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Case report

Epilepsy due to a cortical malformation in a Neurofibromatosis type 1 patient

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Neurofibromatosis 1, an autosomal dominant neurocutaneous disorder characterized by café-au-lait macules, Lisch nodules, neurofibromas, and learning disabilities, affects approximately 1 in 3000 people.[1] Unlike other neurocutaneous disorders such as tuberous sclerosis, epilepsy is not a common clinical feature, occurring in 3.8–7% of NF1 patients.[2] Rarely, case reports have described patients with NF1 and epilepsy due to malformations of cortical development. The types of malformations have included hemimegalencephaly, cerebellar leptomeningeal heterotopias, transmantle cortical dysplasia, periventricular band of heterotopic gray matter, pachygyria, occipital encephalocele, and unilateral as well as bilateral polymicrogyria.[3] We report an additional case of epilepsy in a Neurofibromatosis 1 patient with heterotopic gray matter and closed-lip schizencephaly.

1. Case report

The patient is a 23-year-old woman with an identical twin sister, who was born spontaneously to healthy nonconsanguineous parents. Café au lait macules were noted as a young child. At age 14, she began having migraine headaches, and an MRI scan was completed, revealing a right temporal lobe abnormality. The neurologist treating her migraines suspected Neurofibromatosis based on cutaneous manifestations. At age 15, genetic testing was ordered. Molecular analysis of the NF1 gene was performed via protein truncation assay and was positive for a protein truncation in segment 4 of the NF1 gene.

She began having seizures shortly thereafter. She had one isolated generalized tonic clonic seizure but frequent staring spells and confusional arousals. The staring spells typically lasted one minute and were described as disorientation and stuttering speech with postictal nausea and headaches. These were refractory to oxcarbazepine, lamotrigine, and most recently levetiracetam, occurring several times per week despite good compliance and medication levels. She was hence referred to the Indiana University epilepsy clinic for further management.

Past medical history is significant for Neurofibromatosis type 1, migraine headaches, and seizure disorder as described.

There was no history of febrile seizures, head injury, or central nervous system infection.

Family history was remarkable for an identical twin sister who also has migraine headaches and NF1 but no known seizure history. She has not yet undergone imaging. There is otherwise no family history of NF1, including either parent.

The patient overall met developmental milestones appropriately, but did require special education classes in junior and senior high school. She does not currently work. She lives with her 8-month-old son and boyfriend.

On physical exam, the patient had café au lait macules over the right lateral aspect of her neck and right torso as well as scarce bilateral axillary freckling. Otherwise, there were no stigmata of NF1. Neurologic exam was normal.

A 3-T MRI scan demonstrated gray–white matter disorganization in the posterior right temporal parietal lobes with suggestion of closed lip schizencephaly and heterotopic gray matter (Fig. 1).

Video EEG demonstrated frequent right mid-posterior temporal spike and slow-wave discharges as well as paroxysms of sharply contoured beta frequency activity with a broad field of distribution over the right hemisphere (Fig. 2a).

One electrographic seizure was recorded characterized by 2 Hz rhythmic spike and wave discharges from the right mid/posterotemporal region with evolution over 50 s (Fig. 2b). Clinically this event occurred out of sleep. The patient demonstrated an alerting response, appeared confused, and then returned to sleep immediately afterwards.

PET scan demonstrated the heterotopic gray matter but no significant decrease in PET uptake (Fig. 3a and b).

2. Discussion

Several features of interest differentiate our case from similar cases previously reported. In Vivarelli et al's retrospective analysis, 3 of 198 patients with NF1 were found to have epilepsy and malformations of cortical development.[2] A more detailed review of these patients revealed that all three had severe mental retardation with an IQ below 45.[4] Despite her extensive MRI and EEG

