Neurofibromatosis type 1 associated with moyamoya syndrome. Case report and review of the literature

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Abstract
Neurofibromatosis type 1 (NF1) is a genetic disorder with a very heterogeneous clinical picture, affecting central nervous system, skin and bone system. Cerebrovascular lesions, such as moyamoya syndrome, are rarely seen in NF1. Approximately 250 children with NF1 and moyamoya syndrome have been reported. The clinical picture includes hemiparesis, hemianopsia, paresthesia, seizures, speech disorders, and intellectual disability. In this paper, we report on a 6-year-old girl with NF1 and moyamoya syndrome, with a brief review of the existing literature.

Keywords: neurofibromatosis type 1, moyamoya syndrome, cerebrovascular anomalies, neuroimagistic studies.

Introduction
Neurofibromatosis type 1 (NF1, MIM #162200) or von Recklinghausen disease is a RASopathy caused by germline mutations in neurofibromin 1 (NF1) gene, with multisystemic involvement, affecting skin, central nervous system and bone system [1, 2]. It is one of the most frequent human autosomal dominant genetic diseases, affecting approximately one in 2600–3000 people, irrespective of gender or ethnic origin [3, 4]. The clinical description is extremely heterogeneous, ranging from benign cutaneous lesions to severe manifestations and complications: brain and peripheral nerve tumors, skeletal abnormalities, neurodevelopmental disorders. The main clinical features include café-au-lait spots, axillary or inguinal freckling, neurofibromas, Lisch nodules (hamartomas), optic glioma, and distinctive skeletal abnormalities. These clinical core findings are highly specific for NF1 making genetic testing rarely needed for diagnosis.

Moyamoya disease was described for the first time by Takeuchi & Shimizu (1957) [5], as hypoplasia of bilateral internal carotid arteries. In 1969, Suzuki & Takaku [6] reported this vascular anomaly as moyamoya, which means in Japanese “puff of smoke”, representing the angiographic aspect of collateral vessels. Moyamoya disease is currently defined as a progressive internal carotid arteries occlusion and development of basilar cerebral collaterals, compensatory [7]. It has an incidence of around 0.54 per 100 000 individuals, with a higher incidence in East Asia, and is responsible for one fifth of cases of pediatric stroke caused by a vascular condition [8]. Moyamoya vasculopathy associated with an underlying systemic condition is named moyamoya syndrome. Acquired causes of moyamoya syndrome include autoimmune vasculitis (systemic lupus erythematosus, Sjögren syndrome), Graves’ disease, cranial therapeutic irradiation. Inherited causes of moyamoya syndrome include NF1, sickle cell anemia, Noonan syndrome, Alagille syndrome, aneuploidy disorders (Down syndrome, Turner syndrome) [9, 10].

Aim
Herein, we report on a 6-year-old girl with NF1 and a rare clinical feature – moyamoya syndrome –, with a brief review of the existing literature. Personal consent and approval of the Ethics Committee of “Prof. Dr. Alexandru Obregia” Clinical Hospital of Psychiatry, Bucharest, Romania, were obtained prior to publication of this paper.

Case presentation
A 6-year-old girl was admitted in our Department for acute left-sided weakness. The medical history of the patient revealed a thoracic scoliosis diagnosed one year ago for which physical therapy was recommended. The physical examination revealed numerous café-au-lait spots, with various size (larger than 5 mm), disseminated all over the body (Figure 1, a and b) and freckling in the axillae and the inguinal area, thus fulfilling the diagnostic criteria for NF1 [11]. The neurological examination showed thoracic scoliosis of around 45 degrees, left central facial palsy, left limbs hemiparesis with increased muscle tone of upper and lower limbs, increased tendon reflexes, Babinski sign on the left side, and dysarthria. Psychological evaluation showed a mild mental retardation (IQ 53).

The clinical examination of the patient mother revealed the presence of nine café-au-lait spots disseminated on her body.
Figure 1 – (a and b) Pictures of the patient’s body showing café-au-lait spots with various size.

Biological tests and ophthalmologic examination of the patient were normal. Brain magnetic resonance imaging (MRI) revealed multiple lesions in the parietal and occipital cortex, distributed bilaterally, but with a predominance on the left side; also, multiple small foci of T2 prolongation localized on the right side, in parietal, capsular and basal ganglia white matter (Figure 2, a and b).

Thoracolumbar MRI showed dextroconvex scoliosis with severe T12–L1 angulation, without medullar or radicular compression signs. The cerebral angiography detected moyamoya stage V alterations, with occlusion of right and left internal carotid arteries at bifurcation and presence of neoformation vessels (Figure 3, a–d). After two weeks, the patient had left focal seizures with postictal motor deficit, predominantly affecting the left lower limb. The electroencephalogram (EEG), on the temporal derivations, showed sharp-waves discharges, especially on the right side. The clinical data associated with cerebral imaging studies led us to the diagnosis of NF1 with moyamoya syndrome.

Figure 2 – (a and b) T2-FLAIR axial brain MRI images showing multiple lesions in the bilateral parietal and occipital cortex, and multiple small foci of hyperintensity in the right parietal, capsular and basal ganglia white matter (black arrows). FLAIR: Fluid-attenuated inversion recovery; MRI: Magnetic resonance imaging.

Figure 3 – (a–d) Four-vessels cerebral angiography showing occlusion of both internal carotid arteries at bifurcation (black arrows), with development of neoformation vessels, suggestive for moyamoya stage V.

