malformations; AVMs are ten times more frequent than saccular aneurysms [10]. Other causes include infections and coagulopathies. Lack of warning signs for spontaneous intracranial hemorrhage from vascular malformations makes the diagnosis and management extremely difficult, and mortality is high.

Compared with AVM hemorrhages that mostly occur in childhood, periventricular/intraventricular hemorrhage (PIVH) is a frequent complication of prematurity, occurring in 25 to 30% of all very low-birth-weight preterm infants [11]. Up to 50% of PIVH patients develop post hemorrhagic hydrocephalus (PHH) [12]. Such conditions are usually seen in the perinatal period. The average age at diagnosis of AVM is 13.3 ± 3.8 years (range 3–18 years) [13]. Although AVMs account for only 1 to 2% of spontaneous intracranial hemorrhage in adults, they are the cause of 14 to 57% of intracranial hemorrhage in the pediatric population (age < 18 years) [14]. Hemorrhagic presentation is significantly more common in deep locations (basal ganglia, thalamus, and brainstem) than in cortical locations (frontal, temporal, parietal, and occipital lobes) [15].

The AVMs are considered congenital vascular lesions consisting of abnormal direct connections between the arterial and venous systems. It is proposed that AVMs are formed by a mutation early in embryogenesis, during which absorption of multiple pial-dural subarachnoid veins happens with subsequent dynamic events that lead to growth [8]. Both persistence of a primitive arteriovenous connection and development of such a connection before or after birth have been suggested as being of etiologic importance [7]. Yet the frequent identification of postnatal formation of brain AVMs has challenged this view [2–5]. More than 20 genes or molecules have been reported to cause or associate with formation, growth, and rupture of brain AVMs [6]. AVMs have been described in the families with the hereditary hemorrhagic telangiectasia (HHT) and hereditary neurocutaneous angiomatous malformations [7]. HHT is associated with mutations in the transforming growth factor- β signaling cascade, which is necessary for vascular integrity and vasculogenesis. Affected patients usually have a family history of epistaxis and facial telangiectasia. Infants with a family history of HHT are at risk for sudden and catastrophic intracranial hemorrhage, therefore, a preemptive diagnosis may potentially identify and prevent more serious sequelae [16]. Per HHT international guidelines, for children with possible or definite HHT, screening for cerebral vascular malformations with

Table 1 17 cases of sudden death caused by undiagnosed sporadic brain AVM in pediatric patients

Case	Study series	Age(yrs)	Gender	AVM location	Presentation symptoms	CT angiography (AVM detection)	Surgical intervention [#]	Autopsy
1	Byarda, et al., 1992 [18]	3	М	Parietal	None	Not Performed	No	Yes
2	Rodesch, et al., 1995 [19]	2 m-1 yr	NS	Perimesenceph, multiple	Hydrodynamic disorders*	Yes	Yes	No
3	Morentin, et al., 2000 [20]	12	F	NS	Migraine with aura	Not Performed	No	Yes
4	Chul Suh, et al., 2001 [21]	18d	М	Parieto-occipital	NS	Not Performed	Yes	Yes
5	Tomcik, et al., 2011 [22]	14	F	Thalamus	Headache, LOC	Not Performed	Yes	Yes
6	Matschke, et al., 2013 [23]	14	М	Frontotemporal	Headache, LOC	Not Performed	No	Yes
7	Alapati, et al., 2013 [24]	6	М	NS	Headache, Cardiac arrest	Not Performed	No	Yes
8	Alapati, et al., 2013 [24]	10	М	NS	Headache, Cardiac arrest	Yes	No	Yes
9	Sison, et al., 2017 [25]	13	М	Thalamus	Hemiparalysis, LOC	Yes	Yes	NS
10	Riordan, et al., 2018 [26]	13.4	F	Temporal	Headache, LOC	Yes	Yes	NS
11	Riordan, et al., 2018 [26]	16.4	F	Thalamus	Seizure, LOC	Yes	Yes	NS
12	Riordan, et al., 2018 [26]	11.6	М	Thalamus	Headache, Seizure	Yes	No	NS
13	Riordan, et al., 2018 [26]	12.6	М	Cerebellum	Cardiac arrest	Yes	Yes	NS
14	Riordan, et al., 2018 [26]	7.2	М	Cerebellum	Headache, Cardiac arrest	Yes	Yes	Yes
15	Riordan, et al., 2018 [26]	6.8	F	Cerebellum	Headache, LOC	Yes	Yes	Yes
16	Riordan, et al., 2018 [26]	12.8	М	Cerebellum	Headache, Cardiac arrest	Yes	Yes	NS
17	Zhang, et al., 2019	7w	F	Cerebellum	Respiratory distress, Agonal breathing	Yes (Not found)	Yes	Yes

