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SHORT RESEARCH ARTICLE

The challenge of ultra-rarity: Dual diagnosis of Lafora disease and developmental encephalopathies linked to *TRIO* and *SHANK3* pathogenic variants

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Abstract

We report two cases of dual genetic diagnoses involving Lafora disease (LD) and co-occurring neurodevelopmental disorders caused by pathogenic variants in *TRIO* and *SHANK3*, respectively. LD is an ultra-rare, autosomal recessive, severe form of progressive myoclonus epilepsy affecting previously healthy children or adolescents. In both patients, the presence of developmental delay, intellectual disability, and behavioral abnormalities was consistent with a primary genetic disorder—*TRIO*-related neurodevelopmental disorder in one, and Phelan-McDermid syndrome in the other. However, the onset of epilepsy with atypical features, coupled with progressive neurological decline in one patient and a positive family history of LD in the other, prompted the additional diagnosis of LD. These cases illustrate how overlapping clinical presentations can obscure the presence of concomitant genetic conditions, potentially delaying diagnosis and appropriate management. Our findings underscore the importance of considering dual diagnoses and show that phenotypical variability in ultra-rare disorders such as LD may be influenced by concurrent genetic conditions.

Plain Language Summary: This report describes two patients who have both Lafora disease, an ultra-rare, progressive type of epilepsy, and other rare genetic disorders that affect development and behavior. In one case, the patient showed a progressive and unusual neurological deterioration, while the other had atypical epileptic seizures and a family history of Lafora disease. These cases highlight how different genetic conditions can share similar symptoms, making it difficult

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to identify all the issues a patient may have. Understanding these overlaps is important for proper diagnosis and treatment.

KEYWORDS

double trouble, next-generation sequencing (NGS), Phelan-McDermid syndrome, progressive myoclonus epilepsy, whole-exome sequencing (WES), whole-genome sequencing (WGS)

1 | INTRODUCTION

Lafora disease (LD) is a severe form of progressive myoclonus epilepsy, characterized by drug-resistant epilepsy, myoclonus, and psychomotor deterioration.[1] LD is ultra-rare, with an estimated prevalence <1 case per million people.[2] It affects previously healthy children or adolescents, with a median onset at 13 years.[3] Biallelic pathogenic variants in *EPM2A* or *NHLRC1* result in the accumulation of insoluble polyglucosan aggregates in various organs, particularly the brain.[1] At present, treatment for LD is only symptomatic, and death usually occurs in early adulthood.[3]

The phenotype is relatively consistent across cases, but there can be some variability in terms of age at onset and rate of progression.[1] Genotype–phenotype correlations have been established for certain mutations,[4,5] however, the mechanisms underlying some cases with atypical features, including early-onset cognitive impairment preceding epilepsy, remain unclear.[1]

TRIO-related neurodevelopmental disorder (*TRIO*-NDD) is an autosomal dominant condition characterized by developmental delay, intellectual disability (ID) and behavioral disturbances.[6] Patients may also present with absence and myoclonic seizures (about one third of cases),[7] abnormal head circumference, and systemic manifestations. This condition is rare, accounting for fewer than 1% of individuals with ID,[6] and may be caused by gain-of-function and loss-of-function heterozygous variants in the *TRIO* gene, the latter being associated with a less severe phenotype.[6]

Phelan-McDermid syndrome (PMS) is a genetic condition caused by *SHANK3* haploinsufficiency, usually occurring de novo, manifesting with global developmental delay and ID, impaired language, autism spectrum disorder (ASD), hypotonia, epilepsy (about one third of cases), and systemic features.[8] PMS is a rare condition, being diagnosed in around 0.5% of individuals with ASD and ID.[8]

We describe two patients with developmental encephalopathies linked to *TRIO* and *SHANK3* pathogenic variants showing an atypical course, leading to the diagnosis of concomitant LD.

Key points

- Two patients had both Lafora disease and distinct rare neurodevelopmental disorders related to pathogenic variants in *TRIO* and *SHANK3*.
- Atypical symptoms masked dual diagnoses, delaying proper identification and treatment.
- Broad genetic testing is key when symptoms do not match known single-gene disorder profiles.
- Dual genetic conditions may explain phenotypic variability in Lafora and other rare disorders.

2 | METHODS

Among a cohort of over 30 Italian patients with LD known through direct referrals and the national LD registry hosted by the Italian National Institute of Health, we identified two cases with a dual diagnosis of a concomitant genetic condition that influenced the neurological phenotype. Clinical, genetic, and instrumental data were gathered from clinical records. Informed written consent for publication was obtained from the parents of case 2, while case 1 was deceased at the time of writing.

