Cardiac Myxoma as a Rare Cause of Pediatric Arterial Ischemic Stroke: Case Report and Literature Review

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Abstract

Background Cardiac disorders are the second leading cause of pediatric arterial ischemic stroke (AIS). Limited literature is available on pediatric AIS caused by cardiac myxoma, a rare tumor in childhood.

Methods We describe a new case of pediatric AIS due to a previously unknown atrial myxoma and we conduct a literature review on children with AIS due to cardiac myxoma.

Results We identified 41 published pediatric cases of AIS and cardiac myxoma, including ours (56% males, median age at AIS was 11 years [range: 3–18]). AIS presentation was most frequently with hemiparesis/hemiplegia (89%). Multiple brain ischemic lesions were detected in 69% of patients, and arteriopathy in 91%. Seven patients underwent mechanical thrombectomy. At AIS presentation, 73% of children had one or more of the following clinical symptoms/signs suggesting a possible underlying cardiac myxoma: Carney’s complex, cardiac auscultation abnormalities, extraneurological symptoms/signs, such as skin signs (12, 38, and 65%, respectively). Cardiac myxoma was diagnosed within 72 hours in 68% of cases. Death occurred in 11%, and 40% had persistent neurological deficits.

Conclusion Neurological presentation of AIS due to cardiac myxoma is similar to that of AIS with other etiologies, although clues suggesting a possible underlying cardiac myxoma can be detected in most cases. A timely diagnosis of cardiac myxoma in patients with AIS may favor prompt identification of candidates for endovascular therapy. Therefore, we suggest that in otherwise-healthy children presenting with AIS, transthoracic echocardiography should be performed early after stroke presentation.

Keywords ► cardiac myxoma ► arterial ischemic stroke ► transthoracic echocardiography ► pediatric ► children

Introduction

Cardiac disorders, a potentially modifiable risk factor of stroke in children, are the second leading cause of arterial ischemic stroke (AIS) in the pediatric population (31%, outside the neonatal period).1 The incidence of AIS in children with cardiac disease is higher (132 of 100,000 per year)2 than the incidence of AIS in the general pediatric population (~2 of 100,000 per year).3,4 Congenital heart malformations are three times more common than acquired conditions as a cause of AIS in childhood and 25% of AIS due to cardiac disease follows surgical procedures or catheterization.1,5

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Among acquired conditions, limited data are available in the literature about pediatric AIS caused by cardiac myxoma, a benign primary tumor, rare in childhood, which can present with neurological signs, including stroke as the most common neurological presentation.

Cardiac myxoma may be complicated by AIS due to embolization not only of myxomatous material but also of a thrombus adherent to the cardiac mass. Cardiac myxoma may also be complicated by hemorrhagic stroke caused by (usually fusiform) aneurysms of the brain vessels. The current hypothesis about the formation of these aneurysms assumes that tumor cells from cerebral myxomatous emboli invade the vasa vasaorum of the cerebral artery walls, where they proliferate, infiltrating, and weakening the internal elastic lamina and the subintimal tissue. The possibility of delayed cerebral aneurysm formation after the complete excision of the myxoma is reported in the literature, with an interval time of up to many years between surgical removal of cardiac myxoma and aneurysm detection.

Carney's complex is an autosomal dominant, multiple endocrine neoplasia, and lentiginosis syndrome; defects of the PRKAR1A gene are found in most patients. At presentation, spotty skin pigmentation is the most common clinical manifestation (77%) and other skin abnormalities can be present such as epithelioid-type blue nevi, combined nevi, and depigmented lesions. Other features of this syndrome include heart myxoma (53% of patients at presentation), skin myxoma (53%), primary pigmented nodular adrenocortical disease (26%), large-cell calcifying Sertoli's cell tumor (33% of male patients), acromegaly (10%), psammomatous melanotic schwannoma (10%), thyroid nodules or cancer (5%), and breast ductal adenoma (3% of female patients). Heart myxomas are the most common noncutaneous manifestation in Carney's complex; they can develop at any age in these patients (median age at detection: 20 years), can be multifocal, affecting any cardiac chamber, and can have multiple relapses. Heart myxoma and its complications account for the most important morbidity and mortality in patients affected by Carney's complex.

