Neurology Perspectives 3 (2023) 100124

NEUROLOGY PERSPECTIVES

www.journals.elsevier.com/neurology-perspectives

LETTER TO THE EDITOR

Bálint syndrome as the presenting manifestation of adrenoleukodystrophy

Bálint syndrome (BS) is a rare and disabling higher-level visual cognitive impairment consisting of a triad of optic ataxia, oculomotor apraxia, and simultagnosia.[1,2] It is usually found in lesions involving bilateral parieto-occipital cortices, such as stroke, corticobasal degeneration, Alzheimer's disease, posterior cortical atrophy, Jakob-Creutzfeldt disease, neuro infections, autoimmune encephalitis, progressive multifocal leukoencephalopathy, traumatic brain injury, neoplasms, posterior reversible encephalopathy syndrome, and rarely, cerebral leukodystrophies.[1,2]

We report the case of a teenager from a socio-economically deprived area of rural India who presented with extremely difficult-to-comprehend higher-order visual symptoms mimicking psychiatric symptoms co-incidentally following his parents' separation. Although progressive gait unsteadiness, academic decline, emotional lability, and speech and behavioral abnormalities accompanied the higher-order visual syndrome, the diagnosis of BS heralding adrenoleukodystrophy (ALD) was missed by more than one clinician.

A 13-year-old male child, born out of non-consanguineous wedlock from a poor socio-economic background, was brought to an out-patient department with complaints of insidious onset and rapidly progressive unsteadiness of gait, slurring of speech, behavioral abnormalities, and academic decline for the last three years. According to his father and other caregivers, the boy's condition started deteriorating following this event. The father denied any history suggestive of perinatal asphyxia and any delay in reaching different developmental milestones since birth. His father also complained that till the age of 10 years, both academic and creative performance was beyond satisfactory, as evidenced by the progress reports provided by his school. He also explained that his wife (the child's mother) had left them and stayed separate for the last four years after a marital dispute. Family history revealed an unclassifiable neurological disorder on the maternal side.

The boy was seen by several pediatricians and psychiatrists for the last 3–4 years but with no symptomatic improvement. At present, he communicated little, even with his father. His speech became extremely slurred and almost incomprehensible. He always wanted to be alone/undisturbed, felt frightened, and maintained a posture where he kept his head down so that he did not have to witness anything/anyone. He also tried to keep his eyes shut most of the time, even during spontaneous or forced conversation. When, after repeated requests, he opened his eyes, his stare looked vacant and as if searching for something; he had difficulty fixing his gaze on either static or moving objects in the visual field. On detailed neurological examination, he had manifestations of pure/complete Balint syndrome characterized by visual inattention, optic ataxia, oculomotor apraxia, and inability to attend to more than one object (simultanagnosia). He had associated emotional lability. Additionally, there was spastic-ataxic speech, spastic asymmetric quadriparesis (left more than right), and spastic gait. There was asymmetrical (left more than right) loss of dexterity in upper limbs and mild asymmetric (left more than right) weakness, stiffness, and dragging of lower limbs. All the deep tendon reflexes were asymmetrically (left more than right) exaggerated with ankle clonus and extensor plantar responses. Cognitive function was so grossly affected that detailed neuropsychological evaluation, sensory examination, and cerebellar examinations were impossible.

Contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed bilaterally somewhat symmetrical T2/FLAIR hyperintense lesions over white matter predominantly involving parieto-occipital regions suggestive of leukodystrophy (Fig. 1). Whole-genome exome sequencing detected a hemizygous nonsense pathogenic variation in exon 8 of the ABCD1 gene (chrX:g.153743008G > A; Depth: 56x) that resulted in a stop codon and premature truncation of the protein at codon 601 (p.Trp601Ter; ENST00000218104.6). The observed variation has previously been reported in patients affected with ALD.[3] The p.Trp601Ter variant had not been reported in the 1000 genomes, gnomAD, and our internal databases, so the validation of the variant's pathogenicity was confirmed by doing Sanger sequencing. Over the next six months, he developed hypoadrenalism (and received treatment for it) and became wheelchair-