3 | RESULTS

3.1 | Case description #1

The patient was born at term to non-consanguineous parents of Italian ancestry. There was no family history of epilepsy, yet the mother and his older brother presented with mild ID, which had never been further investigated. His early developmental milestones were reported as normal. However, during school age, moderate ID became apparent, necessitating social assistance and academic support. He continued his studies until high school with the aid of an educator.

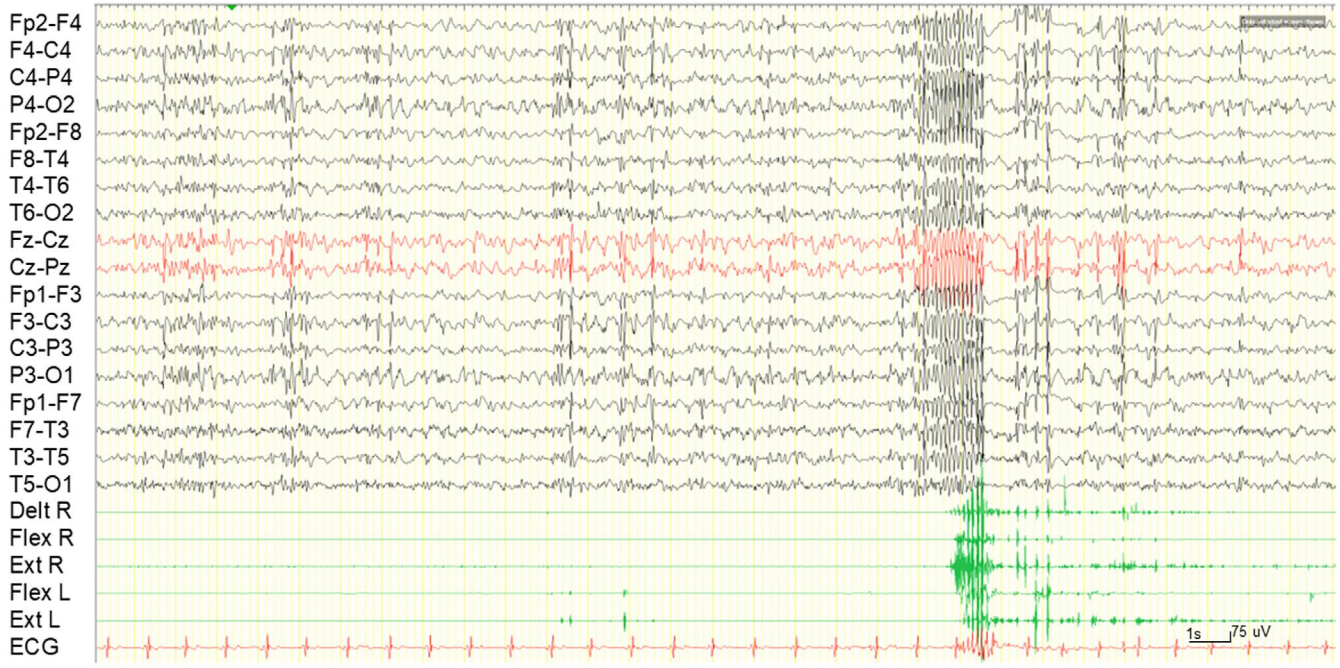

FIGURE 1 Polygraphy (Case#1). The EEG shows diffuse background slowing and frequent interictal generalized epileptiform discharges. A prolonged, high-amplitude generalized polyspike-and-wave discharge is observed, accompanied by diffuse phasic activity on surface EMG with agonist–antagonist co-contraction, corresponding to a generalized myoclonic seizure. Delt, deltoid; Flex, forearm flexors; Ext, forearm extensors; L, left; R, right.

Next-generation sequencing (NGS) targeting ID genes, performed elsewhere at the age of 17, identified a pathogenic variant in *TRIO* NM_007118 (c.2431C>T, p.Arg1411Ter), which was inherited from his mother and carried by his affected brother.

At 14 years of age, the patient experienced weekly seizures characterized by impaired awareness, myoclonia of the eyelids and upper limbs. A year later, he had his first generalized tonic–clonic seizure (GTCS). EEG showed background slowing and generalized epileptiform discharges.

By age 17, the patient's seizures had significantly worsened, with myoclonic seizures occurring multiple times per week and GTCS occurring weekly, despite trials of various antiseizure medications (valproate, ethosuximide, topiramate, levetiracetam, zonisamide, lamotrigine).