To better clarify the role of cardiac myxoma in pediatric stroke, we added a new illustrative case and reviewed the pertinent literature.

Methods
Case Report
We describe a new clinical case of a 12-year-old girl who presented with arterial ischemic cardioembolic stroke due to a previously unknown atrial myxoma. The patient was managed according to the best clinical practice established by the Ethics Committee of our University Hospital and the Neuripedia vas and therapeutic acts were performed with the consent of child's parents.

Literature Review
We conducted a literature review looking for pediatric cases (age range: 0–18 years) of AIS related to cardiac myxoma; cases with hemorrhagic stroke were excluded. The search was performed in PubMed, from inception up to date to December 7, 2019, with the following search-term combinations: “stroke AND (cardiac myxoma OR atrial myxoma),” “(pediatric cardymyxoma OR pediatric atrial myxoma),” and “neurological symptoms AND (cardiac myxoma OR atrial myxoma).” Articles were searched manually to extract relevant clinical information on pediatric patients with stroke caused by cardiac myxomas. We contacted authors to request the full text of pediatric stroke articles of which only abstract was available; whenever the full text remained unavailable, we extracted clinical data from the abstracts. Cases included in large series of patients with unavailable individual data were excluded. Data collection was subject to data availability, therefore in the result denominators may differ.

Results
Case Report
A previously healthy 12-year-old girl presented to the emergency room (ER) with acute-onset psychomotor agitation after an accidental fall, while she was playing on the beach with her sister. Vital signs were stable and physical examination was negative. Blood analysis were unremarkable, urinary toxicology was negative, and electrocardiogram revealed a QTc of 465 ms. History taking was hindered by an important language barrier between the family and the medical staff. Because of persistent psychomotor agitation, not responsive to benzodiazepines and alternating with drowsiness, the girl was soon sedated, intubated, and admitted to the pediatric intensive care unit where a computerized tomography (CT) scan of the brain was taken 2.5 hours from symptoms’ onset, which was negative. Although, when sedation weaning was attempted 7 hours after the onset, right-sided hemiparesis and aphasia became clear. A second brain CT scan revealed an area of hyperacute ischemia in the left-middle cerebral artery (MCA) territory; ASPECTs 7 (Insula, M2, M5). CT angiography (CTA) of the intracranial vessels showed a distal M1 segment occlusion of the left MCA (Fig. 1), confirmed by angiography (Fig. 2, on the left). CT perfusion (CTP) revealed a ratio of the volume of ischemic tissue (estimated 83.7 mL by MTT) to infarct volume (estimated 112 mL by CBV) of 7.5, indicating a large area of potentially salvageable brain tissue despite late time window.

The patient urgently underwent mechanical thrombectomy through a right femoral access, removing a yellowish and jelly thrombus (Fig. 3) and achieving a first pass recanalization of the MCA vascular territory with an modified thrombolysis in cerebral infarction (mTICI) (thrombolysis in cerebral infarction) score of 2B (i.e., partial perfusion, ≥50% filling of the vascular territory), with persistent slowdown in the angular artery in M4 and in the middle frontal branch of the anterior cerebral artery in A4 (occlusions already evident in the preoperative CTA; Fig. 2, on the right).

