Case Report

Endovascular management of a stroke in a 9-year-old child with neurofibromatosis type 1 and a common carotid artery occlusion

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Abstract

Strokes are being more frequently recognized as a cause of morbidity and mortality in the pediatric population. Thrombotic strokes are rare in childhood and most of them are associated with non-atherosclerotic cerebral arteriopathies, which can be induced by genetic association like neurofibromatosis type 1. This case report illustrates this pathology, associated to an unusual vasculopathy of the common carotid artery, and reports the optimal management of a thrombotic stroke in an official European Stroke Center.

Introduction

Strokes are being more frequently recognized as a cause of morbidity and mortality in children. The annual incidence for arterial ischemic stroke (AIS) is about 2,4 per 100.000 children (1). The mortality rate is 4% but the morbidity is 50%, and this is varying by age, gender and ethnicity (1,2).

Due to an optimal management with effective surgical revascularization or thrombolysis, early diagnosis is important to avoid long-term impairments (2).

In contrast to adults, risk factors for pediatric AIS are less well understood (1). Traditional pediatric stroke risks are congenital heart disease, sickle cell disease, radiotherapy, trauma, hypercoagulable states, infections and post-infectious inflammatory disorders like post-varicella arteriopathy (1).

In many pediatric stroke cases, pathogenesis is multifactorial (3). Recent studies (2-4) show that most of AISs are associated with non-atherosclerotic cerebral arteriopathies, which is an important predictor. Recurrent events will happen in about 21% of these patients (2-4). Pediatric cerebral arteriopathy has two important causes: environmental and genetic associations (4).

One of the genetic associations is neurofibromatosis type 1 (NF1). NF1 has an autosomal dominant inheritance pattern linked to germline mutations in the *NF1* gene encoding neurofibromin (5). This gene regulates the RAS signaling pathway, that controls cell proliferation, which corresponds to a tumor-suppressor gene (6). The diagnosis of NF1 is based on clinical criterias, involving: i) dermatologic, ii) ophthalmologic and iii) radiologic specificities (5). This point shows that NF1 is a multisystem disorder, implying that this has a large impact on a child's health.

Important complications of NF1 are vascular manifestations. Patients with NF1 can develop congenital heart disease (2%), aneurysms, arteriovenous fistulae and peripheral and cerebral arteriopathy (2.5% to 6%) (6-8). This vasculopathy is probably caused by the loss of neurofibromin function, complicated by proliferation of smooth muscles (7,8). In addition, neurofibromin serves to maintain the integrity of endothelial cell layer. Unopposed proliferation of the vascular smooth muscle cells can be caused by alteration of its integrity (7).

This vasculopathy is often asymptomatic, but can have major consequences. The most common sites are the kidneys and the brain (9). In children with NF1, renal artery stenosis is the most frequent site of symptomatic vasculopathy and an important cause of hypertension (6,7).

On the other hand, in children cerebral arteriopathy can have dramatic end result. The most frequent are stenotic lesions, particularly of the intracranial internal carotid (ICA), middle cerebral (MCA), or anterior cerebral (ACA) arteries (6). These stenotic lesions can be progressive and lead to an increased risk for ischemic and hemorrhagic stroke (<1%) and focal neurologic signs (6,9).

Description of the Case

A 9-year-old boy was admitted to the emergency department (ED) due to a right-sided hemiplegia. He woke-up with these complains and he had no fever or headaches. He is known to have NF1, for which he had been genetically tested that showed a mutation of *NF1* (c.8107del). Further, he has a delay in language development associated with NF1. He was not known with cerebral pathology, only with choroidal nodules and typical hyperintense lesions (unidentified bright objects, UBO) on brain magnetic resonance imaging (MRI).

Clinical examination revealed right-sided hemiplegia, a right Babinski sign, and a right inferior facial palsy associated with dysarthria. He had more than six café-au-lait spots (bigger than 0.5 cm) and axillary freckling. At admission, the cardiovascular parameters were normal (cardiac rhythm 87 bpm, arterial pressure 114/71 mmHg, oxygen saturation 99%).