**Discussions**

The diagnosis of NF1 is based on the clinical criteria established by the National Institutes of Health (NIH) Consensus Development Conference [11]. According to these criteria, a definitive diagnosis of NF1 is considered if two or more of the following clinical features are present: six or more café-au-lait spots, with a diameter more than 5 mm pre-puberty or 15 mm post-puberty, axillary or inguinal freckling, two or more neurofibromas of any type or one reticular neurofibroma, two or more Lisch nodules (hamartomas), an optic glioma, skeletal abnormalities (sphenoid dysplasia or pseudarthrosis of the tibia), and a first degree relative suffering from NF1 [11–13].

NF1 is an autosomal dominant genetic disorder caused by mutation in NF1 gene, located on chromosome 17 (17q11.2) [1]. The protein product of NF1 gene is neurofibromin, has a guanosine triphosphatase activating domain that negatively regulates Ras activity [2]. NF1 may present a high intra-familial and inter-familial clinical variability. There is a large spectrum of central nervous system manifestations, including learning disability, mental retardation, seizures, attention-deficit with hyperkinesia disorder, neurofibromas, optic nerve glioma [14]. Cerebrovascular...
lesions, such as moyamoya syndrome are rarely seen in NF1 [15].

The incidence and prevalence of vascular lesions, both peripheral and cerebral, in children with NF1 varies between studies, ranging from 1% (in symptomatic children) to 3% (in asymptomatic children); however, cerebral vasculopathy may be under-recognized, as only a proportion of patients undergo neuroimaging studies [16]. Both arterial and venous vessels can be affected, different lesions being reported (occlusion, aneurysm, pseudoaneurysm, ectasia, stenosis, fistula, rupture) [16].

In patients with NF1, the prevalence of moyamoya syndrome is estimated at around 0.6% [17]. However, other authors reported a higher prevalence (3–6%), most of the patients being asymptomatic in the first stages of the disease [10, 16]. Since 1976, approximately 250 children with NF1 and moyamoya syndrome have been reported in the literature [17]. The clinical picture includes hemiparesis, hemianopsia, paresthesia, seizures, speech disorders, and intellectual disability, mostly secondary to ischemic events; however, most patients are initially asymptomatic [17].

Brain computed tomography (CT) may show hypodense images, corresponding to the area of infarction or, less frequent, hemorrhage [18]. For diagnosis of moyamoya syndrome, magnetic resonance angiography (MRA) has a sensitivity of 73%, which can increase to 92% when is associated with MRI, and a specificity of 100%, showing particular vascular aspect; brain MRI provide information about ischemic or hemorrhagic brain lesions [16]. Angiography is the gold standard for diagnosis of moyamoya vasculopathy and for surgical intervention, it allows description of the six degree of severity of vascular anomalies: first degree – stenosis of the carotid artery, the second and third degree – development of the moyamoya type of collateral vessels; the fourth and fifth degree – disappearing of the collateral vessels; the sixth degree – the collateral vessels are invisible, there are only collateral vessels from external carotid arteries [18–20].

In our patient, the diagnosis of moyamoya syndrome was established by MRI with MRA and by angiography. Interestingly, the diagnosis of NF1 was established in the same time with diagnosis of moyamoya. An early diagnosis of NF1 in this girl could have identified early vascular lesions in an asymptomatic phase, and a neurosurgical intervention could have been planned.

The histopathological findings of moyamoya vasculopathy are represented by smooth muscle proliferation with thickened intima and tortuous duplicated internal elastic lamina [17]. Some authors described also anomalies of inflammatory mediators and vascular growth factors [17].

The pathogenic mechanism of moyamoya vasculopathy in NF1 is not very clear. It is suggested, however, to be due to other neurofibromin roles, besides disruption of Ras activities, as moyamoya syndrome is a rare occurrence in other RASopathies (Noonan and Costello syndrome) [10, 18]. Neurofibromin was found in the endothelial layer of cerebral arteries, in experimental models. It was suggested that lack of neurofibromin expression may account for the proliferation of vascular smooth muscle cells [17], which is responsible for the development of obstructive vascular disease.

Although some authors are in favor of a routine MRI screening in all NF1 patients, the current guidelines for NF1 patient’s management recommend, for asymptomatic patients, clinical monitoring for features suggestive for ischemic events (motor deficits, seizures), taking into consideration the small incidence of vasculopathy, a routine brain MRI/MRA is not recommended in these patients, but only in symptomatic patients [11].

Regarding the management of moyamoya vasculopathy in NF1 patients, the surgical treatment is the only one which can improve the vascularization and prevent the ischemic strokes by increasing the collateral flow from external carotid artery [21]. The revascularization techniques are divided in three main groups: indirect bypass (non-anastomotic), direct bypass (anastomotic) and combined procedures, and include encephaloduroarteriosynangiosis and pial synangiosis [21]. It has to be taken into consideration that revascularization surgery gives good results in cases with early moyamoya syndrome diagnosis [18, 22].

5 Conclusions

Moyamoya vasculopathy, although rare, is one of the most serious complications of NF1 syndrome and a cause of ischemic stroke in children. A MRI with MRA screening in children with NF1 could identify this anomaly in an early stage, even in asymptomatic patients. This could prevent the neurological problems secondary to vascularization deficit characteristic to the advanced stages of the moyamoya syndrome.

Conflict of interests

The authors declare that they have no conflict of interests.

Funding

This work was partially supported by UEFISCDI, Grant No. 249PED/2017.

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Received: June 20, 2018
Accepted: October 23, 2019