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Case Report

Posterior circulation ischemic stroke in childhood and neurofibromatosis type 2

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ABSTRACT

Neurofibromatosis 2 (NF2) is a genetically inherited tumor predisposition syndrome. It predisposes to the development of multiple tumors of the central nervous system including schwannomas, meningiomas and ependymomas. Bilateral vestibular schwannomas (VS) are pathognomonic for the disease. In childhood, non-auditory symptoms often mark the onset of the NF2, such as facial palsy, peripheral neuropathy, and neurosurgical emergencies. In this article, we describe the case of a 6-year-old child presenting with an ischemic brain-stem stroke, who was later diagnosed with NF2. We report the clinical and genetic findings and review the previous literature on vasculopathy reported in association with NF2, with a focus on the symptoms presenting at disease onset. For our case patient, an unpublished germline mutation resulting in frameshift (c.876_877insT) was identified on blood screening. We report our full multidisciplinary assessment with vascular angiography, volumetric MRI and audiometry. Vasculopathy is not currently included in the criteria traditionally used for diagnosis of NF2. We suggest that vascular stroke in childhood may be considered a presenting symptom for NF2.
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1. Introduction

Neurofibromatosis type 2 (NF2) is a genetically inherited tumor predisposition syndrome and its prevalence is 1:60 000 [1]. Neurofibromatosis type 2 is a monogenic disease and the gene responsible of the condition was identified on the long arm of chromosome 22 [2–4]. Loss of function of the gene product Merlin/Schwannomin will occur as the result of a two-hit inactivation process, which is generally an inactivating mutation followed with a loss of heterozygocity (LOH) [5,6]. In half of the cases the disorder is inherited in a Mendelian autosomic-dominant fashion and is highly penetrant [7]. There is classically no anticipation in NF2; most of the change in severity occurring from first generation to an offspring being ascribable to somatic mosaicism in the affected parent [1]. Indeed, somatic mosaicism is frequent (25 to 30% of all NF2) in cases of a new mutation [8]. Genetic testing for NF2 yields identification of the putative NF2 mutation in 50% of pediatric cases [9]. Identification of the causative mutation allows targeted DNA sequencing in family and can be used for pre-symptomatic diagnosis.

NF2 is a life-threatening disease; 66% of NF2 patient mortality is directly linked to NF2. In addition, NF2 patients have a notable

Abbreviations: CPERH, Combined Pigment Epithelial and Retinal Hamartoma; ERM, epiretinal membanes; LOH, loss of heterozygocity; NF2, neurofibromatosis type 2; PSC, posterior subcapsular cataract; PTA, pure tone average; SDS, speech discrimination score; SRT, speech recognition threshold; VS, vestibular schwannoma.

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reduction in life expectancy when compared to the general population (69 versus 80 years respectively) [10]. Epidemiologic data supports that an early age at presentation results in increased risk of early mortality [11]. Although usually diagnosed in young adults, NF2 is diagnosed before 15 years old in 18% of the cases as one of ten NF2 may be symptomatic before age of 10 [9]. NF2 predisposes to the development of multiple tumors of the central nervous system including schwannomas, meningiomas and ependymomas. Bilateral vestibular schwannomas (VS) are the hallmark of the disease. Non-auditory symptoms are often present at the onset of pediatric NF2; in particular, facial palsy, peripheral neuropathy, and neurosurgical emergencies commonly. Therefore, the diagnosis of NF2 at its onset can be challenging. In this article, we report the case of a NF2 patient for whom the first symptom was a brainstem stroke in childhood and review the literature focusing on vascular features occurring in NF2.

2. Case report

A 6-year-old right-handed girl suddenly developed an acute right hemiplegia rapidly evolving to spasticity. On history, her mother had developed toxoplasmosis during the pregnancy for which prophylactic treatment with Rovamycin was introduced at 10 weeks' gestation. At birth, the newborn weighed 3.4 kg, was 50 cm long with 34 cm cranial circumference. Clinical examination and serologic follow-up during the 4 months following birth confirmed the absence of congenital toxoplasmosis. Therefore, prophylactic treatment with Rovamycin was stopped after 3 months.

On ophthalmologic examination at the age of 4, a unilateral decrease of visual acuity secondary to childhood amblyopia and retinal abnormalities was noted, but not attributed to toxoplasmosis. Further examination suggested the diagnosis of bilateral Combined Pigment Epithelial and Retinal hamartoma (CPERH) without leakage on fluorescein angiography. Neither posterior subcapsular cataract (PSC) nor epiretinal membranes (ERM) were noted.

