Case Report

Endovascular management of spontaneous intracranial pseudoaneurysms in a pediatric patient with Noonan syndrome. A mere coincidence or a possible association with the disorder?

Sofia Athanasiou¹, Christina Aslanidi¹, Vasileios Mamalis¹, George Markogiannakis², Antonios Tsanis¹, Eftichios Arhontakis¹

¹Department of Interventional Radiology, Red Cross Hospital, ²Department of Neurosurgery, Children’s Hospital Agia Sofia, Athens, Greece.

E-mail: Sofia Athanasiou - sofathanasi122@gmail.com; *Christina Aslanidi - christina.aslanidi178@gmail.com; Vasileios Mamalis - marios76m@hotmail.com; George Markogiannakis - markogiannakisgeo@hotmail.com; Antonios Tsanis - antontsanis1@gmail.com; Eftichios Arhontakis - arhodakise@gmail.com

**Corresponding author:**
Christina Aslanidi,
Department of Interventional Radiology, Red Cross Hospital, Athens, Greece.
christina.aslanidi178@gmail.com

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**ABSTRACT**

**Background:** Noonan syndrome (NS) is a rare autosomal-dominant neurodevelopmental disorder, which typically develops abnormalities of the craniofacial development and congenital heart defects. A number of cerebrovascular anomalies have also been occasionally described previously in the setting of NS. The assumption that NS can induce the formation of intracranial pseudoaneurysm (IAP) or the rupture of an already existing abnormality is yet unknown.

**Case Description:** We encountered a rare case of a 9-year-old NS patient with two IAPs presenting with episodes of intracerebral hemorrhage that were successfully managed with endovascular embolization.

**Conclusion:** This case represents a possible association between NS and the presence of ruptured IAPs.

**Keywords:** Intracranial pseudoaneurysm, Endovascular treatment, Noonan syndrome, Pediatric

**INTRODUCTION**

Noonan syndrome (NS) is an autosomal-dominant neurodevelopmental disorder caused by germline mutation in genes coding for proteins that are part of the RAS/mitogen-activated protein kinase pathway, with an incidence of between 1 in 1000 and 1 in 2,500 live births.⁴ Typical features of the syndrome include facial dysmorphism, eye pathology, congenital heart defects, skeletal abnormalities, short stature, and cryptorchidism.⁵ Although less frequently, cerebrovascular abnormalities have also been described previously.³ However, intracranial pseudoaneurysms (IPAs) have not yet been associated with NS. IPAs constitute an uncommon cause of intracranial hemorrhage, and they account for <1% of all intracranial aneurysms.³ They are highly unstable lesions, characterized by a disruption in the vessel wall, resulting in an encapsulated hematoma in communication with the ruptured artery.⁶ IPAs may occur secondary to infection, trauma or iatrogenic causes whilst spontaneous IPAs are extremely rare.⁷ We present a case of a 9-year-old boy with NS, who presented with two episodes of intracerebral hemorrhage, secondary to IPAs in different locations. The patient was successfully treated with endovascular embolization.
CASE DESCRIPTION