NS not specified, LOC loss of consciousness, ASD autism spectrum disorder

[#] Procedures including craniotomy, suboccipital craniectomy, C1 laminectomy, extraventricular drainage, ventriculoperitoneal shunt or embolization were performed to decompress the elevated incranial pressure caused by large hemorrhage

*Macrocephaly, atrophy, ventricular enlargement [19]

unenhanced MRI is recommended in the first 6 months of life or at the time of clinical diagnosis [17].

The majority of pediatric AVMs are sporadic with no characteristic symptoms during childhood other than sudden hemorrhage, which makes diagnosis and management difficult. We performed a literature search on PubMed with key words "death", "brain AVM", or "pediatric patients". We focused on previously undiagnosed sporadic intracranial AVM only; we reviewed studies from 1992 to 2018 and found out 10 studies that met our criteria. Among the 221 cases reported, 16 children had acute death from previously undiagnosed brain AVM (Table 1). Riordan et al. reported 7 cases, the largest group reported on this topic [26].

We analyzed the characteristics of the reported cases together with our case. Among 17 children, there were 1 neonate, 2 infants, and 14 children with age range from 3 to 16 years. The youngest child had died at the 19th day of life [21]. Ruptured AVM affected male children (58.8.5%, 10/17) more commonly than females. Cerebellum (29.4%, 5/17) was the most frequent location of the fatal AVM, followed by thalamus (23.5%, 4/17), frontotemporal (5.9%, 1/17), temporal (5.9%, 1/17), parietal-occipital (5.9%, 1/17), and parietal lobe (5.9%, 1/17) were reported. One infant had multiple AVMs in the perimesencephalic area [19]. Headache (52.9%, 9/17) was the major presenting symptom, followed by loss of consciousness (35.3%, 6/17), and cardiac arrest (29.4%, 5/17). Seizure was found in 1 child (11.8%, 2/17) and hemiparesis was found in 1 child (11.8%, 2/17). Respiratory distress (5.9%, 1/17), migraine with aura (5.9%, 1/17), hydrodynamic disorders (macrocephaly or ventricular enlargement, 6.3%, 1/17) were also identified. One child presenting with autism spectrum disorder was diagnosed with a large AVM in the basal ganglia/thalamus/internal capsule [25]. Of these children, 64.7% (11/17) had CT angiography performed: 6 did not have CTA because of rapid deterioration of vital signs. In our case, although confirmed by autopsy, the lesion was not found on CTA (Fig. 1B), probably due to its small size. All 17 children had intracranial hemorrhage and 11 children (64.7%) received surgical intervention for their hemorrhage. 10 out of the 17 children (58.8%) had autopsy confirmation of the lesion.

Ding et al. found that deep venous drainage, female sex, and small AVM size are strong predictors for hemorrhagic events [27]. Ellis, et al. have found that in pediatric patients who survived the diagnosis of AVM, small size of the lesion, exclusive deep venous drainage, and infratentorial location are independent risk factors for future hemorrhagic events [28]. In a pediatric patient group with unruptured brain AVMs in China, periventricular location, and smaller size were independent risk factors for hemorrhagic events [29]. Our review of 17 cases shows that consistently, infratentorial (e.g. cerebellum), and deep locations (e.g. thalamus) are the most frequent sites of fatal AVM lesions. Since pediatric AVMs are usually discovered because of devastating intracranial hemorrhage, and the overall mortality rate after initial hemorrhage is as high as 25% [30], the management of such conditions is critical.

Furthermore, those who survive AVM hemorrhage are often left with neurocognitive or functional impairments [15].

In summary, we report a 7-week-old female infant with a sudden onset of a large deep cerebellar hemorrhage. Autopsy confirmed the hemorrhage was due to the rupture of an AVM. The sudden onset of catastrophic intracranial hemorrhage without any noticeable prodrome in early life makes the diagnosis and management difficult and the prognosis is extremely poor.

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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