CASE REPORT

Acute Ischemic Stroke in a 13-Year-Old Girl: An Unusual Etiology

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Port J Pediatr 2022;53
DOI: https://doi.org/10.25754/pjp.2022.25476

Abstract

Acute ischemic stroke is rare in children and is associated with heart, hematologic, and vascular conditions. A high index of suspicion is required for proper diagnosis and intervention. We report a case of an acute ischemic stroke in a 13-year-old girl with a past medical history of left subscapular arteriovenous malformation. She started complaining of fever and nasal obstruction four days before admission, followed by a brief episode of blurred vision and vomiting two days later, as well as a headache on the day of admission. Facial asymmetry and slowed speech started at admission, and examination revealed right hemiparesis with homolateral facial involvement and ataxia. Magnetic resonance imaging confirmed a left pons ischemic lesion, and we started anticoagulation / anti-aggregation treatment. Angio-magnetic resonance revealed occlusion of the basilar artery and narrowing of the right vertebral artery. A complete resolution of basilar artery occlusion was noted after 40 days, while narrowing of the vertebral artery persisted. We discuss factors contributing to acute ischemic stroke and strategies to prevent future events.

Keywords: Adolescent; Ischemic Stroke/diagnosis; Ischemic Stroke/drug therapy; Ischemic Stroke/etiology; Treatment Outcome

Keypoints

What is known:
- Acute ischemic stroke are rare events in children, associated with multiple etiologies and difficult to diagnose, requiring a high index of suspicion.

What is added:
- A revision of the main causes and investigation of acute ischemic stroke in children, exemplified by a case of acute ischemic stroke in a 13-year-old girl.

Introduction

Acute ischemic stroke is a rare condition in children with an annual incidence that varies from 0.6-7.9 per 100 000, depending on the country.[1-3] For unknown reasons, acute ischemic stroke is more prevalent in boys (approximately 60% of cases), independently of age, as reported in a large multicenter international study.[4]

The main risk factors for acute ischemic stroke include[5]:

- Heart conditions, such as paradoxical embolism, infective endocarditis, dilatation of cardiac chambers with intra-cardiac thrombus, and arrhythmias;
- Hematologic changes, mostly sickle cell disease, and prothrombotic disorders (*eg* iron deficiency anemia, antiphospholipid syndrome, factor V Leiden or prothrombin gene mutations, protein C, S or antithrombin III deficiencies, and elevated homocysteine);
- Vasculopathy, either acquired or inherited.

In fact, arteriopathies were shown to be present in over 50% of acute ischemic stroke cases worldwide, as reported in a large multicenter study conducted on 667 subjects in the age range of 0-19 years.[6] Among these, approximately 25% corresponded to focal cerebral arteriopathy, defined as cerebral arterial stenosis of unknown cause, while other important arteriopathies related to acute ischemic stroke were moyamoya (22%) and arterial dissection (20%). Genetic causes are considered to be responsible for a large proportion of acute ischemic stroke, although the majority (20%-40%) are cryptogenic, and a gene has been identified in less than 1% of cases, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry, Marfan, Ehlers-Danlos, or mitochondrial disorders.[7]

In the pediatric population, clinical signs of acute ischemic stroke may be subtle, typically presenting as seizures and altered mental status in infants, while older children may display focal deficits (hemiparesis,

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Received: 27/08/2021 | Accepted: 01/07/2022 | Published online: 22/08/2022 | Published: 01/10/2022

visual disturbances, or cerebellar signs).[8] Therefore, a high index of suspicion is essential for timely diagnosis and intervention. In this case report we aim to discuss the diagnostic orientation and management of acute ischemic stroke in the light of current knowledge, exemplified by an acute ischemic stroke episode in a 13-year-old adolescent.

Case Report

We present a pediatric emergency episode of a 13-year-old girl with fever and nasal obstruction four days before admission, followed by brief ocular pain (one minute) two days later as well as blurred vision and vomiting, associated with headache, on the day of admission. There was no relevant family history. Past medical history of an arteriovenous malformation (AVM) due to a visible deformity was detected in the left sub-scapular region. There was no history of recent infections, including *herpes zoster* viral infection in the last year.