Computerized tomography (CT) and MR- angiographies showed a proximal left MCA occlusion (M1 segment) *(figure 1)* due to a thrombus, as well as common carotid artery (CCA) occlusion (*figure 2*). There was a delay from onset exceeding 4.5 hours, so intravenous lysis was not administrated *(table)*. After a multidisciplinary discussion involving pediatricians, neurologists and interventional neuroradiologists, a mechanical thrombectomy (by right femoral artery puncture) was performed without complications. Access to the left MCA was obtained through the posterior circulation by the left posterior communicating artery. Thromboaspiration and thrombectomy using

a stentriever were performed resulting in a partial recanalization (mTICI2a) (*figure 3*). We started antiplatelet therapy with acetylsalicylic acid (2.4 mg/kg/day) and clopidogrel (1 mg/kg/day). The clinical evolution was quickly favorable. Within 48 hours, a partial recovery of the strength of the right hemibody (4/5) and a minimal dysarthria was seen. After 5 days Clopidogrel was stopped.

One day later, the patient presented a recurrent transient right-sided hemiplegia lasting for 3 hours. MRI confirmed the partial reocclusion of the left MCA but it didn't show new ischemic injury and clopidogrel was restarted again. Transcranial doppler showed a partial spontaneous re-sealing of the left MCA.

The final diagnosis is a left MCA thrombotic (ischemic) stroke related to an occlusion of left CCA, followed by a transient ischemic attack related to a MCA stenosis post mechanical thrombectomy. At discharge, the patient only kept a mild right hemiparesis. The entire stroke-examinations assessment has been completed: there was no argument for an infection, no recent history of varicella infection, echocardiography was normal and coagulation check-up showed no thrombophilia. The boy had no hemoglobinopathy or lipid abnormalities and immunological tests were normal. He presented no lifestyle risk factors and his family medical history of stroke was negative.

Six weeks later, MRI still shows a left CCA occlusion, a partial stenosis (50%) of the second half of the left MCA and partial permeability of branches of left MCA division, without new ischemic injury. During the clinical follow-up, we have seen that the patient is autonomous despite a mild right residual hemiparesis and right inferior facial palsy, without dysarthria. He has resumed his schooling and is undergoing weekly physiotherapy treatment.

Discussion

We presented a case of a young boy with cerebral arteriopathy associated to NF1. This pathology has been illustrated in several studies. The prevalence varies from 4,8% in a study made by Ghosh et al. on 398 children, up to 6% in a study of Rea et al. on 419 children (7,8). Some associations have been observed: for example, arteriopathy was more common in patients with NF1 with optic gliomas (47% to 52%), who had no history of intracranial radiotherapy (7,8). The most common arteriopathy was moya-moya syndrome (MMS) (from 47% up to 76%), while distal ICA is the most commonly affected artery (7,8). Clinical presentation varies. In the first study, half of the cases were asymptomatic at presentation and none had focal neurologic deficits or complications attributable to their vasculopathy (7). Neuroimaging was indicated for headache, seizures, brain tumor or screening (7). In opposite, 47% had focal neurologic deficits in the second study (8).

The study of Rea et al. showed that during follow-up (mean of 7 years), 35% had progressive arteriopathy (progressive vessel stenosis, new infarct or MMS) requiring revascularization surgery (8).

Compared to those results, our patient had a symptomatic vasculopathy, presenting like a sylvian left stroke and a left CCA occlusion, with no suggestive image of MMS on the arteriography. Vasculopathy of the CCA is an unusual arteriopathy and is rarely described, as opposed to the distal ICA arteriopathy. We only found one other case report reporting an occlusion of CCA linked to NF1, fortuitously discovered during orthognathic surgery for right hemifacial hypoplasia (10). Occlusion of CCA is mostly due to atherosclerosis and thus affecting old patients suffering from comorbidities. Other etiologies are arteritis, radiotherapy exposure, trauma, thrombophilia and cardiac embolism, which have been ruled out in the check-up at the admission of our patient. Dissection, aneurysm, vasculitic involvement or fibromuscular dysplasia have been excluded by MRI of the vascular walls (*figure 2*). This CCA occlusion is thus probably associated to NF1, by physiopathology of neurofibromin described before.

Children with NFI have a risk of developing cerebral arteriopathy. Some authors recommend to perform regular brain MRAs and a close follow up for progression of the vasculopathy (3, 7, 8). Those recommendations may improve the management of those patients.

