

Case Report

A Case of Refractory Epilepsy; Neuronal Migration Disorders

Bhaskar Roy¹ and Francis J. Di Mario Jr^{2*}¹Department of Neurology, University of Connecticut, USA²Department of Pediatric Neurology, University of Connecticut, USA

*Corresponding author

Francis J. Di Mario Jr, Department of Pediatric Neurology, University of Connecticut, 202 Washington Street, Hartford, CT 06106, USA, Tel: 860-837-7500; Fax: 860-837-7550; Email: fdimari@ccmckids.org

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Abstract

Refractory epilepsy in childhood is a common presentation of cortical heterotopia, a form of neuronal migration disorders. Subcortical band heterotopia or double cortex syndrome, subependymal heterotopia and subcortical heterotopia are three common types of cortical heterotopia. Here we present a case of 10 year old non dysmorphic boy with static encephalopathy who was evaluated for refractory epilepsy. He had significant cognitive impairment, developmental delay, aggressive behavioral outbursts and self mutilating behavior. He started to have seizures approximately at age six month and over the years seizures evolved to different patterns representing Lennox Gastaut syndrome. His EEG reflected a slow and disorganized pattern with bitemporal slow spikes. His brain MRI revealed band cortical heterotopia without hippocampal pathology or mesial temporal lobe sclerosis. He did not have any genetic abnormality on karyotyping, chromosome micro-array or whole exome sequencing. He was diagnosed with double cortex syndrome based on clinioradiological findings without any identifiable genetic abnormality. This case report along with review of literature reinforce the different spectrum of clinical manifestations of different types of cortical heterotopia.

Keywords

- Brain malformation
- Seizure disorder
- Encephalopathy
- Double cortex syndrome

ABBREVIATIONS

MRI: Magnetic Resonance Imaging; SBH: Subcortical Band Heterotopia; EEG: Electroencephalography; PNH: Periventricular Nodular Heterotopias; SCH: Subcortical Heterotopia.

INTRODUCTION

Cortical heterotopias a form of neuronal migration disorders often presents with refractory epilepsy and developmental delay. Based on the type of heterotopia, the pattern and severity of clinical manifestations vary. In severe cases the epilepsy disorder typically manifests during first decade of life. It often evolves into intractable epilepsy, defined as inadequate seizure control despite appropriate medical therapy with two anti epileptic drugs at maximally tolerated dose for more than 18 months, with no more than 3 consecutive seizure-free months during that 18 months [1,2]. Neuronal migration disorders originate from the disruption of normal movement of neurons from their origin to their target destination, which occurs mostly during 3 to 5 months of gestation. An organized activation of different cytoskeletal molecules, signalling molecules, glycosylation modulating molecules, neurotransmitters and trophic factors is essential to orchestrate the complex series of processes that result in neuronal cellular proliferation, migration, axonal sprouting and dendritic pruning among others. Genetic mutations in regulatory genes, even exogenous factors like trauma and toxins can induce

and alter this complicated developmental process leading to different patterns of migrational diffects. Cortical heterotopia is a common form of neuronal migrational disorder where clusters of normal cortical neurons at non physiological sites resulted from premature termination of neuronal migration [3,4].

Here we present a case of subcortical band heterotopia with Lennox Gastaut syndrome along with literature review to capture the ciniopathological spectrum of these disorders.

CASE PRESENTATION

This is a 10 year old boy who developed chronic static encephalopathy, cognitive impairment and long standing refractory epilepsy.

He was born to 30 year-old G3P1 woman with prior spontaneous fetal loss. She experienced hyperemesis during pregnancy requiring ondansetron but ultimately delivered via induced vaginal delivery for decreased fetal heart rate with APGAR scores of 8 and 9. He was noted to have a right extra-axial non-functional digit, which was later resected. He demonstrated global developmental delays in addition to seizures. Seizure episodes started by approximately age six months with sudden motion arrest and staring that evolved into atonic drops and later additionally included generalized convulsive seizures. Frequently he grunted with tonic posturing associated with slight head turning towards the right lasting about 5 seconds.