A 9-year-old male patient was admitted to our emergency department with a sudden onset of headache, nausea and vomiting, and severely altered mental status. His medical history included NS. Subsequently, he underwent a computed tomography (CT) scan of the brain, which depicted a massive left-side frontoparietal intracerebral hematoma with associated subarachnoid hemorrhage [Figure 1]. However, he had no history of major trauma or severe infection. After taking into consideration the clinical signs, symptoms and imaging findings, the patient was sedated, intubated and admitted immediately to the Interventional Radiology Unit of our hospital for endovascular treatment. In particular, digital subtraction angiography (DSA) (4-vessel study) was performed, which revealed a fusiform aneurysmal dilatation in the left pericallosal artery, a distal segment of anterior cerebral artery [Figure 2]. It also revealed delayed contrast medium filling and emptying without a clear aneurysmal neck, typical characteristics of pseudoaneurysms. Under general anesthesia, a 5F multipurpose guiding catheter was placed in the left internal carotid artery, and a microcatheter was navigated and positioned in the left callosomarginal artery. Embolization of the pseudoaneurysm of the callosomarginal artery was achieved using coils (MicroPlex 10 Hypersoft 3D 5 mm/10 cm (MicroVentionInc, Tustin, CA, USA), MicroPlex 10 HyperSoft Helical 5 mm/8 cm, MicroPlex 10 HyperSoft Helical 3 mm/6 cm and a ev3 Axium Helix 2 mm/6 cm (ev3, Irvine,CA, USA). Then, injection of Onyx18 (cv3, Irvine, CA, USA) was performed to occlude the distal part of the callosomarginal artery [Figure 3]. Twenty-two months later, the patient was readmitted with the same clinical presentation, and the DSA demonstrated a second IAP in the frontoparietal branch of the right middle cerebral artery in the M2 segment [Figure 4]. On the same day of the admission, the decision was to emergently proceed to endovascular repair. The aim of the endovascular approach was to occlude the pseudoaneurysm as well as the parent

Figure 1: Non-contrast CT demonstrates a left-side frontoparietal intraparenchymal hemorrhage with associated subarachnoid hemorrhage.

Figure 2: Lateral angiogram showing pseudoaneurysm of the left callosomarginal artery.

Figure 3: Postembolisation lateral global angiogram showing complete occlusion of the pseudoaneureysm and the segment of the callosomarginal artery prior to the pseudoaneurysm using coils and Onyx18.

Figure 4: Lateral angiogram showing pseudoaneurysm of the M2 branch (superior division) of the right middle cerebral artery.
artery using coils and glue (Glubran 2/Lipiodol). Complete embolization of the second pseudoaneurysm was achieved following the same endovascular technique [Figure 5]. The postoperative period presented no major complications. Seven weeks after endovascular repair, the patient was fully conscious and cooperative, with no focal neurologic deficit. The first follow-up after endovascular treatment is scheduled 3 to 6 months after the procedure, and then MRI angiography should be performed for annual surveillance.

DISCUSSION

Cerebrovascular abnormalities that have been previously reported in association with NS include cerebral arteriovenous malformations, intracerebral occlusive artery disease, aneurysms, hypoplasia of the posterior cerebral vessels, cerebral cavernous malformations, and moyamoya disease. To the best of our knowledge and extensive literature research, only a few cases of intracranial aneurysms in the setting of NS have been reported, whereas IPAs have not yet been associated with the syndrome. Nonetheless, a few cases of coronary artery aneurysms have been reported in adolescent and adult patients with NS. The etiology of the coronary artery aneurysms remains unclear; it has been postulated that the PTPN11 gene mutation might be responsible along with other causes including a jet flow from a bicuspid aortic valve, concomitant hypertrophic cardiomyopathy and connective tissue disorders.

IPAs are an infrequent but rather underdiagnosed cause of intracranial hemorrhage, constituting <1% of all intracranial aneurysms in adults. Despite their rarity, according to previous studies, the incidence rate in the pediatric group is more than 19%. IPAs can occur spontaneously or secondary to trauma, infections, iatrogenic causes, or malignancies. IPAs have also been associated with Marfan syndrome, fibromuscular dysplasia, vasculitis, moyamoya disease, and radiotherapy. They are highly unstable lesions characterized by the lack of complete aneurysm wall structure and the presence of organizing hematoma and fibrosis instead of normal vascular elements. Reports of spontaneous IPAs are exceptionally rare and are limited to only a few clinical case reports. In the present case, we could not determine the exact etiology of the IPAs. Even though moyamoya disease, which may manifest with intracranial aneurysms in the setting of NS, our patient did not meet the diagnostic criteria of the disease. Unfortunately, our patient was not investigated for the mutation associated with coronary artery aneurysms in NS, so a possible association cannot be ruled out.

