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Case Report

Spontaneous intracerebral hemorrhage: A pediatric case of undetermined etiology and review of literature

Swaroopa Pulivarthi[a], Gustavo J. Rodriguez[a,b], Eric M. Bershad[c], Alexander Mckinney[d] and Afshin A. Divani[a,b]

[a]*Department of Neurology, University of Minnesota, Minneapolis, MN, USA*
[b]*Department of Neurosurgery, University of Minnesota, Minneapolis, MN, USA*
[c]*Department of Neurology, Baylor College of Medicine, Houston, TX, USA*
[d]*Department of Radiology, University of Minnesota, Minneapolis, MN, USA*

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Abstract. Cerebrovascular disorders, particularly intracerebral hemorrhage (ICH), rarely occur in children. The most common underlying cause for ICH in the pediatric population is arteriovenous malformation (AVM). The best approach to diagnostic evaluation of pediatric ICH is unknown due to its low incidence (2–3/100,000 children). In recent years, early discovery of underlying cause of pediatric ICH has been possible due to a more widespread use of imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and digital subtraction angiography (DSA). We report a case of a 5-year-old boy with a ICH of unknown etiology. He presented with left hemiparesis and left facial droop for one hour. Non-contrast CT scan demonstrated right periventricular hematoma extending to all ventricles. Follow-up MRI, CT angiography and DSA were unremarkable. Laboratory findings including liver function tests, hematologic studies were normal. Screening for hemoglobinopathies was negative. Transthoracic echocardiography was unremarkable. Surgery for ventricular drain placement and intense physical therapy were performed. During the follow ups at 1 and 6 mo of initial admission, repeat brain MRI and magnetic resonance angiography were unremarkable.

The complete diagnostic evaluation in children presenting with ICH of undetermined origin is critically important, but still the etiology may not be identified in some cases. As AVMs are the most common cause of ICH in children and may rarely regress following hemorrhage, our patient's normal follow-up imaging may be related to such a spontaneous thrombosis of an underlying AVM.

Keywords: Intracerebral hemorrhage, pediatric, etiology, stroke

1. Introduction

Stroke occurs in 2 to 3 children/100,000/year in developed countries and hemorrhagic strokes accounts approximately 50% of pediatric strokes [1,2]. The incidence of intracerebral hemorrhage (ICH) among children younger than 10 yr is considered to be higher than subarachnoid hemorrhage, the most common form in teenagers [3]. The rate of ICH among children is reported to be 0.8/100,000 person-years [4] resulting in mortality up to 33% and major deficits up to 40%, including seizures,

*Corresponding author: Afshin A. Divani, University of Minnesota, Department of Neurology, MMC 295, 420 Delaware Street S.E. Minneapolis, MN 55455, USA. Tel.: +1 612 624 305; Fax: +1 612 624 3031; E-mail: divani@umn.edu.

cognitive and motor impairments [4–6]. The rate of pediatric ICH peaks in the first year of life especially in neonatal period with hematological abnormalities or structural vascular disorders such as arteriovenous malformations (AVM) or aneurysms [3,4,7,8].

In this case report, we present a pediatric case of spontaneous ICH, with an undetermined etiology despite thorough evaluation.

2. Case report

The following relates a case of a 5-year-old boy with a spontaneous ICH of unclear etiology. He presented with acute left-sided weakness, headache, nausea, and vomiting. The child was in good health before the onset of symptoms. He had no history of major head trauma, seizures, stroke developmental delay, or spontaneous bruising or bleeding. His initial blood pressure was 108/74 mmHg, heart rate was 123/min, and respiratory rate was 23/min. He was also afebrile. His neurological examination was significant for drowsiness, plegia of the left arm and withdrawal in his left leg, clonus of his left ankle, and a left Babinski sign. Laboratory findings including complete blood count and liver function tests were unremarkable. Hematological workup including serum hemoglobin electrophoresis, factor VIII, ristocetin, von Willebrand factor antigen, fibrinogen, and platelet function assays were normal, except the level of factor XIII (44%) that was mildly decreased. Noncontrast computed tomography (CT) scan demonstrated right periventricular hematoma with intraventricular extension. Magnetic resonance imaging (MRI) brain, magnetic resonance angiography (MRA) head and neck, magnetic resonance venogram, CT angiogram (CTA) of head and two cerebral digital subtraction angiography (DSA) (day 1 and 9) were non-diagnostic (Fig. 1). Urine screening for drugs including methamphetamine and cocaine were negative. Cerebrospinal fluid examination was within normal limits. A summary of the patient's lab results on admission are shown in Table 1. Transthoracic echocardiography was unremarkable. Brain biopsy was not performed due to the deep location of the hemorrhage, with the possibility of worsening clinical status.