On examination at admission, she was conscious and oriented, the speech was slowed and dysarthric, and she had a right hemiparesis with homolateral facial involvement associated with ataxia, intention tremor, and past pointing on the same side. Differential diagnoses included a vascular lesion (ischemic / hemorrhagic), central nervous system infection, or a space-occupying lesion. Computed tomography (CT) scan performed immediately at admission revealed spontaneous hyperdensity of the basilar artery (Fig. 1) which was further clarified by a magnetic resonance imaging (MRI) with diffusion performed about nine hours after admission, showing a left anterolateral hyperintense pons lesion (Fig. 1) and confirming early-stage acute ischemic stroke. Acetylsalicylic acid, 100 mg/day, and low molecular weight heparin, 40 mg twice a day, were administered immediately. The initial etiologic investigation was normal, including blood testing (full blood count, C-reactive protein, d-dimers, fibrinogen, homocysteine, protein C and S, antithrombin III, coagulation factors II and V, lupus anticoagulant, cardiolipin, beta 2 glycoprotein 1, antineutrophil cytoplasmic antibodies ANCA proteinase 3, ANCA myeloperoxidase, glomerular basal membrane antibodies), cerebrospinal fluid (cytochemical and cultural) (Table 1), and cardiac evaluation (electrocardiogram, Holter and transthoracic echocardiograms, complemented with agitated saline solution injection).

The more specific vascular evaluation included cervical and transcranial Doppler which revealed increased resistance at the right vertebral artery. Angio-MRI on day six revealed narrowing of the basilar artery with total occlusion of the distal portion (Fig. 2). Repeated angio-MRI on days 12 and 40 (Fig. 2) revealed progressive resolution of the occlusion, persisting the asymmetry of the vertebral arteries initially documented. There was a progressive clinical improvement with almost complete resolution of symptoms at the time of discharge (14 days). Magnetic resonance imaging on day 40 still showed a well-defined hyperintense pons lesion (Fig. 3). Head and neck angio-MRI was performed but no association was found between the left scapular arteriovenous malformation and the posterior circulation responsible for the ischemic lesion (Fig. 3). Low molecular weight heparin was suspended while acetylsalicylic acid prophylaxis was maintained. At 16 months follow-up there was a complete resolution of the symptoms. However, acetylsalicylic acid is currently maintained.

Discussion

In the case reported, basilar artery occlusion was diagnosed in a 13-year-old girl, with a favorable outcome after anticoagulation / anti-aggregation treatment. There are no randomized controlled trials for the treatment of stroke in pediatric age and it is often managed based on recommendations for adults and clinical experience. Short observational studies comparing low molecular weight heparin with aspirin alone did not reveal statistical differences between both treatments.[9]

However, we were concerned with a possible association between arteriovenous malformation and a thromboembolic event, and low molecular weight heparin in combination with aspirin was administered empirically. Identification of the underlying cause or predisposing factors, including the role of vertebral artery narrowing or the subscapular arteriovenous malformation, was considered essential in preventing

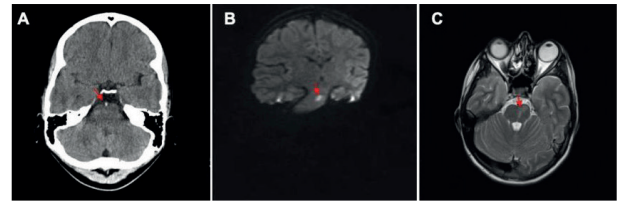


Figure 1. Initial radiological evaluation of 13-year-old girl at the emergency department confirming acute ischemic stroke. A) Computed tomography axial scan showing basilar artery spontaneous hyperdense lesion. B) Magnetic resonance imaging diffusion coronal image showing hyperintense pons lesion, further complemented with C) Magnetic resonance imaging T2 axial scan showing also hyperintense pons lesion. Red arrows indicate lesions.

further episodes. No hematological, prothrombotic, or systemic diseases were identified.

There was no evidence to suggest embolization, namely a cardiac shunt or other anomalies, and direct communication between the arteriovenous malformation and posterior cerebral circulation was not identified. A steal phenomenon from the arteriovenous malformation was also considered unlikely since this vascular malformation occurred downstream the emergence of the vertebral artery. Nevertheless, we observed that the narrowing of the right vertebral artery persisted after anticoagulation therapy, corresponding to an anatomical variant, and possibly contributing to the ischemic event.

