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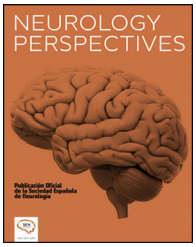

SCIENTIFIC LETTER

Bálint syndrome in a patient with drug-resistant epilepsy having underlying X-linked lissencephaly with subcortical band heterotopia/"double cortex" syndrome

Síndrome de Bálint en un paciente con epilepsia farmacorresistente con lisencefalia subyacente ligada al cromosoma X con heterotopia de banda subcortical/síndrome de "doble corteza"

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Dear Editor,

Lissencephaly (LIS) ("smooth brain") represents a spectrum of rare malformations of cortical development associated with deficient neuronal migration and abnormal gyri formation (i.e., agyria, pachygyria, and subcortical band heterotopia [SBH]/"double cortex" syndrome).[1] Subcortical band heterotopias/"double cortex" syndrome is characterized by the presence of smooth bilateral ribbons of gray matter interposed within the white matter between the cerebral cortex and ventricular surface and associated abnormal gyri formation.[1–3] Clinical manifestations are diverse and protean, but it classically manifests with difficult-to-control seizures (which usually start in the first decade of life), intellectual impairments, and progressive cognitive decline.[1–3] It is an X-linked genetic disorder almost exclusively occurs in females and is commonly caused by mutation in the doublecortin (DCX) gene, which is sine-qua-non for neuronal migration during in-utero cerebral embryogenesis.[1–3] Though most cases are considered sporadic, familial inheritance is increasingly suspected with molecular genetics progress[1–3] (see Fig. 1).

Clinical signs of Bálint syndrome (BS), a complex conundrum of simultanagnosia, optic ataxia, and oculomotor apraxia due to posterior cortex dysfunction, for their subtlety, difficult historical elicitation/interpretation, and rarity, often remain unrecognized during clinical examination.[4–6] BS has been traditionally described as a result of ischemic stroke involving bilateral parieto-occipital regions.[4–6] However, Creutzfeldt-Jakob disease (CJD),

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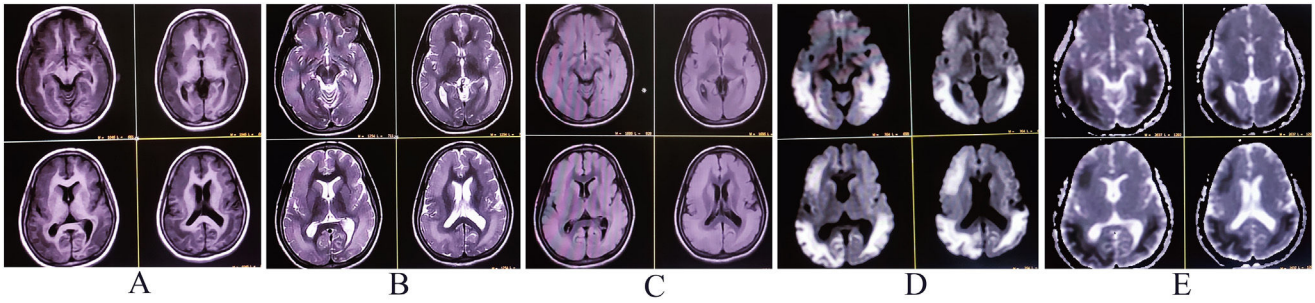

Fig. 1 Thick band noted in the subcortical region of bilateral cerebral hemispheres, which is iso to gray matter in all sequences (A-T1, B-T2, C-T2-FLAIR), shows no contrast enhancement and is separated from cortical gray matter and ventricles by white matter—s/o subcortical band heterotropia. The overlying cortex shows broad gyri and shallow sulci, i.e., pachygyria—notice diffusion restriction in bilateral temporoparietal lobes on DWI (D) and ADC (E).

posterior cortical atrophy, Alzheimer's disease, corticobasal degeneration syndrome, several leukodystrophies (posterior-predominant), neuro infections, progressive multifocal leukoencephalopathy, anti-NMDA-R encephalitis, posterior reversible encephalopathy syndrome, non-convulsive status epilepticus, head injury, and cerebral metastasis can also give rise to this complex syndrome.[4–7]

We herein report a case of a young female, born out of consanguineous wedlock with uneventful perinatal history and normally acquired developmental milestones, who presented with drug-resistant epilepsy for 8 years and acute-onset BS in a drug-refractory epileptic patient.

A 16-year-old right-handed female from rural West Bengal (India) was referred to our clinic with a diagnosis of "seizure disorder". Her family members complained that she was having difficulties reaching for objects in her field of vision for the last 7 days following the last seizure episode (for which she was hospitalized, and doctors documented the episode as "status epilepticus", and the condition was managed accordingly). It was also associated with new-onset difficulties in reading (seeing letters as reversed) and feeling confused while doing tasks that required complex visual orientation. Caregivers complained that for the last few days, she was behaving as if she was always "searching for something", though the object she was searching for remained in close visual proximity. They also complained that she was knocked against the wall while entering through the door. On asking, she said that despite knowing where she wanted to go and could see the door but could not localize where the door was in the room while entering our clinic. The same navigational problems had been occurring in her residence too. The caregivers also said that while pouring tea from a teapot, she was pouring it outside the tea cups, despite denying any weakness.