The presenting symptoms may vary depending on the rupture status, location, and size of the IPA. Headache is the most common presenting symptoms of ICAs. Other usual complaints include nausea and vomiting. Loss of consciousness and seizures may also be encountered. According to Chen et al. the most frequent neurological signs in pediatric patients include meningeal irritation, followed by cranial nerve deficit and homonymous hemianopia. In cases of intracavernous internal carotid artery pseudoaneurysms, epistaxis is commonly seen due to the proximity to the sphenoid sinus.

Early diagnosis and treatment are essential, as IPAs have a mortality rate of 50% if left untreated, due to the high risk of embolic events and rupture. DSA remains the gold standard imaging modality for the diagnosis of IPAs. A globular shaped aneurysmal sac without a neck along with delayed filling and stagnation of contrast agent designate a pseudoaneurysm. That explains why some pseudoaneurysms may only be visualized in the late injection stages of the angiography.

There are a number of potential treatment options, all of which require consideration to determine the most appropriate management. Historically, surgical intervention has been the treatment of choice, including trapping, in which clips are placed on the parent vessel, both proximal and distal to the pseudoaneurysm, with or without bypass revascularization. However, concerns remain about craniotomy surgery regarding the sacrifice of the parent artery and consequent ischemic complications. With improvement in endovascular skills and availability of newer technology, endovascular techniques including coil embolization, stent reconstruction, or parent artery balloon occlusion are becoming the treatment of choice. These methods have become the preferred choice for many pediatric and adult patients due to their minimal invasiveness.

Packing of the IPA with coils is preferable for narrow-necked pseudoaneurysm. The main advantage of this selective embolization is the complete IPA exclusion with integrity of the parent artery. However, due to the fragility of the pseudoaneurysm wall, it has the risk of microcatheter or coil perforation throughout the procedure. Moreover,
IPA recurrence remains a major issue for patients treated with simple coiling, as its impaction into the thrombus may force the flow pulsatility into the interstices of the coil mass.[7] Consequently, other studies suggest that it may be unavoidable for distal IPAs to occlude not only the pseudoaneurysm, but also the parent artery. This technique represents a rapid and safe method of treatment, due to the presence of good collateral supply or retrograde flow from the distal to the trapped segment.[12] Coils or liquid embolic agents including N-butylcyanoacrylate and Onyx can be used in the occlusion of the parent artery. Furthermore, another promising option for wide-necked IPAs is stent-assisted coiling, which allows preservation of the parent artery, but carries a high risk of IPA recanalization.[3] On the other hand, overlapping stents with coils, as an alternative technique, effectively prevents rebleeding and regrowth of the IPA, diverting the flow away from the IPA, accelerating intra aneurysmal thrombosis and promoting neointima formation of the parent artery.[6]

In addition, covered stent implantation constitutes another reconstructive endovascular treatment, which can exclude blood flow through the stent as a physical barrier and retain the normal anatomic flow through the parent artery. In contrast to uncovered stents, covered stents decrease the possibility of neointimal proliferation and restenosis, reducing embolization risk caused by thrombus debris during the procedure of stent deployment.[11,16] The main limitation for its usage is the improbability of passing in the tortuous intracranial vasculature.[16]

Flow-diverting strategy has emerged as a viable treatment option for selected intracranial aneurysms and IPAs, as they are specifically designed to maintain laminar flow in the parent artery and side branches, reducing flow velocity and promoting thrombosis of the aneurysmatic sac.[9] However, the disadvantages of flow-diverter stents are delayed aneurysm obliteration due to a lack of immediate thrombosis and the absolute requirement of antiplatelet therapy, which may increase the risk of postoperative intracranial hemorrhage.[1]

CONCLUSION

We report the case of a young patient with NS who had two IAs, a hitherto unreported finding in patients with this syndrome. Nonetheless, this case represents a possible association between NS and cerebral pseudoaneurysms, which definitely needs further research to assess whether a true correlation between the aforementioned pathologies exist.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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