The hospital course was remarkable for a intensive care unit stay of 6 d, need for external ventricular drain placement with eventual wean on day 12, mechanically assisted ventilation for 5 d, intravenous cefotaxime for hospital acquired pneumonia with sputum culture growing *Haemophilus influenza* and *pneumococcus*,

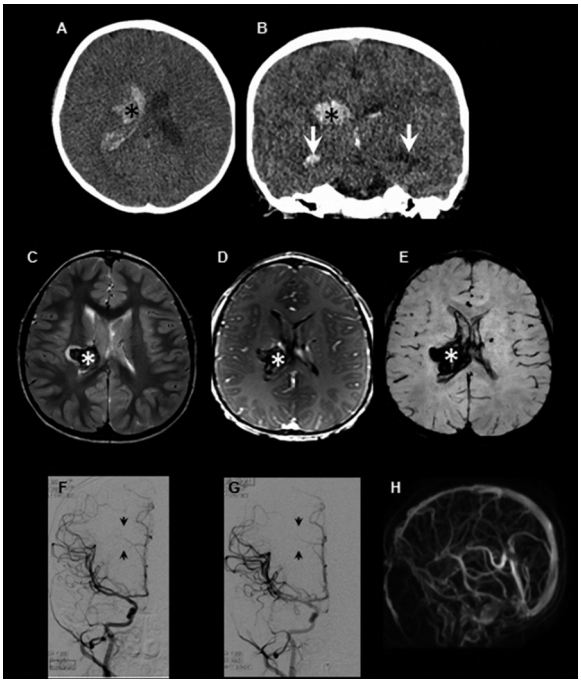

Fig. 1. The initial noncontrast computed tomogtaphy (A-B) demonstrated that the intracerebral hemorrhage (*) extended into the lateral ventricles; note mild dilatation of the temporal horns (arrows). A 3.0T magnetic resonance imaging (C-E) further depicted the intraparenchymal hemorrhage (IPH) (*) on T2-weighted images (C), postcontrast T1-weighted images (D), and susceptibility-weighted images (E); there were no enhancing lesions on the postcontrast images. Catheter angiograms performed initially (F) and at 8 days (G) found no vascular lesions (both right internal injections, location of IPH is denoted between arrows). Magnetic resonance venography (H) was negative.

and discharge to home with physical therapy. Follow-up MRI and MRA at one and six months were unremarkable. The patient's neurological status at six months was completely normal.

3. Discussion

Non-traumatic ICH is an acute spontaneous extravasation of blood into the brain parenchyma that may also extend into the ventricles or subarachnoid space [8]. The most frequently observed cause of pediatric ICH is a structural vascular disorder such as an AVM, cerebral aneurysm, or moyamoya disease. Other etiologies include hematological abnormalities, brain tumor, cavernous hemangioma, vasculopathy, vasculitis, cerebral and systemic infections, and more rarely due to illicit drug use [5,9]. Despite comprehensive diagnostic evaluation in children presenting with spontaneous ICH, the etiology in some cases remains indeterminate.

Table 1
Laboratory test results for the pediatric intracerebral hemorrhage case on admission

Test	Results	Normal range
Platelet count	299 k/mm^3	150–575 k/mm^3
Prothrombin time	12.5 sec	9–12.5 sec
International normalized ratio	1.1	0.8–1.2
Activated partial thromboplastin time	25.9 sec	25–38 sec
Platelet factor closure time assay	100 sec	<185 sec
Factor XIII assay	44 U/dL	60–130 U/dL
Hemoglobinopathies	Normal	
Fatty acid oxidation disorder assay	Negative	
Factor VIII	130%	60–140%
Ristocetin	127%	50–175%
Von Willebrand factor antigen	120%	55–160%
Fibrinogen	211 mg/dL	200–400 mg/dL
Hemoglobin	9.3 g/dL	10.5–13.5 g/dL
Mean corpuscular volume	77 fL	10–87 fL
Creatinine	0.3 mg/dL	0.7–1.4 mg/dL
Liver function tests		
Total bilirubin	0.2 mg/dL	0.3–1.9 mg/dL
Albumin	3.7 g/dL	3.4–5 g/dL
Alanine transaminase	16 IU/L	7–56 IU/L
Alkaline phosphatase	180 IU/L	70–480 IU/L
Rapid plasma reagin (syphilis screen)	Reactive (1:1)	
Fluorescent treponemal antibody absorption test	Reactive	
Urine drug screening – Acetaminophen, Amphetamine and Cocaine	Negative	
Cerebrospinal fluid		
Neutrophils	30%	
Lymphocytes	35%	
Macrophages	23%	
Monocytes	5%	
Eosinophils	7%	
Protein	10 mg/dL	12–60 mg/dL
Glucose	81%	60%–70% of the plasma level
Cerebrospinal fluid culture – gram stain	Negative	
Cerebrospinal fluid red blood cell	64,0000/mm^3	
Cerebrospinal fluid appearance	Xanthochromic	
Cerebrospinal fluid nucleated cell count	611/mm^3	

