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Case report

# Twig-like middle cerebral artery in a case of neurofibromatosis type 1

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**Abstract.** Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder with multisystemic involvement, affecting central nervous system, skin, bone system and vessels, with a very heterogeneous clinical presentation. Vascular abnormalities are typically recognized in neurofibromatosis type 1 affecting cardiovascular and cerebrovascular systems. The incidence of circle of Willis anomalies in children with NF1 is twofold higher than in general population. In this paper, we report of 19-years-old female with NF1 and twig-like middle cerebral artery. (www.actabiomedica.it)

**Key words:** Neurofibromatosis type 1, Twig-like anomaly, TOF-MRA

## Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant phacomatose with NF1 gene mutation located on chromosome 17q11.2. Only in 1/3 of cases it is a "de novo" mutation. More than 250 mutations have been identified in affected individuals. The neurofibromin is an inhibitor of the ras/mitogen-activated protein kinase pathway, important regulator of cellular growth and differentiation. The estimated incidence of NF1 is 1:3000. It is a multisystem pathology whose clinical presentation is very varied; the organs most affected are the skin, the nervous system and the vessels (1).

Diagnostic criteria were defined in 1987 by National Institutes of Health (NIH) Consensus Development Conference and revised in 2021 by Legius et al (2).

Vasculopathy linked to NF1 is significant but underdiagnosed, it can affect venous and arterial vessels. Most affected systemic arterial vessels are the renal arteries, however, among the brain vessels the most affected are the internal carotid branches middle cerebral artery (MCA) and posterior cerebral artery (PCA). The most frequent vascular anomalies are stenosis, aneurysms, vascular ectasias, Moya-moya disease (MMD) and anomalies of the circle of Willis (3).

We present a case of young female patient with NF1 with an occasional finding of vascular MCA anomaly.

## Case description

A 19-years-old female with NF1 was admitted to our hospital for routine follow-up.

The neurological examination was normal. Physical examination revealed one left ankle neurofibroma and ophthalmological examination revealed the presence of two Lisch nodules in left eye, and one into the right one.

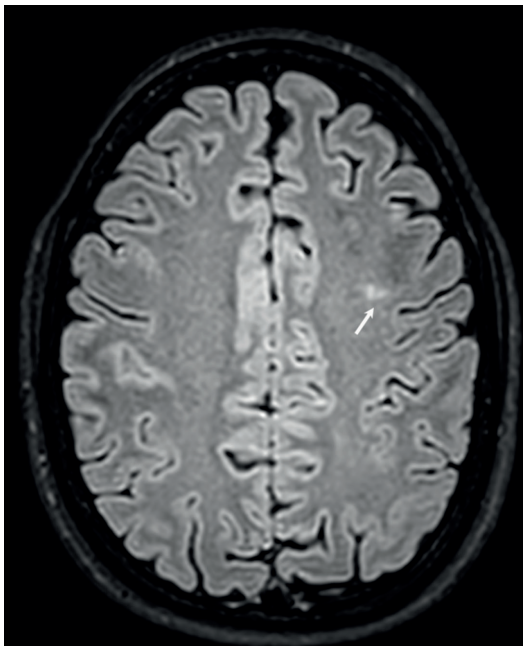

**Figure 1.** Axial T2-FLAIR brain MRI shows multiple small foci of hyperintensity localized in left fronto-parietal white matter (white arrow).

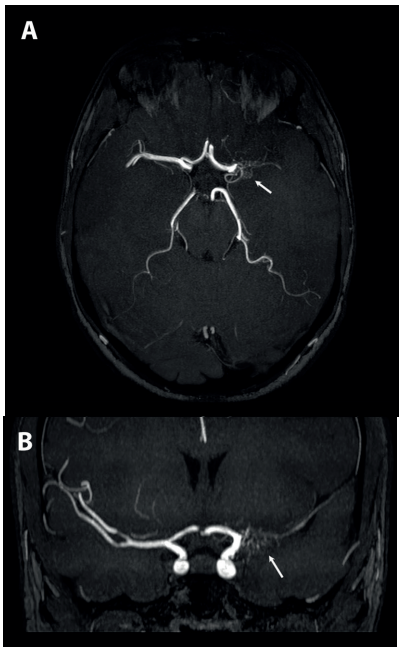


**Figure 2.** A) 3D MRA Time of flight (TOF) Circle of Willis, axial MIP reconstruction B) 3D MRA Time of flight (TOF) Circle of Willis, Coronal MIP reconstruction reveal the lack of flow in the segment M1of the left middle cerebral artery (MCA) replaced from many small serpiginous vessels (white arrows) and regular delineation of the left opercular vessels. Notice hypertrophy of left posterior cerebral artery (PCA).