At age 6, the child developed hemiplegia. A CT-scan revealed a left brainstem ischemic stroke (Fig. 1A). There was no significant anomaly on arteriography of the posterior circulation at the time of stroke (Fig. 1B). After cardiac-ultrasonography, carotid and vertebral ultrasonography, capillaroscopy, haemostasis, her posterior circulation ischemic attack remained idiopathic. No additional neurologic deficits were observed on follow-up. As a consequence of the stroke, the patient developed a spastic hemiparesis. At age of 17, she developed intense vertigo with right-beating horizontal nystagmus. A brain MRI was acquired and the radiologist did not find any significant anomaly, with attention to the posterior fossa (Fig. 1C). The patient was later referred to a specialized center for otoneurosurgery after she developed bilateral sensorineural hearing loss at age 26. At this point, we identified bilateral vestibular schwannomas (VS) extending to the cochlear apertures bilaterally, reducing the possibility of successful hearing preservation surgery [12,13]. Multiple intracranial meningiomas on the falx cerebri and the posterior left petrous bone were associated. Although the neurological examination did not reveal other focal deficits, multiple spinal tumors were noted on imaging as well (Fig. 2). Genetic testing was performed on DNA extracted from peripheral leucocytes, including direct sequencing of all seventeen exons of the NF2 gene and multiple ligation-dependent probe amplification (MLPA). It allowed the identification of an unpublished germline mutation of the NF2 gene affecting exon 8 and resulting in frameshift (c.876_877insT). At follow-up, hearing levels progressively decreased on the right side while both VS continued to grow (Fig. 3A and B) requiring resection of the right VS. Use of a combined approach (e.g. middle fossa craniotomy and retrosigmoid craniotomy) allowed preservation of a normal facial function and of an electrically stimulable cochlear nerve. Her cochlear nerve is currently eligible for cochlear implantation [14,15]. The left VS is being monitored using volumetric imaging, as it is her only hearing ear. Her meningiomas and ependymomas have not required surgery as of yet.

3. Discussion

3.1. Pediatric NF2 and presenting symptomatology

Children typically present severe NF2 phenotypes meanwhile literature is sparse on the subject. Only 20% of the children reported in the literature present with hearing loss or tinnitus [9].

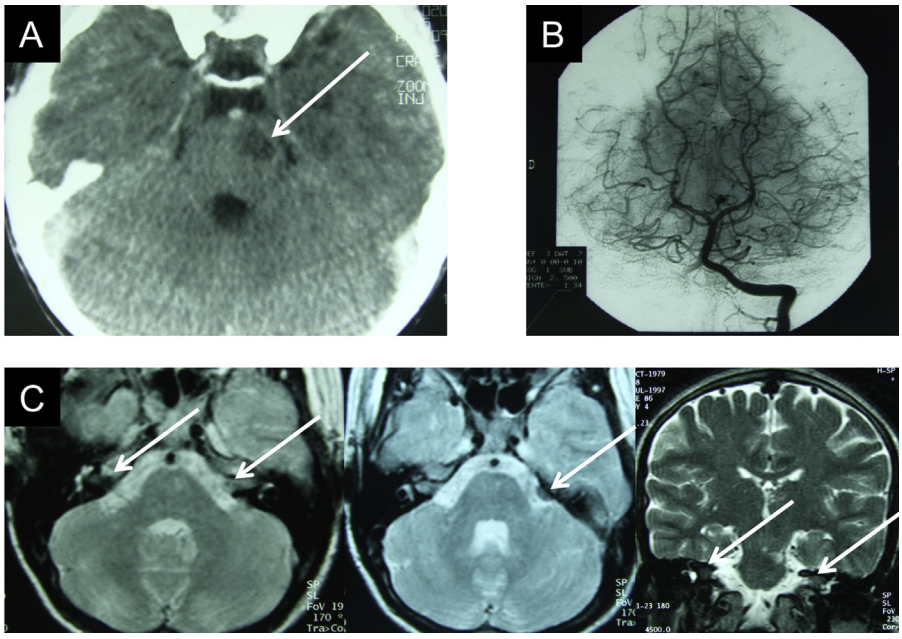

Fig. 1. (A) CT-scan at the onset of hemiplegia revealing a left brainstem ischemic stroke. An arrow is indicated the region of the evolving stroke, (B) normal posterior circulation arteriography. (C) Brain MRI at age 17. Arrow denotes a cerebellopontine angle tumor on the left and bilateral intracanalicular signal abnormalities.

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