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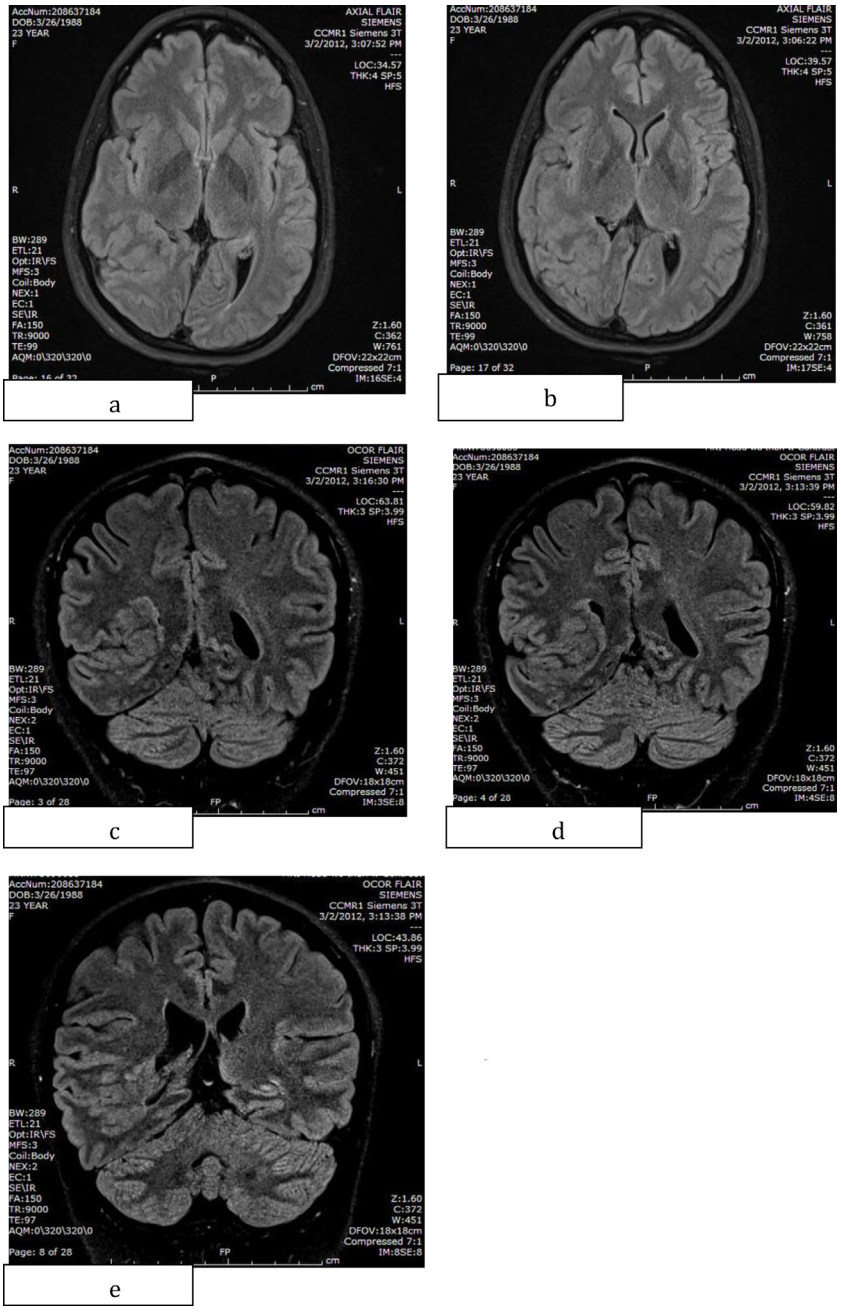

Fig. 1. 3 T MRI demonstrating gray–white disorganization, clozed-lip schizencephaly, and heterotopic gray matter. (a and b) Axial flair images; (c–e) coronal flair images.

abnormalities, our patient is high-functioning, completed high school with only some assistance from special education, and is raising a son. In addition, Vivarelli's three patients all began having seizures in infancy or early childhood, between 2 months and 13 months of age,[4] while our patient did not develop seizures until adolescence. Mastrangelo et al. reported a patient with NF1 and a complex epileptic syndrome due to bilateral polymicrogyria with a normal IQ of 98.[5] However, her additional NF1 stigmata were multiple, including café-au-lait spots, freckling, cutaneous neurofibromas, a patent ventricular septum, lumbar kyphosis, and hypertelorism.[5] Other than epilepsy, our patient has minimal clinical features of NF1, including only café-au-lait spots and axillary freckling. Finally, each of these patients had a different type of cortical malformation. These differences highlight the clinical hetereogeneity of NF1, even among those patients with epilepsy and malformations of cortical development.

Nevertheless, this small group of reported cases share some features in common with our patient. All of these patients with NF1, malformations of cortical development, and epilepsy had medically refractory seizures. While Mastrangelo's patient was seizure-free at the time of publication, she had suffered several episodes of prolonged partial status epilepticus.[5] Similarly, our patient continues to have several seizures per week despite trials on several first-line anti-epileptic medications. In addition, all of these reported patients had complex partial seizures, similar to our patient. Finally, all had EEG abnormalities which were focal or multifocal in distribution, similar to our patient, whose interictal and ictal EEG abnormalities involved the right mid-posterior temporal region.

This additional case report of a patient with NF1, epilepsy, and a malformation of cortical development supports the hypothesis of previous authors that these clinical features may not be an