https://doi.org/10.1016/j.neurop.2023.100124

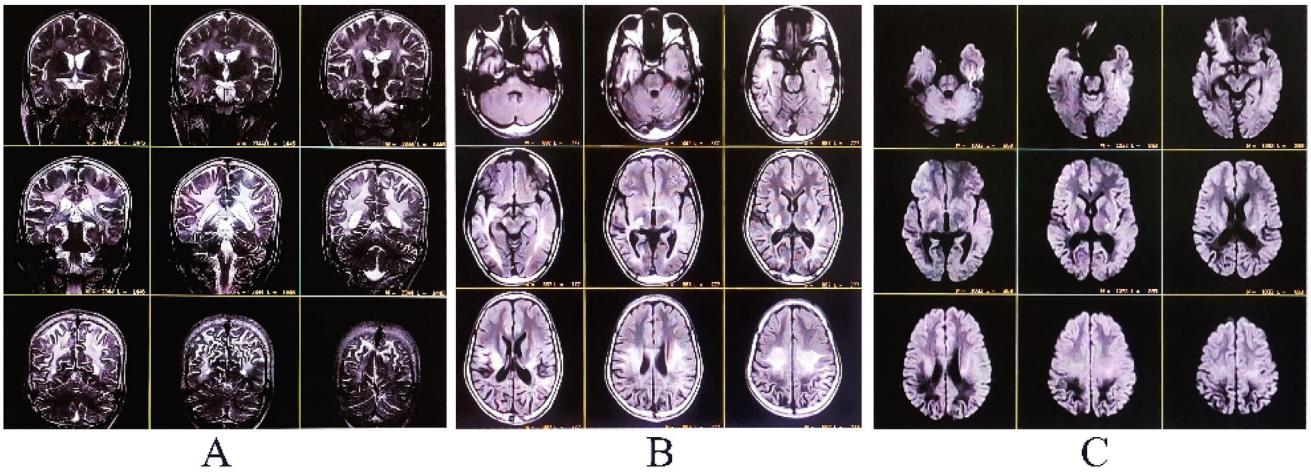

Fig. 1 MRI of the brain revealed non-enhancing altered intensity lesions hyper on coronal-T2-WI (A), axial-T2-WI (B), and axial-DWI (C) involving bilateral temporal-parietal-occipital region, posterior limb of the internal capsule, thalamus, and splenium of the corpus callosum with adjacent dilated sulci and dilated occipital horns of both lateral ventricles suggestive of posterior-predominant leukodystrophy.

bound. No definitive treatment could be offered to this child because of the advanced stage of the disease, lack of therapeutic options (e.g., Lorenzo's oil is not available in India), poor financial status, and the family's unwillingness.

X-linked ALD (X-ALD) (OMIM#300100) is a rare genetic disorder that affects white matter.[4–7] It is caused by mutations in the ABCD1 gene (OMIM#300371), which encodes for a peroxisomal very long-chain fatty acids (VLCFAs) transporter.[4–7] This disorder is characterized by a defect in peroxisomal beta-oxidation and accumulation of the VLCFAs in all body tissues.[4–7] The clinical manifestations occur primarily in the myelin of the central nervous system (which can produce bilaterally symmetrical, predominantly parieto-occipital white matter lesions), the adrenal cortex, and the Leydig cells of the testes.[4–7] The differential diagnosis should be made with childhood cerebral leukodystrophies, complicated hereditary spastic paraparesis, undiagnosed/untreated childhood primary demyelinating disorders, mitochondrial cytopathy, and moyamoya angiopathy.[4–7]

X-ALD represents a real diagnostic challenge due to its heterogeneous clinical manifestations, from slowly progressive myelopathy to rapid demyelination of brain white matter (cerebral X-ALD [C-X-ALD]).[7] Adrenocortical insufficiency appears mainly in the pediatric age group, and it can occur as the onset manifestation of the disease.[7] Female carriers may also develop symptoms of myelopathy later in life.[7]

In males, childhood C-X-ALD causes progressive behavioral, cognitive, and neurologic deficits, often leading to total disability and death within four years of diagnosis.[5] The pathologic hallmark is inflammatory cerebral demyelination, with a reported cumulative frequency of 31–35% and age of onset at 3–11 years.[5] On the other hand, adolescent C-X-ALD's presentation, and pathology are as in childhood C-X-ALD, with a reported cumulative frequency of 4%, age of onset at 11–21 years, and somewhat slower progression than childhood C-X-ALD.[5]

Currently, the standard therapy for childhood C-X-ALD with early brain involvement, detected by MRI with contrast enhancement, is allogeneic hematopoietic stem cell transplantation (HSCT).[5,7] Ideal candidates for intervention are individuals with a Loes score of 9 or lower, without any neurologic deficits, who receive HLA-matched sibling or related donor HSCT.[5,7] Nevertheless, this intervention has high morbidity and long-term sequelae related to immunosuppression and graft versus host disease. It is important to note that disease progression continues for 6–9 months following HSCT.[5,7] Particularly, adrenal dysfunction is not corrected following an HSCT transplant for cerebral disease.[5]

BS is underdiagnosed in children, though it may not be uncommon. As we mentioned, C-X-ALD is linked to demyelinated lesions in the bilateral posterior or parieto-occipital white matter, which could develop into Balint's syndrome, especially the incomplete form, with the most frequent initial ophthalmological abnormality being strabismus.[8] If symptoms of BS are not recognized in patients with C-X-ALD, the diagnosis may be overlooked. Besides, visuoperceptual tests used to diagnose BS are not easily applied to children because of their young age and lower visual acuity and mental ability. Furthermore, it is difficult to differentiate among types of agnosia in patients with a progressive degenerative disease that involves cognitive deterioration, such as C-X-ALD. Detailed medical history and clinical evaluations (including a neurological exam) are needed during the early stages of C-X-ALD before clinical progression becomes apparent.[8]

The main aim of publishing this case is not solely the rarity of the clinical entity. Rather, the authors believe BS has a high chance of remaining undiagnosed and misdiagnosed because of the unfamiliarity of primary-care physicians with this entity and lack of precise perception, even among the subject experts, about higher-order visual cognitive symptoms. Patients (especially children) with BS do not usually complain of visual symptoms as in this case. In most cases, BS is diagnosed retrospectively after the neuroimaging demonstrates bilateral parietal–temporal-occipital lesions.