Vertebral artery dissection was hypothesized. However, there were no changes in the MRI sequences to suggest this possibility. Eventually, the focal cerebral arteriopathy was considered to be the triggering event for the stroke. Focal cerebral arteriopathy is a frequent cause of acute ischemic stroke in the pediatric population, and it is usually preceded by an upper respiratory tract infection,[6] as occurred in our patient. It seems reasonable to assume, although speculatively, that right vertebral artery narrowing AND associated focal

Table 1. Summary of the blood and cerebrospinal fluid investigation at the emergency department

Blood count	
Red blood cells	4.48 x 10^{12} cells/L
Hemoglobin	133 g/L
White blood cells	4.1 x 10^{9} cells/L
Platelets	137 x 10^{9} cells/L
Coagulation test	
International normalized ratio	1.1
Partial thromboplastin time Mod	Negative
Dilute russell viper venom time	Negative
Free S protein	63.3%
C protein	76.0%
Antithrombin	103%
Factor V (Leiden) resistance	Negative
Homocysteine	7.2 µmol/L
Fibrinogen	3.5 g/L
Autoimmune	
Lupus anti-coagulant	Negative
Anti-cardiolipin	Negative
Anti-beta 2 glycoprotein 1	Negative
Antineutrophil cytoplasmic antibodies myeloperoxidase	Negative
Antineutrophil cytoplasmic antibodies (proteinase 3)	Negative
Anti-glomerular basement membrane diseases	Negative
Genetic	
Prothrombin G20210	Negative
Factor V (Leiden)	Negative
Fabry test	
Alpha-galactose activity	Negative
Cerebrospinal fluid test	
Glucose	59 mg/dL
Protein	20 mg/dL
White blood cells	3 cells/µL
Adenosine deaminase	1.4 UI/L
Lactic acid	1.3 mmol/L
Bacteriological	Negative
Víral	Negative

cerebral arteriopathy induced by a respiratory infection, could both have played a role in this thrombotic event. Regarding prognosis, it should be reminded that children with acute ischemic stroke, who present abnormal cerebrovascular imaging, have a five-year cumulative recurrence rate of 66%, compared to no recurrences in children with normal vascular imaging.[10] This is crucial for the development of preventive strategies for future acute ischemic stroke events. In this case, acetylsalicylic acid prophylaxis was the preventive strategy of choice. However, there are no specific studies showing the efficacy or optimal duration of this or any other strategy. Treatment of arteriovenous malformation is also being considered.

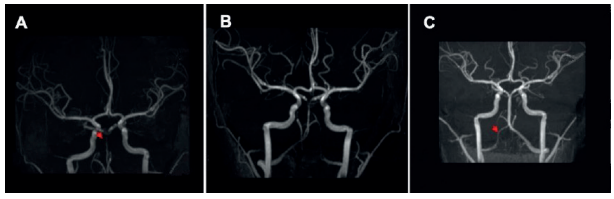
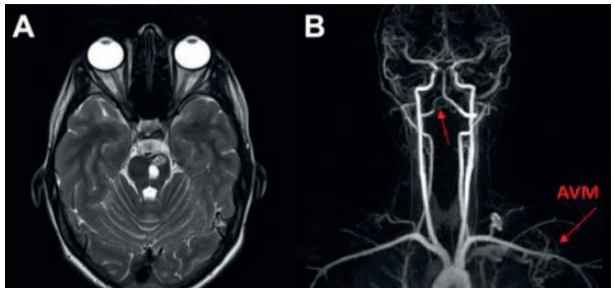


Figure 2. Time sequence of magnetic resonance angiography at six, 12, and 40 days after admission. A) Initial narrowing of the basilar artery on day six after admission with total occlusion of distal portion (red arrow). B) Ongoing recanalization of basilar artery observed on day 12 after admission. C) Complete recanalization of the basilar artery and narrowed right vertebral artery at day 40 after admission.



AVM - arteriovenous malformation.