An outline of published data looking at the etiologies of ICH among pediatric population is shown in Table 2. The most frequently reported cause of pediatric ICH is AVM, and it accounts for about 50% of ICH cases [5,10–13]. In a pooled analysis study done by Jordan and Hillis [9], AVM accounts for 14 to 46% of hemorrhagic stroke in children and nearly 50% of ICH. Cavernous malformations are generally detected on MRI and may account for 3 to 22% of ICH [4,6,10,11,13–16].

Hematological abnormalities are reported to be one of the major risk factors in 10–30% of the patients; that includes thrombocytopenia, hemophilia and coagulopathies related to liver failure, disseminated intravascular coagulation, clotting factor deficiencies (factor VIII or IX), or rarely may be iatrogenic due to anticoagulation with heparin during cardiac surgery or extracorporeal membrane oxygenation [4,5,14,17]. Extracorporeal membrane oxygenation treatment for severe cardiopulmonary failure was the main culprit for the high frequency of ischemic neuronal necrosis (50%), focal cerebral infarcts (50%), intracerebral hemorrhages (50%), and periventricular leukomalacia (41%) in 44 children who had undergone neuropathological autopsy among 94 patients [17]. As shown in Table 2, hemorrhagic stroke among the pediatric population due to hematologic abnormalities constitutes 4 to 64% of cases in the published studies [4–6,10–15,18–21]; however, the

Table 2
Published etiologies of hemorrhagic stroke in pediatric population

Author	Year	Number of cases	Age	Arteriovenous malformation	Hematological abnormalities	Cavernous hemangioma	Tumor	Aneurysm	Others	Unknown
Broderick et al. [16]	1993	9	0–14 yr	33%	–	22%	22%	11%	–	11%
Visudhiphan et al. [12]	1996	30	6 mo–15 yr	40%	20%	3%	–	17%	10% hypertension	10%
Giroud et al. [14]	1997	23	1 mo–15 yr	39%	18%	21%	–	9%	9% throat infections	4%
Earley et al. [18]	1998	17	0–14 yr	29%	29%	–	–	–	18% vasculopathy 12% surgical complications	12%
Lin et al. [13]	1999	42	0–15 yr	45%	5%	5%	–	–	–	–
Al-Jarallah et al. [4]	2000	68	3 mo–18 yr	34%	32%	3%	13%	6%	9% hemorrhagic infarct 3% spontaneous dissection 6% miscellaneous	10%
Lanthier et al. [19]	2000	21	1 mo–18 yr	38%	10%	19%	10%	5%	5% venous malformation	14%
Blom et al. [5]	2003	56	1 mo–16 yr	41%	18%	–	2%	9%	4% vaculitis 4% meningitis 2% Menkes syndrome	20%
Meyer-Heim and Boltshauser [10]	2003	34	2 mo–17 yr	53%	12%	6%	3%	15%	–	12%
Chung and Wong [20]	2004	14	7 mo–11 yr	14%	64%	–	–	–	–	21%
Zahuranec et al. [22]	2005	6	2 mo–19 yr	17%	–	–	–	–	33% congenital heart disease 17% drug abuse	33%
Liu et al. [15]	2006	50	1 mo–16 yr	26%	16%	18%	10%	8%	10% venous sinus thrombosis	12%
Strouse et al. [21]	2006	15	0 mo–18 yr	–	27%	–	–	7%	20% moyamoya disease	53%
Lo et al. [6]	2008	85	0–17 yr	13%	12%	8%	15%	2%	16% congenital heart disease 7% acute renal failure, aplastic anemia, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Menkes syndrome 6% infection 2% venous angioma 2% moyamoya	15%
Kumar et al. [11]	2009	50	2 mo–17 yr	44%	4%	4%	4%	34%	6% moyamoya	4%

higher end of this range has been supported by only one published study by Chung et al. [20] in Chinese pediatric patients from Hong Kong. The upper limit of hematologic abnormalities causing hemorrhagic stroke for the remaining studies was 32% [4]. Pediatric idiopathic thrombocytopenic purpura and sickle cell disease are also associated with risk for ICH [9].