The family members reported multiple daily seizure episodes, especially generalized-onset tonic–clonic seizures. These seizures have been occurring since 8 and have increased in frequency in the last 6 months. She stopped going to school at 14 when her seizure control worsened, and her scholastic performance deteriorated progressively. Multiple seizures semiologies were described (i.e., focal-onset motor seizures with or without altered consciousness, myoclonic, and atonic seizures were also reported to be occurring between generalized-onset seizures). The mother and other family members disclosed an uneventful perinatal history and denied any neonatal or infantile seizures and need for any neonatal or pediatric intensive-care unit stay to date. Early developmental milestones were accomplished in normal time. Her younger brother also had been diagnosed with a well-controlled seizure disorder. The history of consanguineous marriage in parents was positive. Over the last 8 years, she was prescribed multiple antiseizure drugs in different dosages by numerous pediatricians, physicians, neurologists, and psychiatrists. The seizures were, in fact, initially controlled with antiseizure medication, but as time progressed, seizure frequencies increased, and multiple new seizure types were identified. At present, she was getting valproate (1500 mg/day), levetiracetam (1500 mg/day), and clobazam (10 mg/day).

General systemic survey and gynecological evaluation were unremarkable. Neurological examination revealed higher-order complex visual cognitive dysfunction, such as being unable to process multiple simultaneous visual stimuli (simultanagnosia) and smartly grasp/reach out for objects held in her visual field. Noticeably, she was trying to hold a pen as if she was holding a glass of water (optic ataxia). She also had severe difficulty voluntarily shifting her eyes to any specific object held in her peripheral visual field and seeing fast-moving objects (oculomotor apraxia), suggestive of BS. Neuroophthalmological examination revealed pupils were equal (3 mm) and reacting normally to light and accommodation. Voluntary saccades were accomplished according to directional commands. However, visually guided saccades were impaired. Visual acuities were 20/20 in both eyes (unaided). Contrast sensitivity and color vision testing were normal too. Computerized and manual testing for perimetry were also normal. Cerebellar functions, cranial nerves, motor, sensory, and autonomic system examinations revealed no significant abnormalities.

Complete blood cell count, renal, hepatic, thyroid function tests, serum electrolytes, and glycemic indices were within normal limits. Urinalysis revealed no abnormality. Magnetic resonance imaging of the brain revealed laminar/subcortical band heterotopia/"double cortex" syndrome. MR-angiography of the brain revealed no abnormality. A cerebrospinal fluid examination ruled out infective causes. Panels for autoimmune connective tissue disorders and autoimmune/paraneoplastic encephalitis were negative. Electroencephalogram showed a

multifocal slow spike-and-wave pattern (1.5- to 2.5-Hz) with a chaotic background.

Next-generation sequencing for neuronal migration disorder revealed a heterozygous missense variant in exon 2 of the DCX gene (chrX:g.111410173G>A; Depth: 144x) that results in the amino acid substitution of Cysteine for Arginine at codon 76 (p.Arg76Cys; ENST00000636035.2). A different amino acid (p.Arg76Ser) has previously been reported in patients affected with X-linked LIS,[8] and it lies in the Doublecortin domain of the DCX protein [http://pfam.xfam.org/protein/O43602]. The p.Arg76Cys variant has not been reported in the 1000 genomes, gnomAD, and our internal databases. The in-silico predictions # of the variant are probably damaged by PolyPhen-2 (HumDiv) and damaged by SIFT and LRT. The reference codon is conserved across species. Due to a partial phenotype match, this DCX variation is classified as a variant of uncertain significance, but the careful interpretation of clinical symptoms, neuroimaging features, and positive family history makes this a novel pathogenic variant. However, due to extreme financial restraints, genetic testing of the other first-degree relatives could not be carried out.

Topiramate (100 mg/day) and zonisamide (100 mg/day) were added to her regimen. She was followed up after 3 months, and though there was a significant improvement from a seizure-control point of view, her higher-order visual cognitive deficits partially did so.