Our patient was treated in an official European Stroke Center, so that immediate mechanical thrombectomy could be performed. Although he is

Figure 1.
a. Axial diffusion-weighted magnetic resonance imaging apparent diffusion coefficient (ADC)-MAP: hypointensity in paraventricular frontal white matter due to restricted diffusion : acute ischemic stroke.
b. Axial T1-weighted magnetic resonance imaging after gadolinium injection: occlusion on the proximal M1 segment of the left middle cerebral artery (arrow).

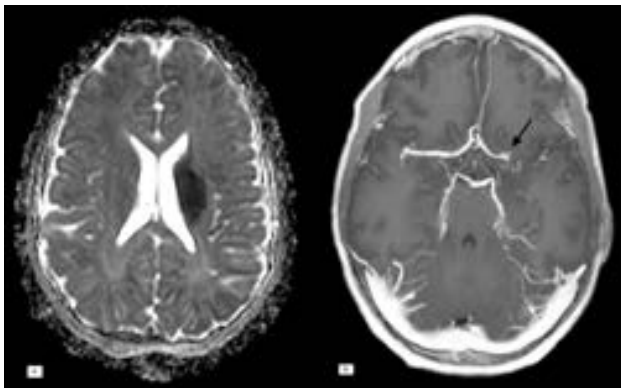


Figure 2.
Maximal intensity projection (MIP) frontal view obtained from a Phase Contrast Angiography (PCA) acquisition: absence of signal due to an occlusion of the proximal part of the common carotid artery (CCA) (arrow 1). Segmental stenosis of the CCA (arrow 2) and upper permeability of the CCA (arrow 3) due to retrograde flow via the Willis circle.

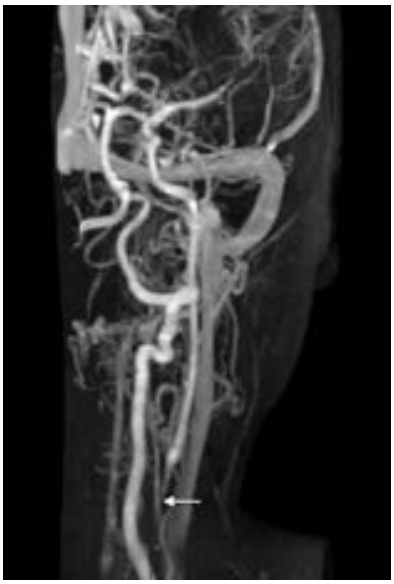


Figure 3.
a. Pre-thrombectomy digitalized subtraction angiography (DSA): anteroposterior view of the right vertebral artery opacification. The left supraclinoid internal carotid artery (ICA) is opacified through the posterior communicating artery (arrowhead). The arrow indicates the proximal stop on the M1 segment of the left MCA.
b. Post-thrombectomy DSA: oblique view of the left vertebral artery opacification. Partial recanalization of the left MCA territory has been achieved. The M1 (arrow) and M2 segments (arrowhead) are now opacified. The petrous ICA is indirectly opacified through opening of cervical collaterals (double arrow).