A transthoracic echocardiography revealed a 35 mm × 30 mm left atrial mass, attached to the atrial septum (Fig. 4). Magnetic resonance imaging (MRI) of brain demonstrated an acute ischemic lesion in the left MCA territory and a smaller lesion in the ipsilateral anterior cerebral artery (ACA) territory (Fig. 5). At hospital day 2, the cardiac mass was removed through a median sternotomy approach (Fig. 6), and the
atrial septum was closed with a CardioCel patch, without perioperative complications. In the following days, the right-sided hemiparesis persisted, prevalent at the proximal segment of the right arm, and the speech was slowed and dysphasic. Subcutaneous heparin was started (65 IU/kg/dose in every 12 hours), in view of the immobilization and the possible persistence of myxomatous material in the cerebral vessels. Postsurgery CT and MRI of brain did not reveal any complications (e.g., hemorrhagic infarction, brain edema, or new ischemic lesions). During hospitalization, the girl underwent intense neurorehabilitation with progressive motor improvement of the right lower extremity and with recovery of independent walking. At discharge, 3 weeks after onset, she had persistent right upper arm paresis with hand flexor muscle hypertonus, although with improvement over time and regained sensitivity and normalized speech.

**Literature Review**

We identified 43 published pediatric cases of stroke caused by cardiac myxoma (time span: 1952–2019), including our...
Stroke was ischemic in 41 patients (41/43, 95%), and hemorrhagic in 2 (2/43, 5%). Of these latter two cases, one was an 18-year-old male patient who had undergone resection of a previously neurologically silent left atrial myxoma 4 months earlier; the poststroke cerebral angiography showed multiple fusiform aneurysms in the distal anterior, middle and posterior circulations, and the patient underwent a neurosurgical intervention of aneurysm resection. The second patient with hemorrhagic stroke was a 15-year-old girl, in whom angiography revealed small fusiform aneurysms of the right MCA; after resection of a left atrium myxoma, she had tumor recurrence in the right atrium. As per inclusion criteria, we excluded these two cases of hemorrhagic stroke from our literature review.

Demographics: 56% (23/41) of patients with AIS and myxoma were male. Median age at AIS was 11 years (mean, 10.9 [range: 3–18] years).

Stroke presentation: overall, 89% (34/38) of patients presented with hemiparesis/hemiplegia, isolated in 13% (5/38), and associated with one or multiple other neurological symptoms/signs in 76% (29/38; such as dysarthria/aphasia in

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**Fig. 2** The angiography demonstrates a M1–M2 segment occlusion of MCA (on the left [arrow]); after mechanical thrombectomy, the angiography reveals the recanalization of the vessel (on the right). MCA, middle cerebral artery.

**Fig. 3** Yellowish and jelly thrombus removed through mechanical thrombectomy through a right femoral access.

**Fig. 4** At transthoracic echocardiography, left atrial mass (35 mm × 30 mm) attached to atrial septum.
20 cases, alternated mental state in 12, seizures in 5, visual symptoms [e.g., visual field defects] in 4, headache in 4, and psychomotor agitation in 1). Finally, 10% of children (4/38) presented with other neurological symptoms/signs without hemiparesis/hemiplegia, such as ataxia, behavioral disturbance, altered sensorium, and visual symptoms.

Neuroimaging: among patients with available neuroimaging data (29/41, 71%), multiple parenchymal lesions were described in 69% (20/29), lesions were unilateral in eight patients and bilateral in eight patients (data not available in the remaining four). Multiple vascular territories were involved in 61% (11/18) of the patients with available data.

Arteriopathy was described in 91% of patients with available data (20/22), involving one (13/20, 65%) or multiple cerebral arteries (7/20, 35%; i.e., occlusion, absent flow, and thrombosis) detected at angiography, CTA, or MRA (magnetic resonance angiography); vessel involvement was unilateral in 90% (18/20).

Stroke treatment: data on stroke treatment were available in 32% (13/41). Of these patients, 31% (4/13) underwent mechanical thrombectomy (2014–2019); additional 23% (3/13) received intravenous fibrinolysis, followed by rescue mechanical thrombectomy (2014–2017), and 8% (1/13) were administered local intra-arterial thrombolysis with recombinant tissue plasminogen activator (2010). One patient underwent superficial temporal artery to middle cerebral artery bypass (1/13, 8%; 1975). Heparin was administered in 31% (4/13) (1998–2005–2017).