LIS includes a spectrum of malformations of cortical development caused by insufficient neuronal migration.[1,2] The distinctive features of LIS are an abnormally thick cortex with reduced or absent cerebral convolutions (sulci and gyri), while in SBH (also known as "double cortex" syndrome), there are abnormal bands of neurons under a normal cortex, although shallow sulci may separate gyri.[1,2] LIS-SBH severity grade tends to correlate with clinical outcome, with severe LIS (agyria) more severe than intermediate LIS (pachygyria), and both more severe than SBH.[1,2] Besides, the severity of neurological phenotype generally correlates with the type and extension of LIS on magnetic resonance imaging (MRI).[1,2] Diffuse LIS, especially with diffuse agyria, has been associated with a profound ID, early and intractable epilepsy, and reduced lifespan.[1,2,8]

LIS can be subdivided based on the gradient of the malformation into frontal-predominant, posterior-predominant, and temporal-predominant LIS (a more uncommon variant) with ARX mutations. Diffuse agyria is the most severe subtype of the spectrum.[2,8]

Most LIS patients' clinical onset occurs during the first year of life, presenting with hypotonia, feeding difficulties, global developmental delay, and seizures. Nevertheless, there are other LIS distinctively later-onset subtypes (i.e., females with DCX-associated thin SBH may present average cognitive skills or borderline ID with no other symptoms, while thick SBH is typically linked to more severe difficulties).[2]

More than 90% of LIS patients develop seizures typically during the first years of life but infrequently do they appear until the second decade, being an important challenge since 30%–50% of patients become refractory to antiseizure therapy.[1,2] They often present as infantile spasms with or without hypsarrhythmia and other seizure subtypes, including focal seizures, generalized tonic–clonic seizures, persisting spasms, focal seizures, tonic seizures, atypical seizures absence, and atonic seizures).[1,2] Systematic studies addressing seizure semiology and antiseizure drug response in these patients are scarce, with a few cohorts with LIS1 and DCX variants.[2]

Patients with SBH have a heterogeneous clinical course ranging from mildly to severely disabling. Neurological examination is normal in most cases, but hypotonia, poor fine motor control, and behavioral disturbances may be present.[3] This brain malformation is often revealed by the onset of seizures within the first decade. These usually evolve into refractory and multifocal epilepsy. Patients with tubulinopaties responded better to the current antiseizure drug therapy than patients with LIS1- and DCX-associated LIS.[2]

DCX encodes a microtubule-associated protein involved in neuronal migration during brain development. X-linked isolated LIS sequence and subcortical band heterotopia are human allelic disorders associated with mutations of DCX, giving both familial and sporadic forms. DCX-related disorders are clinically variable, with severe sporadic and milder familial subcortical band heterotopia, each linked to specific DCX mutations.[3]

The clinical picture of BS (simultanagnosia, optic ataxia, and oculomotor apraxia) can be explained by an impaired ability to accurately represent simultaneous localization following asymmetrical, bilateral superior parietal lobule-intraparietal sulcus (SPL-IPS) damage. The lateralized attentional bias (neglect) depends on the asymmetry of the bilateral lesions and tends to recover spontaneously, leaving the patient with only 2 of the initial symptom triad.[4,5]

To diagnose BS is necessary a careful neurological examination. The core deficit of BS is attentional since covert attention improves spatial resolution in the visual periphery. A deficit of covert attention would thus increase spatial uncertainty and subsequently impair visual object identification and visuomotor accuracy; this explains why perceptual symptoms (simultanagnosia, neglect) could result from visual mislocalization. Visuomotor symptoms (optic ataxia) can be justified by visual and proprioceptive mislocalizations in an oculocentric reference frame, leading to field and hand effects, respectively. If the right parietal damage also includes the inferior parietal lobule, additional representational mislocalizations across time and saccades (spatial working memory and visual remapping impairments) worsen the clinical picture of peripheral mislocalizations due to an impairment of covert attention. When only the right inferior parietal lobule is damaged, a syndrome of clinical neglect comprising both spatial disorganizations and left visual extinction is present in the acute phase. The attentional bias is due to the right SPL-IPS's temporary "virtual lesion" and recovers evolving into chronic constructional apraxia.[4,5]

The lesions that cause BS are usually bilateral, involving the parietooccipital junction, whereas lesions in the hemineglect syndrome are located in the temporoparietal junction. Seizures of posterior cortex origin are easily overlooked, probably because of subtle and non-motor signs emerging from this part of the brain, being able to evolve to a non-convulsive status epilepticus.[7]

The prognosis of BS depends on the underlying etiology. Acute etiologies (i.e., stroke, infectious diseases, or PRES) have a good prognosis with proper management. Conversely,

BS secondary to neurodegenerative conditions (i.e., posterior cortical atrophy, corticobasal degeneration) has a poor prognosis.[5,6] Ours is the first case of X-linked LIS with subcortical band heterotopia/"double cortex" syndrome presenting with reversible BS (secondary to status epilepticus) in a drug-resistant epileptic subject.

Clinical signs of posterior cortex dysfunction are usually overlooked due to their non-specificity, paucity, and subtle symptoms during a clinical examination. Neuroimaging, especially MRI of the brain, may help to find the source of these subtle clinical manifestations. When facing a patient with any complaint of underlying higher-order visual cognitive dysfunction, i.e., simultanagnosia, optic ataxia, and oculomotor apraxia in a post-ictal patient, BS should be suspected to avoid misdiagnosis, adjust treatment, and improve clinical outcomes and prognosis.

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Disclosures

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Ethics statement

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

Author contributions

All authors contributed significantly to the creation of this manuscript; each fulfilled criterion as established by the ICMJE.

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