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CASE REPORT

Movement Disorder and Epilepsy in Subependymal Nodular Heterotopia

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Subependymal nodular heterotopia is a cortical development malformation that is commonly associated with refractory epilepsy. Patients with heterotopia show a wide spectrum of clinical manifestations, from being asymptomatic to presenting with intractable seizures and intellectual impairment. We report a case of drug-resistant epilepsy with normal intelligence, having bilateral subependymal heterotopic nodules in the brain, presenting to us with a movement disorder in the form of myoclonus of bilateral lower limbs which is an unusual manifestation of gray matter heterotopias. Although rare, gray matter heterotopias may present as movement disorder and should be considered in differential diagnosis while workup of movement disorders.

Key words: Subependymal nodular heterotopia, epilepsy, movement disorder, myoclonus

INTRODUCTION

Subependymal nodular heterotopias (SNHs) are one of the most frequent malformations of cortical development.[1] Gray matter heterotopias are best divided into three categories: subependymal, subcortical, and band heterotopia. According to the classification system developed by Barkovich *et al*., SNH are classified as malformations due to abnormal neuronal migration (Group II).[2] The main presenting feature in most patients with nodular heterotopias is focal drug-resistant epilepsy[3] with onset in the second decade of life; development and neurological examination are otherwise normal. Here, we present a patient with generalized epilepsy and movement disorder in the form of myoclonus, and her magnetic resonance imaging (MRI) was consistent with bilateral subependymal nodular heterotopia.

CASE REPORT

A 19-year-old female with a history of convulsions for the past 9 years presented to our department with myoclonus of bilateral lower limbs for 3 months. The onset of convulsions was at the age of 10 years occurring with a frequency of 2–3 episodes per month. The convulsions were preceded by aura, described by the patient as heaviness in head, and were generalized tonic–clonic in nature, each episode lasting for 1–2 min followed by 15–20 min of postictal confusion. Medically, she was initially treated with valproic acid with a starting dose of 1000 mg/day, gradually increased to 2500 mg/day. In view of partial response to valproate, levetiracetam was added, titrated to a maximum of 3000 mg/day. Despite the use of two antiepileptic drugs, her convulsions persisted and clobazam was used as an add-on drug in a dose of 20 mg/day titrated to a maximum of 60 mg/day. The patient is seizure free now. Her perinatal history was unremarkable and developmental milestones were achieved at appropriate ages. Although she was unable to complete her schooling after primary school level due to her medical condition, on examination, her intellectual ability was within normal range. There was no family history of seizures. The patient developed abnormal movements of both lower limbs 3 months ago; in the form of sudden, brief, lightening-like jerks occurring at a frequency of 12–15 episodes per day. It was not found to be progressive or sensitive to any stimulus. The patient had both positive and negative myoclonus, clinically evident by a sudden involuntary jerk followed by a fall. Frequency of myoclonus decreased after levetiracetam was started. Neurological examination was unremarkable except for the presence of myoclonus in bilateral lower limbs.

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There was neither cognitive decline nor any progressive ataxia or cerebellar signs. No evidence of neurocutaneous markers was present.

Investigations revealed normal hemogram and serum biochemistry. Concomitant congenital abnormality was present during screening for associated anomalies in the form of the left ectopic (left iliac fossa), malrotated, and small-sized kidney.

MRI of the brain was performed using spin-echo and fast spin-echo pulse sequences. Serial T1- and T2-weighted images were obtained in the sagittal, coronal, and axial planes. Special fast FLAIR images were also obtained. The study revealed nodular lesions isointense to gray matter on all pulse sequences seen along lateral margins of bodies, frontal, and occipital horns of bilateral lateral ventricles consistent with subependymal gray matter heterotopias [Figure 1].

No abnormal enhancement on contrast administration was seen. This allows these nodules to be distinguished from the subependymal nodules of tuberous sclerosis that do not follow gray matter signal and enhance after contrast administration. Electroencephalogram (EEG) was suggestive of generalized epileptiform discharges. Further electrophysiological testing, like EEG-electromyogram polygraphy, could not be done due to nonavailability.

DISCUSSION

SNH was initially thought to be a neuronal migration disorder characterized by nodules of neurons due to arrested migration or failure of neuroblasts to undergo apoptosis,[4] but according to recent research, neuroependymal injury, rather than an intrinsic motility defect of the cell, is thought to be an important pathogenetic factor in the development of SNHs.[5] The denuded ventricular epithelium in periventricular/SNH may cause disengagement of radial glia, resulting in an inability of young neurons to migrate away.[5] The subependymal nodules are the most common form of grey matter heterotopias, which are located close together and form irregular lumps adjacent to the lateral ventricles, bilaterally, or unilaterally.

