Dubai Medical Journal
Volume 7, Issue no. 1, DOI 10.18502/dmj.v7i1.17494
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Case Report

Epilepsy in Loeys-Dietz Syndrome: The Rare Concurrence of a Connective Tissue and Neuronal Migration Disorder

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Abstract

We present a 7-year-old girl who presented to our emergency department in active status epilepticus. Seizures responded to standard antiepileptic medications; however, baseline work-up for seizure etiology remained unremarkable. Her new-onset seizures were further investigated via EEG and MRI brain, which revealed focal epileptiform discharges and periventricular nodular heterotopia, respectively. Concurrently, the clinical evaluation revealed extensive marfanoid features, and a personal history of eczema and asthma. Her family history was pertinent for aortic valve disease, asthma, and tall stature. Given the peculiar skeletal features, allergic propensities and co-existent weighty family history, a molecular genetic panel analysis for Marfan Syndrome and Loeys-Dietz Syndrome (LDS) were sought. Genetic testing revealed an underlying heterozygous variant in the *TGFBR-1* gene; thereby confirming the presence of LDS. The child had responded well to single antiepileptic agent therapy and was discharged in good condition with regular outpatient cardiac and neurology follow-up. This is a unique case reported of a child with genetically diagnosed LDS concurring with an underlying neuronal migration disorder, manifesting in an acute, severe, and life-threatening fashion.

Keywords: epilepsy, Loeys-Dietz Syndrome, neuronal migration disorder, seizures

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Received: June 3, 2024
Accepted: August 15, 2024
Published: October 30, 2024

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How to cite this article: Mir FF and Ashraf M. Epilepsy in Loeys-Dietz Syndrome: The Rare Concurrence of a Connective Tissue and Neuronal Migration Disorder. *Dubai Medical Journal*. 2024;7(1):3–8. DOI 10.18502/dmj.v7i1.17494

1. Background

Loeys-Dietz syndrome (LDS) is an emerging connective tissue disorder with predominant vascular, skeletal, cutaneous, and craniofacial involvement [1]. It is often noticeable in children first due to skeletal malformations. Genetic confirmation of LDS entails rigid systemic assessment for well-recognized complications, most notably systemic aneurysm formation [2]. Existing literature recognizes a reserved degree of neurologic involvement in LDS, primarily cerebral aneurysms, dural ectasia, and complications secondary to craniosynostosis. Seizures in LDS secondary to nonstructural malformations have been scantily reported, with a stand-alone report of febrile seizures during COVID-19 infection in a child [3]. Until the publication of our case report, there stood no proposition of a neuronal migration disorder co-existing in patients with LDS.

2. Case Presentation

Our patient was a 7-year-old girl, known to have asthma and eczema, who presented to the emergency department in status epilepticus. Prior to seizure onset, the child was afebrile and clinically well, with no apparent trauma or triggers identified. Her baseline blood investigations including full blood count, C-reactive protein, glucose, electrolyte levels, and pan-cultures (blood, spinal, urine) were all within reassuring limits. Seizure activity was controlled with standard antiepileptic medications, and she was admitted to the pediatric ward for further care.

The child was born at term to non-consanguineous parents via cesarean section with an uneventful perinatal period. She achieved appropriate milestones for her age and had an average scholastic performance. She had developed symptoms of reactive airway disease at the age of 1 year and was admitted to the hospital twice at the age of 2 and 5 years, respectively for acute exacerbation of asthma. Thereafter, she was on prophylactic medications and regular follow-up in the pediatric clinic.

Initial physical examination was significant for: long, thin build with weight just below the third centile and height at the 50th centile; long narrow facies, wearing glasses, large and protruding eyes with up-slanting palpebral fissures, high arched palate with crowded irregularly shaped teeth, micrognathia; arm span to height ratio 0.99, hyperextensible joints, positive thumb and wrist signs, arachnodactyly, pes planus; pectus carinatum; hyperpigmented dystrophic scars at site of eczema; neurologic exam was grossly unremarkable apart from brisk deep tendon reflexes; cardiovascular exam was within normal limits. The child was continued on sodium valproate, and she had no further seizures during admission.

Noting the child's physical features, family history was further investigated. Father was diagnosed with asthma, Marfan syndrome (based on clinical features), and had surgery for aortic valve regurgitation (metallic valve replacement in 2012). The patient's older brother and three maternal cousins all have tall stature and asthma. Father's paternal grandfather and father's maternal uncle and his son are tall in stature.

Given her prominent clinically marfanoid features, along with allergic propensity and pressing family history, a Marfan and LDS genetic study panel was sent. Further investigations were sought in the interim prior to genetic confirmation, given the strong suspicion of an underlying connective tissue disease. Her skeletal survey report appeared elongated and slim long bones of hands, feet, and a narrow pelvis. Screening echocardiography revealed a normal left aortic root of 21 mm, ascending aorta 18 mm, and descending 14 mm; with mild mitral valve prolapse, but no mitral regurgitation, vegetation, or thrombus. Eye examination revealed bilateral refractive error needing regular glasses use, without any evidence of blue sclerae or strabismus; screening optical coherence tomography showed a slight temporal and superior disc pallor in the right eye.

Her new onset of seizures in the form of status epilepticus was also extensively worked up. Electroencephalography reported with left parieto-temporal epileptiform activities, becoming more frequent during sleep. Screening MR angiography of the brain was reported normal; however, MRI brain revealed prominent periventricular nodular heterotopia (Figure **1**). Genetic testing soon confirmed the diagnosis of LDS with a heterozygous pathogenic variant *c.827T>C p.(Leu276Pro) chr 9:101904839* in the *TGFBR1* gene, which leads to amino acid exchange; and an additional variant of unknown significance in *FBN 2* gene *c.5430T>C p.(Asp1810Asp) cnr5:127641633*. The child was discharged in good clinical condition on regular sodium valproate therapy; and with follow-up in pediatric, cardiology, and neurology outpatient clinics. Upon re-evaluation a few months later, the child had an episode of breakthrough seizures requiring medication adjustment. Her screening echocardiography still remained normal.