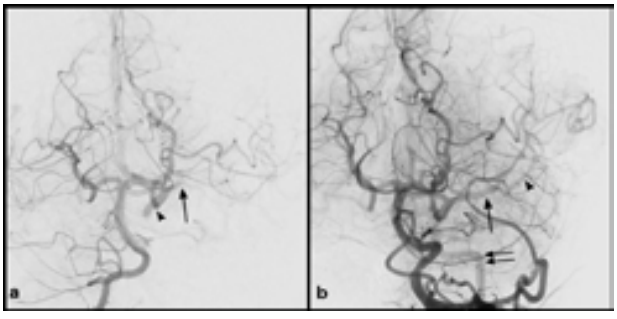
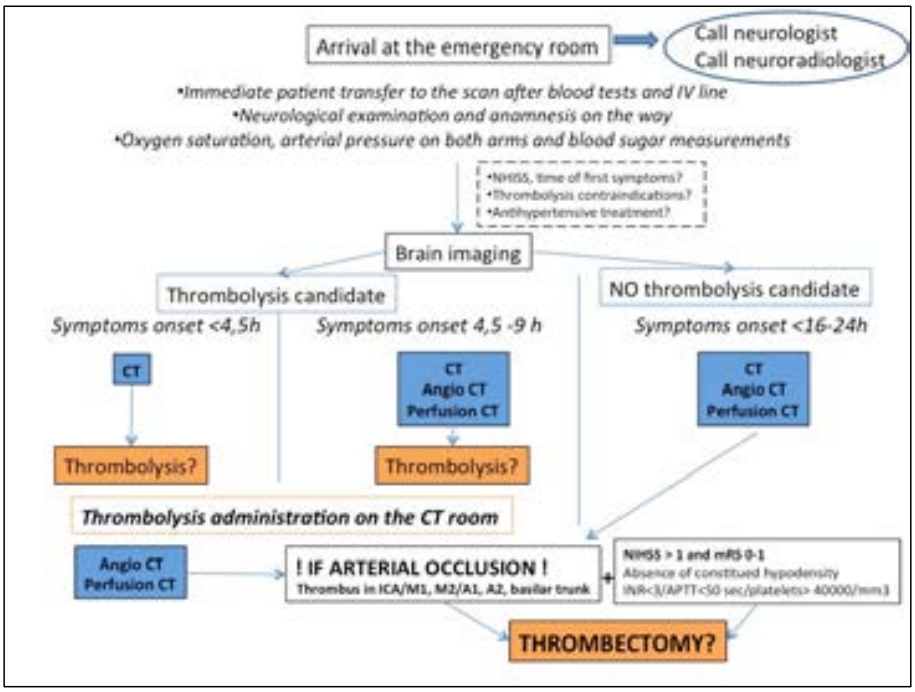


Table.

Guidelines for medical care of a suspected stroke in Erasme Hospital (adults guidelines): The patient of our case report is not a candidate to thrombolysis because there was a delay from onset of symptoms exceeding 4.5-9 hours. Computerized tomography and MR- angiographies showed a proximal left MCA occlusion (M1 segment) due to a thrombus and NIHSS was bigger than 1, so a mechanical thrombectomy has been performed.



CT: computerized tomography; ICA: internal carotid artery; NIHSS: National Institutes of Health Stroke; mRS: modified Rankin Scale ; INR: international Normalized Ratio ; APTT: activated partial thromboplastin time.

not eligible for thrombolysis, in this case, it showed a positive result and evolution. There is lacking data about thrombectomy in children, but in recently published childhood stroke guidelines, treatment with reperfusion therapies is allowed within the recommended time windows for adults (2,3). Some selection criterias are proposed by the American heart association/ American Stroke association : i) persistent disabling neurological deficits, ii) radiographically confirmed cerebral large occlusion, iii) older children (because of size-based limitations about catheter size, use of contrast and radiation exposure but there is no evidence to determine an age-limitation), iv) implication of neurologists with expertise in the treatment of children with stroke, and v) intervention performed by an experimented endovascular surgeon (3). Our patient completed those criterias, and his recanalization therapy has been successful.

Comparing to adults, children are not often exposed to reperfusion therapies, because of diagnostic delays. This is mostly due to clinical misdiagnosis of stroke linked to initial investigation with CT, which only has a sensitivity of 16 to 50% (2). New guidelines recommend thus MRI as the initial imaging modality to shorter the time to diagnosis. If MRI is not available, angio-CT is a good alternative. Although radiation and contrast exposure are better to be avoided. Recent studies, however, have demonstrated the feasibility of obtaining rapid MRI in the ED in children (2).

Finally, antithrombotic therapies are important for stroke prevention, particularly for children with arteriopathy and high recurrence risk (3). There are also few pediatric studies on this subject but a majority recommend the use of acetylsalicylic acid (3-5 mg/kg) (3). While adult recommendations favor a dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) in case of TIA or minor ischemic stroke. We have chosen the adult approach after interdisciplinary discussion. This preventive medication has to be continued for a minimum of two years (3).

Conclusion

The particularity of this case report is that our patient suffers from AIS linked to the occlusion of the CCA, probably due to NF1, which is rarely described. In addition, he has been treated with immediate mechanical thrombectomy, which is uncommon in children because of delayed diagnostics, and showed a good clinical evolution.

Furthermore, he had access to MRI in emergency, which is a major challenge, particularly in younger children requiring sedation or anesthesia.

We therefore wanted to emphasize the need for rapid and effective management of these patients, for particularly referral centers with experimented neurointerventionalists.

Conflicts of Interest

The authors declare there is any conflict of interest for any of the authors.

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