In closing, as far as we know, this is the second reported BS heralding childhood C-X-ALD.[8] Therefore, ALD should be considered when facing a boy with symptoms suggestive of BS, which will allow early diagnosis and proper treatment.

Study funding

Nil.

Disclosures

Dr. Ritwik Ghosh (ritwikmed2014@gmail.com) reports no relevant disclosures.

Dr. Moisés León-Ruiz (pistolpete271285@hotmail.com) reports no relevant disclosures.

Dr. Kunal Bole (bolekunal@gmail.com) reports no relevant disclosures.

Dr. Srijit Bandyopadhay (srijitb63@gmail.com) reports no relevant disclosures.

Dr. Souvik Dubey (drsouvik79@gmail.com) reports no relevant disclosures.

Dr. Julián Benito-León (jbenitol67@gmail.com) reports no relevant disclosures.

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.

Conflict of Interest

No.

Acknowledgments

J. Benito-León is supported by the National Institutes of Health, Bethesda, MD, USA (NINDS #R01 NS39422), European Commission (grant ICT-2011-287739, NeuroTREMOR), the Ministry of Economy and Competitiveness, Spain (grant RTC-2015-3967-1, NetMD—platform for the tracking of movement disorder), and the Spanish Health Research Agency (grant FIS PI12/01602 and grant FIS PI16/00451).

References

1. Parvathaneni A, Das M. J. Balint Syndrome. 2021 Jun 30. In: StatPearls [Internet].Treasure Island (FL): StatPearls Publishing; 2022 Jan. PMID: 31335067.
2. Pisella L, Vialatte A, Khan AZ, Rossetti Y. Bálint syndrome. HandbClin Neurol. 2021;178:233–55. https://doi.org/10.1016/B978-0-12-821377-3.00011-8 PMID: 33832679.
3. Gärtner J, Braun A, Holzinger A, Roerig P, Lenard HG, Roscher AA. Clinical and genetic aspects of X-linked adrenoleukodystrophy. Neuropediatrics. 1998 Feb;29(1):3–13. https://doi.org/10.1055/s-2007-973526 PMID: 9553942.
4. Benito-León J, Zamorano T, Martín-Peña G, Tapia MA, Alvarez-Linera J. Lumbalgia como síntoma inicial de una adrenomieloneuropatía [Backache as the initial symptom of adrenomyeloneuropathy]. Rev Neurol. 2000 Dec 16–31;31(12):1167–70 Spanish. PMID: 11205553.
5. Turk BR, Theda C, Fatemi A, Moser AB. X-linked adrenoleukodystrophy: pathology, pathophysiology, diagnostic testing, newborn screening and therapies. Int J Dev Neurosci. 2020 Feb;80(1):52–72. https://doi.org/10.1002/jdn.10003 Epub 2020 Jan 26. PMID: 31909500.
6. Engelen M, van Ballegoij WJC, Mallack EJ, Van Haren KP, Köhler W, Salsano E, et al. International recommendations for the diagnosis and management of patients with adrenoleukodystrophy: a consensus-based approach. Neurology. 2022 Nov 22;99(21):940–51. https://doi.org/10.1212/WNL.0000000000201374 Epub 2022 Sep 29. PMID: 36175155; PMCID: PMC9687408.
7. Fadiga L, Melo M, Saraiva J, Paiva I. The clinical spectrum of X-linked adrenoleukodystrophy: from Addison's-only in men to middle-age neurologic manifestations in women. Hormones (Athens). 2022 Mar;21(1):33–40. https://doi.org/10.1007/s42000-021-00325-y Epub 2021 Oct 15. PMID: 34652632.
8. Kubota K, Kawai H, Takashima S, Shimohata T, Otsuki M, Ohnishi H, et al. Clinical evaluation of childhood cerebral adrenoleukodystrophy with Balint's symptoms. Brain and Development. 2021 Mar;43(3):396–401. https://doi.org/10.1016/j.braindev.2020.11.010 Epub 2020 Dec 11. PMID: 33309491.

R. Ghosh[a], M. León-Ruiz[b], K. Bole[c], S. Bandyopadhyay[a], S. Dubey[c], J. Benito-León[d,e,f,*]

[a] *Department of General Medicine, Burdwan Medical College and Hospital, Burdwan, West Bengal, India*
[b] *Section of Clinical Neurophysiology, Department of Neurology, University Hospital "La Paz", Madrid, Spain*
[c] *Department of Neuromedicine, Bangur Institute of Neurosciences, Institute of Post Graduate Medical Education and Research & SSKM Hospital, Kolkata, West Bengal, India*
[d] *Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain*
[e] *Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain*
[f] *Department of Medicine, Complutense University, Madrid, Spain*

*Corresponding author.
E-mail address: jbenitol67@gmail.com (J. Benito-León).