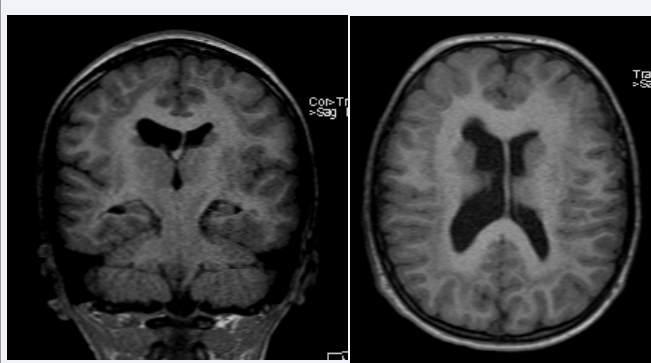


Figure 1 MRI FLAIR sequences showing diffuse posterior subcortical band heterotopia (white and red arrow) without pachygyria; double cortex syndrome.

Abbreviations: MRI: Magnetic Resonance Imaging, SBH: Subcortical Band Heterotopia, EEG: Electroencephalography, PNH: Periventricular nodular heterotopia, SCH: Subcortical heterotopia.

By age 18 months, these spells increased to more than 100 times a day despite various anti-seizure treatments. Less commonly he had localization related seizures, where he would kneel on the floor in a crouched position and then fall over in a tonic posture. These happened typically upon awakening from sleep and lasted for about one minute. At his current age of ten years he experiences intermittent atonic head drops throughout the day and occasionally exhibits a “far away gaze”. Along with these variable seizure types, he also manifests myoclonic limb movements. After having a cluster of seizure episodes he has difficulty with gait and balance such that he veers towards one side when walking. He continues on a regime of lamotrigine, oxcarbazepine, phenobarbital and clobazam.

He has significant cognitive impairment and requires special education. He is able to walk and feed himself finger foods. He is capable of speaking a few single words but is unable to engage in self-help activity such as dressing, tooth-brushing or toileting. He engages in self-injurious behaviors such as eye-poking and self-slapping with occasional aggressive behavioral outbursts towards others.

He has had hypothyroidism and growth hormone deficiency identified. He has required an orchiopexy for a undescended testes, hiatal hernia repair, extra-axial digit resection, tonsillectomy and adenoidectomy. There is no family history of epilepsy. His older sister is healthy. There is a paternal second cousin with Down syndrome.

On examination he is nondysmorphic in appearance with a slightly swollen lip from a fall. The remainder of his general examination is unremarkable. Neurological examination demonstrated cognitive impairment. He is able to vocalize and follow simple instructions but speak only a limited vocabulary of monosyllabic words and utterances. He can wave bye-bye and give a “high five”. He had some stereotypical movements with hand twirling, flapping his ears and occasionally holding his head while rocking. Cranial nerves were normal. He had symmetric and normal muscle bulk, strength and tone. He had a reasonably steady gait. He was able to climb up and down on chairs, and jumped and hopped readily. His reflexes were 2/4 with bilateral

flexor plantar responses. There was no truncal titubation or overt ataxia. He responded to vibration stimuli equally in all limbs.

His electroencephalogram was diffusely slow and disorganized with a background rhythm of 6 Hz. There were symmetric but asynchronous sleep spindles in stage 2 sleep. He had spike discharges over the bi-temporal regions with an irregular 1-1.5 Hz slow spike-wave frequency during sleep. His brain MRI with contrast reflected thin band cortical heterotopia without any pachygyria, hippocampal pathology or mesial temporal sclerosis, consistent with double cortex syndrome.

Given the clinical context and EEG findings, a diagnosis of Lennox Gastaut epilepsy syndrome secondary to the neuronal migration disorder, double cortex syndrome was made. Comprehensive genetic analysis with karyotype, chromosome micro-array and whole exome sequencing did not identify an abnormality.

