Neurological Sciences (2019) 40:1475–1476
https://doi.org/10.1007/s10072-019-3728-8

LETTER TO THE EDITOR

Report on a child with neurofibromatosis type 2 and unilateral moyamoya: further evidence of cerebral vasculopathy in NF2

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Received: 14 November 2018 / Accepted: 14 January 2019 / Published online: 21 January 2019

Letter to Editor

Recently, Lascelles et al. reported on three children with neurofibromatosis type 2 (NF2) and intracerebral vasculopathy and/or ischemic strokes [1]. In our opinion, this report is particularly relevant given that our understanding of features in pediatric patients with NF2 continues to develop as more such reports are published.

NF2 is a rare disorder due to heterozygous mutations in the homonymous gene. Affected patients develop bilateral acoustic schwannomas and are prone to develop central and peripheral meningiomas, ependymomas, and neurinomas. They often present ophthalmological and dermatological findings, some of which are congenital.

Herein, we report an additional case of vasculopathy in a young boy with NF2, caused by an unreported intragenic duplication of NF2. He presented at 11.5 years of age with bilateral scotoma and papilledema in the left eye related to a meningoendothelial meningioma of the left middle cranial fossa. After subtotal removal of the meningioma, he presented some episodes of clonic jerks mainly involving the upper right limb during wakefulness, and complex visual hallucinations. His electroencephalogram (EEG) showed a background activity of 8 Hz and interictal multifocal sharp waves prevalent over the left temporal area, with diffusion during the sleep. Since then, he is being receiving oxcarbazepine (15 mg/kg/die) with seizure control. He also presents bilateral vestibular schwannomas, left-side trigeminal schwannoma, multiple spinal schwannomas and meningiomas, congenital retinopathy, and left cortical temporal dysplasia. MLPA analysis of NF2 revealed a heterozygous intragenic duplication of exons 2–6 [NM_000268.3: c.(114+1_115-1)_(599+1_600-1)dup], confirming the clinical diagnosis. During his radiological follow-up, at 13 years of age, a stenosis of left cerebral middle artery was noted; thus, he underwent magnetic resonance angiography (MRA) that confirmed the stenosis and documented compensating blood vessels, compatible with unilateral moyamoya (Fig. 1a). Any other vessel abnormality was noted. He was, and remains at today, asymptomatic, without any radiological sign of stroke. Magnetic resonance perfusion imaging was normal (Fig. 1b) and hyperventilation during electroencephalography did not show typical anomalies of moyamoya disease. For these reasons, the patient did not receive angiography neither antiplatelet therapy. Soon after vasculopathy's diagnosis, he is being receiving bevacizumab (5 mg/kg i.v. every 14 days), because of radiological worsening of left vestibular schwannoma [2]. After 6 months of therapy, the lesion and acoustic function were stable.

Among other four children with NF2 followed at our center, no other have a history of stroke neither of vasculopathy at conventional brain MRI; none of them yet received MRA.

Lescelles et al. also reviewed literature finding three more cases of NF2 patients presenting with vasculopathies, raising the chance NF2 people might be at risk to developing cerebral artheriopathy. From literature review emerged that both of intra- and extra-cerebral districts can be involved.

This might represent an overlapping feature with neurofibromatosis type 1 (NF1) which is now well known to be associated with cerebral vasculopathies (aneurysms, moyamoya syndrome, ectasias). In particular, our patient presents a unilateral form of moyamoya vasculopathy.

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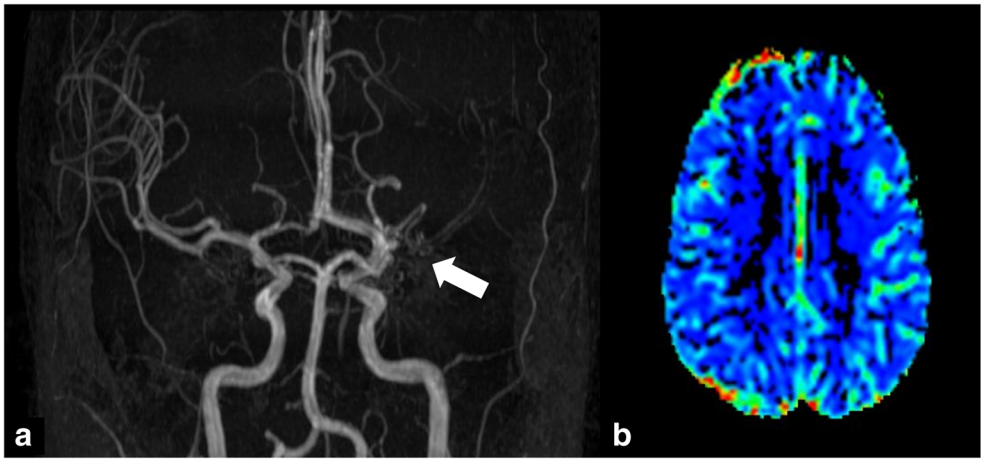

Fig. 1 **a** Intracranial MRA showing a stenosis of the left middle cerebral artery with compensating blood vessels, compatible with unilateral moyamoya. **b** Perfusion-weighted imaging (PWI) was normal

Moyamoya vasculopathy is considered, at today, a typical intracranial vasculopathy associated to NF1. Even if NF1 and NF2 present different clinical manifestations, gene loci, and gene protein products, they are both related to neurooncogenesis. While literature about the role of neurofibromin in vessels homeostasis is abundant, at knowledge just one study has explored the role of merlin from this point of view. In endothelial cells, Boratkó et al. demonstrated that merlin dephosphorylated on its Ser518 side chain influences cell migration and proliferation [3]. Intriguingly, bevacizumab seems to be effective in NF2 acoustic schwannomas thanks to his anti-VEGF effect. There are some evidences that loss of functional merlin decreases the expression of the antiangiogenic protein SEMA3F, promoting angiogenesis through VEGF activity [4].

Wider prospective studies are still needed to confirm whether a higher risk of intracerebral vasculopathy exists in NF2 yet it is likely that merlin plays a role in vascular homeostasis. If confirmed, we agree with Lascelles et al. in performing intracranial MRA screening in children with NF2 who are being considered for bevacizumab therapy, paying particular attention to the vertebro-basilar district. In this matter, we share authors' concerns about the risk to use of bevacizumab in NF2 children with cerebral vessel abnormalities given the hemorrhagic risk due to the drug. A multidisciplinary approach should be applied in similar cases.

Mutations reported by Lascelles et al. are mainly truncating. This type has been characteristically associated to NF2 presenting in infancy [5]. It might be interesting to evaluate the protein effect of the two deletions (exons 2 and 10) reported by the authors, in order to verify any possible genotype phenotype association that, from data actually available, seems to not subsist regarding the vascular feature.

Acknowledgements We are profoundly grateful to the patient and his parents for their collaboration and consent to publish.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from patient's parents.

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