Case Report

**Neurofibromatosis type-1 with seizures and cerebrovascular malformation: a case study**

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**ABSTRACT**

Neurofibromatosis type 1 (NF1) is the most common autosomal dominant neurocutaneous among humans. Epilepsy is more prevalent in NF1 patients than in the general population. NF1 vasculopathy is also a significant but underrecognized complication of the disease, affecting both arterial and venous blood vessels. Herein, we report a 2 year old female child with seizures and multiple cafe-au-lait spots on the body. The patient was diagnosed with NF1 based on clinical findings and family history. MRI Brain revealed middle cerebral artery dysplasia. Here we discuss diagnostic and treatment challenges and briefly reviews the existing literature.

**Keywords:** Case report, Neurocutaneous syndromes, Neurofibromatosis type 1, Epilepsy, seizures, Vascular dysplasia, Vasculopathy, Café-au-lait spots

**INTRODUCTION**

Neurofibromatosis type 1 (NF1), is a common autosomal dominant neurocutaneous disorder, affecting 1 in 3000 individuals worldwide, of which one-half of the cases are familial.1 This genetic disorder caused by mutations of the NF1 gene which is located on chromosome 17 (17q11.2), while de novo mutations occur primarily in paternally derived chromosome.2 Patients with NF1 may present with a variety of central nervous system complaints, such as seizures, learning disability and attention-deficit disorder. Intracranial lesions associated with NF1 include optic gliomas, sphenoid wing dysplasia and “unidentified bright objects”. In addition, cerebrovascular diseases, such as Moyamoya syndrome, have been reported but found to be rare.3 Previous reports have estimated that seizures occur in approximately 4-7% of individuals with NF1.4 This is considerably higher than the 1-2% incidence reported for the general population.

**CASE REPORT**

A two year old female child born out of non-consanguineous marriage was brought to the ER with generalized tonic-clonic type seizures, lasting for 30 minutes. Seizures were aborted by injection. Midazolam and patient was stabilized. Patient had no history of previous seizures, trauma, and fever or toxin ingestion. Family history was highly suggestive of NF1. Patient's maternal great-grandfather, grandmother and mother had history of multiple neurofibromas and cafe-au-lait spots (Figure 1). The patient met all developmental milestones appropriately.

On examination patient was found to have 8 cafe-au-lait spots on the trunk, back, and extremities, measuring more than 5 mm, with the largest one on the back measuring 14 x18 cm (Figure 2). No neurofibromas or axillary freckling was observed. Slit lamp examination revealed tiny hypopigmented lesions on the iris (evolving Lisch nodules). No neurological or cognitive deficit was
observed. Patient had short stature with her height lying between 2SD to 1SD. Head circumference was between third 50th percentile. Cardiovascular, respiratory and per abdominal examinations were also done and no significant abnormality was detected.

Figure 1: Pedigree chart.

Patient was started on intravenous valproate on account of high probability of seizure recurrence. Complete blood cell count, blood biochemistry, radiographs of long bones, echocardiography, abdominal and KUB ultrasound were normal. Electroencephalogram was found to be normal.

A 3T contrast MRI of the brain demonstrated flow void in M1 segment of right MCA and replaced by collateral vessels in the expected area of flow of the right MCA (Figure 3, Figure 4), highly suggestive of vascular dysplasia. Brain parenchyma appeared to be normal with preserved grey-white matter differentiation and no focal lesions. Seizures were well controlled on a single anti-epileptic and no recurrence was observed during the course of hospitalization and subsequent follow up.

DISCUSSION

NF-1 is multisystemic disease, which affect the skin, central nervous system and bone system. Its diagnosis is based on the clinical criteria established by the National Institutes of Health (NIH) consensus development conference. According to these criteria, at least two of the following clinical features must be present to make the diagnosis of NF1: six or more café-au-lait macules >5 mm in diameter in prepubertal and >15 mm in diameter in post-pubertal individuals, two or more neurofibromas of any type or one plexiform neurofibroma, freckling in the axillary or inguinal regions, optic glioma, two or more lisch nodules (iris hamartomas), a distinctive bony lesion, such as sphenoid dysplasia or thickening of the long bone cortex with or without pseudoarthrosis and a first-degree relative (parent, sibling, offspring) with NF1 based upon the above criteria.

These criteria are not sensitive to very young children, since many of them may appear gradually over the years, while children over ten years old who do not meet the NIH criteria are less likely to suffer from NF1. Young children who have only one clinical manifestation without any family history of NF1 should continue to be monitored for appearance of other manifestations since a
definitive diagnosis usually can be made by the time the child is four years of age.

Our patient satisfied the diagnostic criteria with significant cafe-au-lait spots and a positive family history. Unlike other neurocutaneous disorders such as tuberous sclerosis, epilepsy is not a common clinical feature in Neurofibromatosis, occurring in 3.8-7% of NF1 patients, which is considerably higher than the 1-2% value reported for the general population.

The higher frequency of seizures in this population establishes NF1 as a risk factor for epilepsy. Seizures can be of any type and begin at any age and usually are not attributable to a mass lesion in the brain. In some studies a higher incidence of focal seizures has been observed. Focal seizures may be due to an intracranial neoplasm. This subgroup of patients may be heterogeneous in their clinical manifestations, but tend to have medically refractory focal seizures. Thus, new seizures should prompt repeat neuroimaging, even if previous imaging was normal.

Most abnormal EEG recordings revealed focal abnormalities. Cerebral T2-hyperintensities in subcortical white matter or mesial temporal lobes may be associated with an increased risk for seizures, especially those in the mesial temporal lobes. Furthermore, temporal lobe T2-hyperintensities similar in appearance on MRI to those classified as “unidentified bright objects” have been identified histologically as DNET or gliosis. A previous report examining the frequency of T2-hyperintensities in individuals with seizures and NF1 found no association between the two. Within the structural seizures group of patients brain tumours, Moyamoya Syndrome, hydrocephalus, cortico-subcortical atrophy, ischemic stroke has been reported as NF1-related causes of seizures. Usually good seizure control on a single or no AED therapy has been reported.

NF1 vasculopathy is a significant but underrecognized complication of the disease, affecting arterial and venous circulation. The frequency of this vasculopathy is hard to define because screening studies are not routinely done, but the prevalence of vascular lesions in large clinical series is 0.4% to 6.4%. Lin et al. found a 2% prevalence of cardiovascular abnormalities among 2322 participants in the National neurofibromatosis foundation database. Aneurysms or stenoses of the aortic, renal, and mesenteric arteries are the most common lesions. Several retrospective series have noted abnormal cerebral vasculature (e.g. Moyamoya disease, intracranial aneurysm) in 2 to 6 percent of children with NF1 who underwent neuroimaging. Most were asymptomatic, but some required surgery for revascularization.

CONCLUSION

In summary, when a child with NF1 presents with seizures, the clinician should exclude not only brain tumours but also other rarer NF1-related presentations, like hydrocephalus, stroke and vasculopathy. Further study on patients with NF1 and non-structural seizures are desired to determine if NF1 per se might predispose to epilepsy. Careful follow-up and monitoring for signs and symptoms is necessary in case patient does not fulfill the diagnostic criteria initially since a definitive diagnosis usually can be made by the time the child is four years of age. A multidisciplinary team approach is ideal for children with NF1 and seizures, so that the child can be referred to appropriate specialists for a diagnostic work-up and treatment. Genetic testing and ante-natal counselling is also recommended for subsequent pregnancies.

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