DISCUSSION

Subcortical band heterotopia or double cortex syndrome, subependymal heterotopia and subcortical heterotopia are three types of neuronal migrational disorders with cortical heterotopia. They encompass different patterns of clinical spectrum with distinct radiological findings. Advancement of magnetic resonance imaging and identification of associated genotypes and underlying mechanisms have improved our understanding of these disorders in last two decades [5-7].

Subcortical band heterotopia (SBH) or double cortex syndrome

SDH is characterized by the presence of a band of gray matter in the white matter between cortex and ventricular surface. It is formed by well-defined and well-marginated clusters of neurons which failed to reach their cortical target. This is essentially a less severe form of the agyria-pachygyria-band spectrum of malformation [8-10]. More than 90% affected individuals are female and heterozygous *DCX* or *XLIS* mutation (Xq22.3-q23) is often associated. *DCX* mutations usually results in classical lissencephaly in hemizygous males [4,11]. *LIS1* (PFAFH1B1 on 17p13.3) has been identified as a common causative genetic defect for the autosomal form. 80-90% of sporadic females, 25% of sporadic male and all familial cases have been found to have *DCX* mutation. Pattern of mutation can vary widely, starting from missense, nonsense, and frame-shift mutation, deletion of exon to large genomic deletion or duplication [5,9,12,13].

Double Cortin, the protein product of *DCX* gene, is an intracellular signalling molecule associated with microtubular cytoskeletal organization. It is critical for neuronal migration and differentiation. On the otherhand, protein product of *LIS1*, which is occasionally associated with SBH, is an important regulator of microtubule motor protein cytoplasmic dynein mediated nucleokinesis, somal translocation, and cell motility along with neurogenesis and chromosomal segregation. Abnormality of *LIS1* can lead to disrupted neuronal migration and even lissencephaly [4,7,11,13-15]. *DCX* mutation more frequently affects the frontal cortex whereas in *LIS1* mutation parietal and occipital cortexes are more prominently involved [16, 17].

Epilepsy is a clinical feature of SBH in about 85-100% patients. Rate of medically refractory epilepsy can be as high as 65-80% [12,13]. Approximately 80% of the patients will present with seizure in infancy and childhood though first occurrence during adulthood is known. Half of the patient population would have generalized seizure disorder. Evolution of initial partial or generalized seizure pattern into a more generalized form with generalized tonic-clonic seizures along with atonic seizures and drop attacks encompassing characteristics of Lennox-Gastaut syndrome is not uncommon [5,9,13]. Along with epilepsy co-existing cognitive and behavioral symptoms can be present in 60-70% patients. Hyperkinetic movements, self-mutilating behavior, autistic features with perseveration and stereotypical activities have been reported. They can also have motor function abnormality such as hypotonia, spasticity and poor fine motor control [8,9,18]. Thickness of the layer of heterotopia band clinically correlates with neurological disabilities. Patients with thicker band would have earlier onset and more refractory seizures or Lennox-Gastaut syndrome [8,19]. Our patient is unusual in that he has had severe early onset epilepsy and cognitive impairment despite a relatively thinner subcortical band and the absence of cortical pachygyria.

Subependymal heterotopia

Subependymal heterotopia or periventricular nodular heterotopia (PNH), the most common form of heterotopia, is characterized by presence of nodular gray matter along the lateral ventricles. It can affect focal or diffuse area, either unilaterally or bilaterally [5,6,7,20].