Regarding other investigations: x-ray chest, electrocardiogram, biological tests like complete blood cell count, glycemia, blood biochemistry and urine test were normal.

3 Tesla Brain MR examination was performed and revealed small foci of subcortical hyperintensity in long TR sequences in left frontal and parietal white matter (Figure 1).

Time of flight (TOF) MR angiography revealed the lack of flow in the first segment (M1) of the left middle cerebral artery (MCA) replaced by many small serpiginous vessels with consequent recovery flow signals in the M2 and M3 tracts and reduced representation of the left frontal-parietal cortical vessels. Hypertrophy of left posterior cerebral artery (PCA) and compensation by branches originated by P2 segment were seen in order to irrorate left parieto-temporal region. No more stenosis were seen bilaterally in the ICA and in the Circle of Willis' feeders (Figure 2).

A transcranial Doppler ultrasound examination was performed by neurologists as a routine non-invasive examination in vascular diseases and showed an asymmetry of the flow velocities of the middle cerebral arteries; the left one was smaller than the right one with relative increase of the left anterior and posterior cerebral artery velocities, like indirect sign of compensation.

The patient underwent an angiographic examination with selective study of the carotid arteries due to the anomaly reported in TOF-MR and confirmed agenesis of the M1 tract of the left middle cerebral artery, replaced by plexiform arterial network, without more stenotic vessels. Regular delineation of the left opercular vessels of the left MCA (Figure 3).

Due to the absence of focal stenosis, the arterial anomaly revealed by MRA in our patient was not life-threatening and did not require any medical treatment.

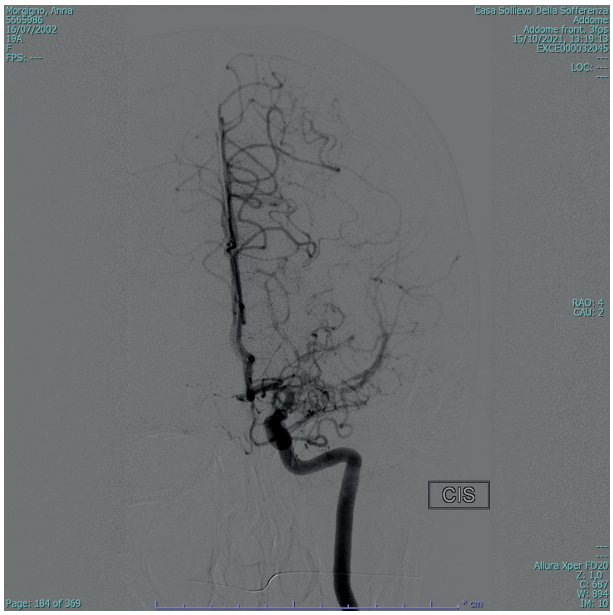


**Figure 3.** Left internal carotid artery angiography, AP view, shows lack of visualization of the M1 tract of the left middle cerebral artery replaced by plexiform arterial network. Regular delineation of the left opercular vessels. The distal MCA beyond the plexiform arterial networks shows thinner caliber than other segments.

## Discussion

The incidence of vasculopathy in NF1 patients has not been determined and varies between studies from 1% in symptomatic children to 8% in asymptomatic children. The vasculopathy mechanisms in NF1 are not well known, but probably the defect in neurofibromin production causes proliferation of smooth muscle cells and consequent hyperplasia of the intima of the vessel and occlusion of the lumen. Usually these anomalies are asymptomatic, in some cases symptoms can be present and they include hemiplegia, nystagmus, aphasia and headache. In order to prevent and treat these young patients, the diagnosis of cerebrovascular anomalies is fundamental (4).