Tumor: cardiac myxoma was diagnosed after stroke in all patients, within 48 to 72 hours from stroke in 68% (21/31) of patients. Tumor localization was the left atrium in 98% (40/41), while in only one patient the tumor was in the left ventricle; no myxoma was detected in the right heart. After surgical excision, tumor recurred in 12% of patients (5/41; in three of five patients with available data, tumor recurred at 2, 6, and 16 months after surgery, respectively).

Cardiac examination: cardiac auscultation abnormalities at the time of stroke (murmur) were reported only in 38% (13/34) of patients with available data (the cardiac examination was otherwise unremarkable). A few months after stroke, one patient who did not undergo surgical excision of the atrial myxoma, developed signs of mitral stenosis and heart failure (dyspnea and orthopnea, distended cervical veins, a palpable liver edge 8 cm below the costal margin).

Carney’s complex: 12% (5/41) patients were affected by Carney’s complex (of these, one also had Marfan’s syndrome); in this subgroup, median age at AISwas 14 years (range: 11–16 years). In four of five patients with Carney’s complex and available data, clinical heart examination was negative; all five children had skin signs, four of five lentigines and one of five purpuric macules on hands and feet. These patients did not present other signs/symptoms of cardiac myxoma.
Extraneurological symptoms/signs: at the time of neurological presentation, extraneurological symptoms/signs were described in 65% (24/37) of patients, most frequently skin signs (mostly spotty skin pigmentation and in four patients with Carney’s complex and lentigines) (13/24, 54%). Other extraneurological symptoms/signs, alone or combined, were signs of limb embolism (pain, paleness, paresthesiae, and absent pulse; 5/24, 21%), fever (3/24, 12%), weight loss (2/24, 8%), dizziness (2/24, 8%), and signs of pulmonary embolism (cough and shoulder pain; 1/24, 4%).

At the time of stroke presentation, 73% (30/41) of all children in our cohort had one or more clinical symptoms or signs indicating the possible underlying myxoma (one or more of the following: Carney’s complex, cardiac auscultation abnormalities, and extraneurological symptoms/signs).

Outcome: median length of follow-up was 60 days (mean: 158.2 days [range: 3–570 days]; data available in 21/41 patients). Of patients with available data, 40% (14/35) had persistent neurological deficits and 11% (4/35) died; two patients died because systemic complications after stroke and one patient (who was being operated months after tumor diagnosis) developed cardiac failure and died during cardiothoracic surgery of tumor removal; the cause of death was not reported in one patient (an edematous brain and systemic embolization of myxoma were found histologically). Stroke relapse occurred in 5% of patients (2/41), in both cases due to tumor recurrence (one of these patients was affected by Carney’s complex).

Discussion

Childhood arterial ischemic stroke (AIS) is characterized by acute-onset neurologic deficits and radiologic images showing cerebral parenchymal infarcts conforming to known arterial territory(ies) and corresponding to clinical manifestations.55 AIS incidence in childhood is 1.6 per 100,000 children per year, higher in children under 1 year (4.14 per 100,000 children per year), with no difference in the risk of AIS between boys and girls.3

After arteriopathy, cardiac disorders represent the second main cause of pediatric AIS; congenital heart malformations are three times more common than acquired conditions as a cause of AIS.1,56 Cardiac myxoma is a benign primary heart tumor, rare in childhood, most frequently localized in the left atrium.6 Cardiac obstructive signs, including congestive heart failure, have been reported to be the most common presentation in children, while constitutional/generalized and embolic signs (including cerebral embolism) seem to be more frequent in adults and older children.6,7,57 Indeed, cardiac myxoma is a rare cause of stroke in childhood, and limited data are available on pediatric AIS caused by this tumor. To the best of our knowledge, 41 pediatric patients with AIS due to cardiac myxoma have been reported, including our personal case (Supplementary Table 1, online only).15–54

In our literature cohort of children with AIS and cardiac myxoma, male gender was slightly prevalent, despite the prevalence of cardiac myxoma is higher among females in mixed (children and adult) populations.7,58 Among them, 12% (5/41) patients were affected by Carney’s complex. Patients with Carney’s complex had a higher median age at stroke presentation compared with the whole cohort (14 vs. 11 years, respectively).