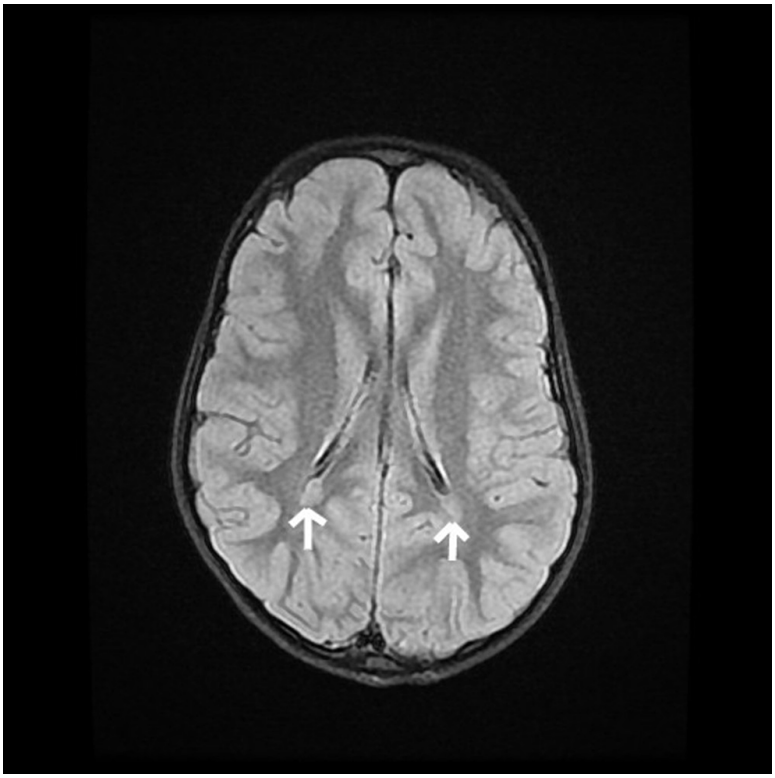

Figure 1: MRI Brain section revealing bilateral periventricular nodular heterotopia.

3. Discussion

LDS is a well-recognized connective tissue disorder falling along the broad spectrum of Marfan syndrome and Marfan-like conditions. Children display clinical features undeniably close to Marfan syndrome, hence LDS proband recognition often stems from astute clinical examination and a focused inquiry of family history. Confirmation of diagnosis with genetic testing must be followed by a meticulous systemic assessment to determine both the extent of organ involvement and the appropriate frequency of further follow up [1].

There are six known pathogenic mutations leading to LDS, among which *TGFBR 1* variant is responsible for 20-25% of LDS cases [1]. Cozijnsen et al., performed a study on the pathogenic effect of *TGFBR-1* mutations, with functional analysis revealing increased fibroblast myogenic differentiation in patient cells with the mutation as compared to healthy controls [4].

Neurologic manifestations in LDS have largely been linked to cerebral and vertebral arterial aneurysms, dural ectasia, craniosynostosis, and Chiari I malformation [5]. In the context of connective tissue disease, new onset of seizures may be attributed to a ruptured cerebral aneurysm, which was ruled out in our patient by neuroimaging on presentation.

Neuronal migration genes have been found to code for cytoskeleton proteins, which are crucial for cell division and axon/dendrite formation [6]. Stouffer et al., performed an animal-based study to investigate the correlation between neuronal migration disorders and various cerebral pathologies. This supports the concept that disturbances in the former objectively lead to lamination, neuronal differentiation, and cell morphology anomalies [5].

The presence of underlying periventricular nodular heterotopia has been linked to the development of seizures; however, our case report is the first in literature to report a potential link between the former and LDS. Further investigation for the presence of a neuronal migration defect may be worthwhile to detect the aforementioned as a culprit for new-onset seizures, especially in cases of LDS without gross neurologic/vascular anomalies.

Moreover, the detection of an *FBN- 2* mutation variant of uncertain significance cannot be proven to have contributed to our patient's clinical presentation. It holds a part in the genetic panel related to syndromic forms of thoracic aortic aneurysms and has been associated with congenital contractural arachnodactyly—a condition closely parallel to LDS.

4. Conclusion

A careful clinical examination serves as the basis for initiating an investigation toward diagnosing LDS. Children with strong family histories of potential connective tissue disorders should be evaluated with a higher index of suspicion as early diagnosis can prevent complications. Status epilepticus has a broad

spectrum of possible etiologies, with prominent neurological disorders in LDS, including cerebral vascular aneurysmal dilation/rupture and critical hydrocephalus secondary to cranial malformations. However, it is worth noting that our case highlights the value of considering underlying neuronal migration defects, particularly in the absence of conventional seizure etiologies.

Acknowledgment

None.

Statement of Ethics

The case report was planned, conducted, and reported in accordance with the World Medical Association (WMA) Declaration of Helsinki. Written patient informed consent was obtained from parents to publish the case. Ethical approval was not required for this study in accordance with Dubai Health Authority Research Committee policies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Artificial Intelligence (AI) Disclosure Statement

AI-Unassisted Work.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Both authors have contributed to the data collection, interpretation, literature review, and formalization of the report.

Data Availability Statement

All data generated or analyzed during this case are included in this article. Further inquiries can be directed to the corresponding author.

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