Few publications are present in literature, but it is known the higher prevalence of cerebrovascular anomalies in patients with NF1 compared to control groups (2.5% - 6%) (5). Monika Bekiesińska-Figatowska et al. (6) proved that the 43,3% of the patients with NF1 had circle of Willis anomalies (fetal configuration, anterior/posterior cerebral artery hypoplasia, anterior communicating artery hypoplasia and vertebral artery hypoplasia). One patient in this group showed the sign of MMD.

In our case, the mother of our patient was affected by NF1 and clinically she had one left ankle neurofibroma and two Lisch nodules in left eye, and one in the right one, meeting the diagnostic criteria for NF1. Our patient underwent MRI examination with Time of Flight 3D angiography that showed some bright spots on long TR sequences in subcortical white matter in left fronto-parietal region. In patients with neurofibromatosis, these hyperintensities could be referred to unidentified bright objects (UBOs). Their pathogenesis is unknown, probably it is the result of intramyelinic edema with consequent alteration of white matter (7).

In our patient, these hyperintense T2 lesions are unilateral on the left (the side of the vascular alteration), for this reason we cannot exclude that they are due to chronic hypoxic phenomena. TOF sequences are easy to perform, they do not require contrast media and depict with high diagnostic performance arterial feeders of the circle of Willis (8). In our patient TOF MRA showed anomaly of left MCA resembling a particular type of MCA aplasia called twig-like anomaly or Moya-moya like manifestation. In NF1 patients and in particular the asymptomatic ones, it seems particularly important to differentiate between congenital malformations and vascular disorders due to the possibility of complications and disability. The most important differential diagnosis of the twig-like MCA is Moyamoya disase, in particular the unilateral form. The pathogenesis and the outcome of these two conditions are very different. Twig-like MCA is a replacement of the M1 segment by a plexiform network of small vessels. It is a rare anomaly with prevalence in patient with NF1 of 0.1-1% in literature. Twig-like is a congenital malformation that occurs during the development of MCA, when the embryo is 28–30 days. At the beginning a plexiform arterial twigs appears, and later develops, by fusion and regression, into lateral striate arteries and the trunk of MCA. The fusion failure of primitive arterial network causes the persistence of plexiform network of small vessels with replacement of the M1 segment (9).

Moyamoya disease (MMD) is progressive stenoocclusive disorder of distal branches of the internal carotid artery. The vessel's occlusion can cause the formation of abnormal collateral compensatory circles, creating the typical angiography pattern, called "puff of smoke"(10-11). Moyamoya vasculopathy associated with an underlying systemic condition is named moyamoya syndrome.

In patient with NF1, it is important to differentiate Moyamoya syndrome from twig-like anomaly of the MCA due to the progression of Moyamoya in bilateral lesions as reported in some literature studies (12-13-14) and the possibility of ischemic events. Moyamoya syndrome represent a potentially serious vasculopathy that needs surgical or neurovascular intervention.

Some features in our case directed the diagnosis to twig-like variant, in particular unilateral involvement, regular delineation of the peripheral branches and the absence of other stenotic vessels.

However, at this moment MMD diagnosis cannot be excluded considering the lack of previous imaging examinations and some literature reports of unilateral Moyamoya (15).

Clinical guidelines recommend regular monitoring of NF1 patients, but actually there is no consensus on the most appropriate screening method in case of vascular anomalies, particularly in asymptomatic patients. MR Angiography could be an accurate routinary diagnostic non invasive technique for evaluating intra and extracranial arterial feeders of asymptomatic patients in order to assess a potential neuroradiologic evolution, due to the risk of early stroke or other complications that contribute to mortality in younger patients. In case of progression or clinical symptoms onset an angiographic examination could be the best modality for diagnosis and therapy.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Ethics Approval and Patient Consent Statements:** An approval from our Institutional Ethics Committee was obtained (protocol number V5-release date 28.04.2022). Written informed consent for publication of their details was obtained from the patient.

**Author Contributions Statement:** OGV contributed to writing and review the case; GD contributed to conceptualization and draft preparation, BC to figures post-processing and editing, GC and VD to revision the text and English; NM and CG contributed with angiographic evaluation.

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