Hemiparesis/hemiplegia was the most frequent neurological sign at AIS presentation (34/38, 89%) in our literature cohort, similarly to pediatric AIS due to all causes (82–85%).1,3,56 Extraneurological symptoms/signs were reported at the time of neurological presentation in 65% (24/37), most frequently skin signs, such as multiple skin lesions, visible also months before stroke presentation, likely caused by myxomatous embolus in the skin9,60 and lentigines (these latter in patients with Carney’s complex). Carney’s complex, cardiac auscultation abnormalities were present in 38% (13/34) of patients.

Multiple cerebral ischemic lesions were reported in 69% (20/29) in our literature cohort, similar to pediatric patients with cardioembolic stroke from all causes, and in 61% (11/18) of cases multiple vascular territories were involved. Remarkably, arteriopathy was described in 91% (20/22) of our literature cohort, apparently more frequently than in pediatric cardioembolic stroke from all causes (71%),61 and suggesting a rationale for thrombectomy.

Mechanical thrombectomy was performed in four cases of our literature cohort, in other three cases the thrombectomy was a rescue chance after ineffective intravenous fibrinolysis.

Death occurred in 11% of our literature cohort (4/35), mostly due to stroke-related or cardiac surgery-related complications; this prevalence is higher than that of pediatric AIS due to all causes (5%) and due to all cardiac disorders (6.3%).4,62 Neurological deficits at follow-up were reported in 40% of children (14/35), in a slightly lower percentage than pediatric AIS by all causes (67%) and pediatric AIS by all cardiac disorders (71.7%).4,56,62 Excluding cases of stroke recurrence caused by tumor relapse, none of the patients had AIS recurrence.

Limitations

The main limitations of our work include the low number of patients, heterogeneity of applied diagnostic techniques, length of follow-up, and availability of information.

Conclusion

In conclusion, clinical presentation of pediatric AIS due to cardiac myxoma is similar to that of AIS due to all causes, including other cardiac disorders. Moreover, clinical clues suggestive of cardiac myxoma are not detectable in all patients at stroke presentation (i.e., Carney’s complex, cardiac auscultation abnormalities, and extraneurological symptoms/signs of cardiac myxoma); at the time of stroke presentation, clinical symptoms or signs indicating the possible underlying cardiac myxoma were described in 73% of all children in our cohort (one or more of the following: Carney’s complex, cardiac auscultation abnormalities, and extraneurological symptoms/signs). This possibly explains why the diagnosis of cardiac myxoma is often delayed in patients with AIS due to cardiac myxoma, delaying tumor resection, and exposing patients to the risk of
new embolisms and of inadequate or potentially harmful antithrombotic therapy. Moreover, a deferred diagnosis of cardiac myxoma in patients with AIS may hinder timely identification of good candidates for endovascular therapy that is potentially more effective in embolic stroke, such as AIS, due to cardiac myxoma than in arteriopathic forms.

In the current guidelines on management of pediatric AIS, mention is made of the need to perform a transthoracic echocardiography in the diagnostic workup, but the timing is not specified. However, the importance of early recognition of acquired cardiac causes of stroke, such as cardiac myxoma, suggests the need to include in the current recommendations, a transthoracic echocardiography among examinations that should be performed in the first hours after stroke presentation, especially in otherwise-healthy children presenting with stroke, namely, without other risk factors.

Disclosures
The authors report no disclosures.

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Conflict of Interest
None declared.

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