Both X-linked and non X-linked inheritance pattern have been reported. X-linked pattern is almost always bilateral and has been linked to filamin 1 gene (Xq28). Almost all the familial cases and 26% of sporadic cases will have Filamin 1 mutation [5,6]. Filamin 1 (FLNA), also known as actin-binding protein 280 (ABP-280), plays a crucial role in the control of cell shape, migration, filopodia formation, and chemotaxis. FLNA mutation results in premature arrest of neurons, confining them in the subependymal region [21,22]. Among non X-linked inheritance pattern, ADP-ribosylation factor guanine nucleotide-exchange factor 2 (ARGFEF2) in chromosome 20q13.13 has been identified in a rare recessive form of PNH. Product of ARGFEF 2, Brefeldin A inhibited guanine nucleotide exchange factor 2 (BIG2), is associated with trans-golgi vesicle and membrane trafficking. Impaired function of this protein leads to disruption of proliferation and migration during cortical development. Occasionally copy number variations including 5p15.1 duplication or 5p15.33 trisomy and deletion of 1p36.22, 4p15, 5q14.3-q15, 6q26-q27 or 7q11.23 have been reported in PNH [5,6,23]. PNH can be associated with other CNS malformations such as Chiari II malformations, basilar cephaloceles, hydrocephalus or agenesis of the corpus callosum. Occasionally PNH can be present in metabolic disorders; such as Zellweger syndrome, neonatal adrenoleukodystrophy and Ehlers-Danlos syndrome, a collagen vascular disease. Though often affected male would have a pre natal death, but live male off springs would typically have other neuro developmental abnormalities like cerebellar hypoplasia and syndactyly, short gut syndrome, congenital nephrosis and fronto nasal dysplasia [5,6,13].

Similar to SBH, PNH is more common in female. Affected male, without any normal X chromosome, has much severe manifestation and rarely survives. 80% of affected individuals would have epilepsy. It can be associated with neurodevelopmental delay or cognitive impairment, especially in individuals with bilateral involvement. Onset of seizure usually occurs in the first or second decade of life. Similar to SBH, epilepsy syndrome can be generalized or localization related particularly with temporo-parieto-occipital auras. Pseudo-localization features to temporal lobe can happen. Progression of seizure in PNH can take two distinct forms. Individuals with late onset seizure reach a peak of seizure frequency and afterwards it slowly regress. Whereas in case of earlier onset of epilepsy, it is generally more frequent [7,24,25].

Subcortical heterotopia

Subcortical heterotopia (SCH), a less prevalent form of cortical heterotopia, is characterized as displaced islands of gray matter in the white matter beneath the cerebral cortex. These heterotopias usually consist of swirling, heterogeneous, curvilinear masses of gray matter along with CSF and vascular structures. It can be classified in different patterns; 1. Large subcortical heterotopia with cortical infolding, abnormal cortex, hypogenetic corpus callosum, 2. Pure subcortical heterotopic nodules, 3. Columnar heterotopia, 4. Ribbon heterotopia, 5. Excessive single neurons in white matter. Agenesis or hypogenesis of corpus callosum is associated with 70% cases of SCH [1,26-28]. Exact mechanism or underlying genetic defect is still unknown for subcortical heterotopia. Premature termination of abnormal neuroblasts or termination of central migration of neuroblasts from a heterotopic germinal zone has been proposed as the possible mechanism [1,7]. Clinical presentation depends on the extent and the location of the lesion. Focal SCH would have variable motor and intellectual disturbances. Extensive unilateral heterotopia may lead to hemiplegia and less severe cognitive involvement. Patients with bilateral, extensive SCH will have more profound developmental delay and motor dysfunction. Small, unilateral lesion typically would not affect motor or cognitive function. Almost all affected individual would have localization related epilepsy, usually during early infancy or first decade of life [1,7].

CONCLUSION

Our patient presented with refractory epilepsy from subcortical band heterotopia or double cortex syndrome. He had early onset epilepsy and eventually developed refractory epilepsy. He also had developmental delay, cognitive impairment and behavioral outbursts. Diagnosis was made based on his radiological findings. His clinical presentation and epilepsy pattern was consistent a diagnosis of Lennox Gastaut epilepsy syndrome secondary to the neuronal migration disorder, double cortex syndrome. Radiological and genetic testing are needed to establish a diagnosis.

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