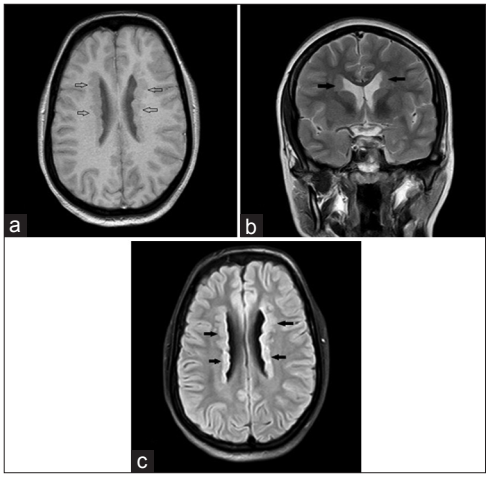

Figure 1: Subependymal heterotopia-magnetic resonance images. (a) T1-weighted axial section showing multiple subependymal nodules (arrows), isointense to cortical gray matter, symmetrically lining the lateral walls of the lateral ventricles. (b) T2-weighted coronal section demonstrating heterotopic nodules along the paratrigonal region of both ventricles. (c) Axial inversion recovery magnetic resonance image showing bilateral nodules indenting the walls of ventricles (arrows)

The true prevalence of nodular heterotopias in the general population and patients with epilepsy is unknown. Subependymal heterotopias usually present sporadically; however, some cases are familial and demonstrate an X-linked pattern of inheritance. Mutations in FILAMIN 1 gene, located on chromosome Xq28, have been associated with both sporadic and familial SNH.[6]

Clinically, the patients with subependymal heterotopias not associated with other types of cortical or cerebral malformations generally have normal development and motor skills. In a long-term follow-up, monitoring the course of epilepsy in 16 SNH patients, d'Orsi *et al*.[7] found that isolated SNH patients without any associated cortical or cerebral malformation have a comparatively "benign" course with seizures beginning during the second decade of life and rare in frequency at onset. The seizure type in these patients is usually partial with secondary generalization and drug responsive, without mental retardation. EEG may be normal or with focal abnormalities. During life, seizures may temporarily increase but without reaching a high frequency and usually disappear or become very rare. A kidney malformation (ectopia) was evident in one of their patients. In the present case, a similar congenital anomaly in the form of the left ectopic (left iliac fossa) and malrotated kidney was present.

In our case, the patient had onset of seizures in her second decade of life which were drug resistant and developed myoclonus of bilateral lower limbs 9 years later. This was similar to two cases reported by Mullin *et al*.[8] in the pediatric age group, both patients manifested as movement disorders as presenting features of heterotopias. Both patients experienced significant improvements following resection of their heterotopias. We believe that myoclonus in this patient was nonepileptic event as myoclonic seizures are often generalized, bilaterally synchronous, commonly involve the neck, shoulders, and arms but only rarely legs. Usually, the myoclonic seizures occur in paroxysms during the first several hours after awakening from a night's sleep or a nap. However, our patient had focal myoclonus involving legs and did not occur in paroxysms after awakening. Furthermore, there were no other clinical seizure phenomena, such as alteration of consciousness, associated with

her myoclonus. Third, no clinical myoclonus was noted during the EEG recording; the interictal EEG recorded generalized spike and slow-wave discharges, the pattern was not suggestive of myoclonic seizures.

MRI is far more sensitive than computed tomography in the detection of subependymal heterotopias. On MRI, subependymal heterotopias appear as ovoid lesions within the subependymal region. Neither perilesional edema nor contrast enhancement is seen. Donkol *et al*.[9] reported three types of heterotopia detected by MRI in a study of 20 patients (female to male ratio 14:6), all having a history of seizures. SNH was the most common type, followed by subcortical heterotopia, whereas band heterotopia was the least common type. The heterotopic tissue was isointense with gray matter on all magnetic resonance pulse sequences. Several studies revealed that most of the heterotopic nodules experience the epileptic activity of their own accord at seizure onset, which is synchronous with the overlying neocortex or ipsilateral hippocampus.[10] The heterotopia usually give rise to synchronous ictal or interictal epileptic discharges. In some cases the EEG activity may be normal and sometimes the epileptic discharges may be independent from the surrounding cortex.[10]

It is proposed that cortical myoclonus arises from abnormal excitation of corticospinal output, as suggested by following: (1) cortical myoclonus shows a time-locked premyoclonus EEG discharge reflecting apical dendrite excitation of pyramidal neurons; (2) myoclonus event latency is consistent with pyramidal tract conduction. Hyperexcitability across the relatively large sensorimotor cortex homunculi allows the multifocal activation. Within this region, large pyramidal neurons of layers III and V are presumed to be subject to the cortical hyperexcitability that causes excessive and brief myoclonus discharges down their axons.[11]

CONCLUSION

Heterotopias are a rare subgroup of cortical malformations characterized by abnormal neuronal migration, usually presenting as refractory epilepsy. In literature, very few cases[8] of heterotopic gray matter associated with movement disorders have been reported. Hence, the case above is reported to emphasize the unusual manifestation of SNHs as movement disorders.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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