Figure 3. Magnetic resonance imaging and magnetic resonance angiography evaluation on day 40 after admission. A) T2 axial magnetic resonance imaging scan showing hyperintense well-defined pons lesion. B) Magnetic resonance angiography with gadolinium indicating complete re-establishment of basilar artery circulation and right vertebral artery maintained narrowing, as well as arteriovenous malformation in the left subscapular region.

Author Contribuitions

DMT participated in the study conception or design. DMT, TM and CM participated in acquisition of data. DMT, TM and CM participated in the analysis or interpretation of data. DMT and CM participated in the drafting of the manuscript. DMT, RJP, TM, MM and CM participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

Funding Sources

There were no external funding sources for the realization of this paper.

Provenance and peer review

Not commissioned; externally peer reviewed.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

Consent for publication was obtained.

References

1. Giroud M, Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: A study of incidence and clinical features from 1985 to 1993. J Clin Epidemiol 1995;48:1343-8. doi: 10.1016/0895-4356(95)00039-9.

2. Earley CJ, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, et al. Stroke in children and sickle-cell disease: Baltimore-Washington cooperative young stroke study. Neurology 1998;51:169-76. doi: 10.1212/wnl.51.1.169.

3. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Paediatric arterial ischaemic stroke and cerebral sinovenous thrombosis in Denmark 1994-2006: A nationwide population-based study. Acta Paediatr 2011;100:543-9. doi: 10.1111/j.1651-2227.2010.02100.x.

4. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G. Male predominance in childhood ischemic stroke: Findings from the international pediatric stroke study. Stroke 2009;40:52-7. doi: 10.1161/STROKEAHA.108.521203.

5. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol 2003;53:167-73. doi: 10.1002/ana.10423.

6. Amlie-Lefond C, Bernard TJ, Sébire G, Friedman NR, Heyer GL, Lerner NB, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: Results of the international pediatric stroke study. Circulation 2009;119:1417-23. doi: 10.1161/CIRCULATIONAHA.108.806307.
7. Buczek J, Czlonkowska A. Stroke and genetics. Period Biol 2012;114:259-66.
8. deVeber GA, Kirton A, Booth FA, Yager JY, Wirrell EC, Wood E, et al. Epidemiology and outcomes of arterial ischemic stroke in children: The Canadian pediatric ischemic stroke registry. Pediatr Neurol 2017;69:58-70. doi: 10.1016/j.pediatrneurol.2017.01.016.
9. Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G. Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischaemic stroke: A multicentre, observational, cohort study. Lancet Neurol 2009;8:1120-7. doi: 10.1016/S1474-4422(09)70241-8.
10. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: The importance of cerebrovascular imaging. Pediatrics 2007;119:495-501. doi: 10.1542/peds.2006-2791.

Acidente Vascular Cerebral Isquémico Agudo numa Menina de 13 Anos: Uma Etiologia Rara

Resumo:
Os acidentes vasculares cerebrais isquémicos são raros em crianças e geralmente estão associados a alterações cardíacas, hematológicas ou vasculares, pelo que o diagnóstico depende de um elevado índice de suspeição. Reportamos o caso de um acidente vascular cerebral isquémico numa adolescente de 13 anos com antecedente de malformação arteriovenosa subescapular esquerda. Quatro dias antes inicia febre e obstrução nasal, evoluindo dois dias depois para vómitos e visão turva episódica, no próprio dia cefaleia de novo, e no serviço de urgência iniciou assimetria da face e discurso lentificado. Na observação apresentava hemiparesia direita com envolvimento facial ipsilateral, dismetria e ataxia. Na ressonância magnética confirmou-se uma lesão isquémica na protuberância, e iniciou anticoagulação / anti-agregação. Na angio-ressonância magnética verificou-se uma oclusão da artéria basilar, que resolveu 40 dias depois, bem como uma estenose da artéria vertebral direita, provável variante do normal. Discutimos os fatores contributivos para este acidente vascular cerebral isquémico e as estratégias preventivas para prováveis episódios futuros.

Palavras-Chave: Acidente Vascular Cerebral Isquémico/diagnóstico; Acidente Vascular Cerebral Isquémico/etiologia; Acidente Vascular Cerebral Isquémico/tratamento farmacológico; Adolescente; Resultado do Tratamento