Intracranial aneurysms are attributed to causing 2 to 34% of cases of pediatric hemorrhagic stroke [4–6, 10–12,14–16,19,21]. The anatomic localization at the internal carotid bifurcation is a distinguishing location of aneurysms affecting children and adolescents and it is the most common site of aneurysms (27.8%), followed by middle cerebral artery (22.2%), and anterior communicating artery (16.7%) [11].

Brain tumors are another well known cause of ICH and may account for 13% of children but mainly present with epidural, subdural or subarachnoid hemorrhage, whereas intraparencyhmal hemorrhage accounts only in 3% of the patients [9]. As shown in Table 2, brain tumors account for 2 to 22% of hemorrhagic stroke in pediatric population [4–6,10,11,15,16,19]. Other etiologies that accounted for greater than 10% of ICH are moyamoya disease, drug abuse (cocaine or methampheatmine), hypertension and vasculopathy [12,15,18,21].

In contrast to other studies [4,5,10–16,18–20], in retrospective studies conducted by Lo et al. [6] and Zahuranec et al. [22], congenital heart disease patients on anticoagulation therapy accounted for a greater proportion of ICH than AVM (16% vs. 13% and 33% vs. 17%, respectively). Schmitz et al. [23], in their case report, stated that hypocholesterolemia may also increase the risk of hemorrhagic stroke in children.

As shown in Table 2, hemorrhagic stroke due to the unknown etiology accounts for 4 to 53% of cases. The possible etiologies in our case may include a small AVM that was ruptured into the ventricles and spontaneously thrombosed, which could not be detected. There are reports of brain or spinal AVM regressing following hemorrhage due to presumed thrombosis [24,25]. Another consideration in our case may include the decreased level of factor XIII, though one would still expect normal coagulation function at this level. We excluded factor XIII deficiency as per hematologist consult. Similar to our case, a report by Jordan et al. [26] describes a 4-year-old boy who presented with ICH that occurred twice approximately one year apart. In this case, neither the initial nor the follow-up imaging workups with CT scan, MRI, and MRA at two and seven months revealed the cause of the hemorrhage. After the second episode of ICH, a cerebral angiogram revealed a right parietal AVM. Therefore, prolonged clinical follow-up and consideration for repeat neuroimaging in cases of cryptogenic ICH in children may be warranted.

The most common location of hemorrhage in children is lobar or the cerebellum, and rarely in the putamen or thalamus [11]. This is in contrast to the putamenal and lacunar vessel distribution in adults, due to the fact that the most common cause of ICH in pediatric population is AVM and not hypertension. The common clinical symptoms are non-specific and include severe headache, emesis, altered mental status, seizure, syncope and focal neurological deficits [4,6,9,11]. Some patients may have acute intracranial hypertension or herniation syndrome requiring urgent intervention.

Typically, the initial imaging modality of choice for pediatric patients with suspected ICH is a non-contrast CT scan. Further testing as clinically indicated may include CTA, MRI, MRA, cerebral angiography and screening for coagulation abnormalities. Interestingly, in one study [15], comparison was made between DSA and a combination of MRI, MRA, and magnetic resonance venography for detecting ICH in the pediatric population. It was found that DSA alone had a diagnostic yield of 61% that was statistically equivalent to combination of all of the other three imaging modalities. Another study indicated that the use of DSA for identifying the cause of ICH was relatively safe as only 0.2% of major complications were reported among 241 children [27]. These studies reinforce the point that when non-invasive tests are unrevealing, DSA should be considered in children with spontaneous ICH.

In conclusion, thorough diagnostic evaluation including cerebral angiography may be necessary to determine the etiology of ICH in the pediatric population due to the heterogeneous etiologies. Taking a detailed history from the parents and the child is important for determining any history of head injury and bleeding episodes. One should also perform a urine toxicology screen to rule out drug abuse (methamphetamine or cocaine) as the cause of ICH. Despite comprehensive evaluation, it may not be possible to determine the cause of ICH in some pediatric cases.

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