Behavioral disturbances also emerged, including outward-directed aggression. At age 18, episodes of self-harm and agitation developed, necessitating psychiatric hospitalization. Quetiapine improved his behavioral symptoms, while perampanel helped control his seizures but was discontinued due to exacerbation of psychiatric issues.

By age 21, his cognitive function declined further; myoclonic jerks in all four limbs and ataxia became prominent, resulting in frequent falls and loss of independence in daily activities, and he developed dysphagia. Seizures further increased in frequency, with multiple GTCS per week.

At age 22, the patient was admitted for re-evaluation. Neurological examination revealed pronounced ideomotor slowing and frequent myoclonic jerks exacerbated by movement. In addition to epileptic seizures, he exhibited psychogenic non-epileptic seizures. EEG-polygraphy confirmed background slowing with frequent epileptiform discharges, both generalized and focal in the posterior regions, along with positive and negative myoclonia (Figure 1). Brain MRI revealed mild diffuse cerebral and cerebellar atrophy.

Given that the *TRIO* mutation did not explain the patient's progressive deterioration, further investigations were pursued. A muscle biopsy revealed the accumulation of Lafora bodies (Figure 2). Whole-exome sequencing (WES) identified a homozygous pathogenic variant in *NHLRC1* NM_198586 (c.721C>T, p.Arg241Ter), confirming the diagnosis of LD.

In the months that followed, the patient's cognitive and motor function deteriorated further, progressing to dementia. By age 24, he was bedridden and passed away in a long-term care facility.

3.2 | Case description #2

This 9-year-old patient was born at term to consanguineous parents (first-degree cousins) of Moroccan ancestry. His 17-year-old sister has LD due to a homozygous

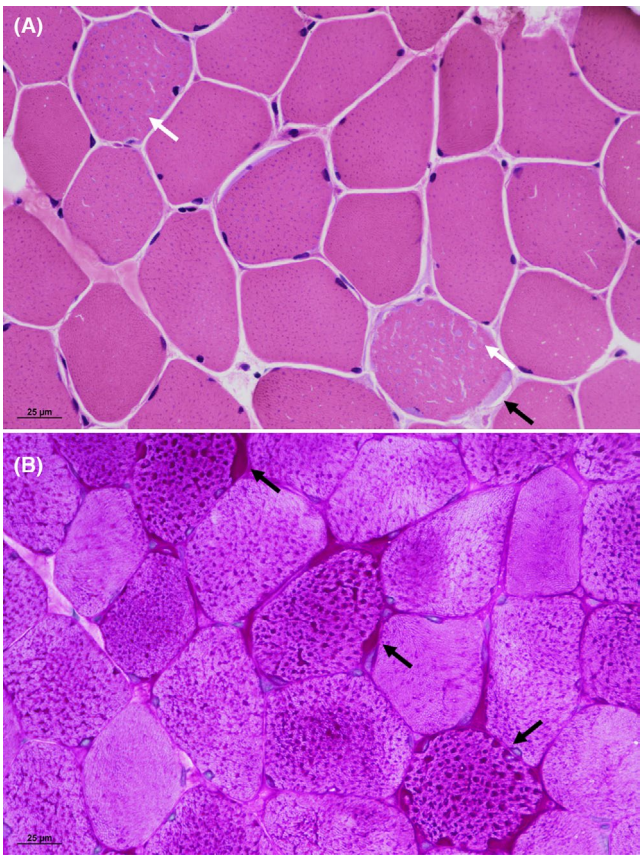

FIGURE 2 Muscle Biopsy (Case#1). (A) Hematoxylin and eosin staining showed multiple fibers characterized by subsarcolemmal accumulation of basophilic material (black arrow), also present like multiple dots in the cytoplasm (white arrows). (B) Periodic acid Schiff (PAS) staining showed that the aggregates of basophilic material contained in the fibers were strongly reactive with PAS (black arrows), thus indicating their nature of polyglucosan aggregates consistent with Lafora bodies.

NHLRC1 variant (c.205C>G, p.Pro69Ala), which manifested at age 12 with GTC and focal visual seizures.

Signs of neurodevelopmental abnormalities were evident from early infancy. By 6 months, he lacked parental engagement, eye contact, vocalization, and had hyperreactivity to auditory and visual stimuli. He showed normal gross motor milestone achievement: sitting and crawling before 12 months, cruising at 14 months, and independent walking by 16 months. Language development began appropriately with babbling at 12 months but plateaued, followed by developmental arrest at 16 months. By age 2 years, significant social impairment was evident, including limited age-appropriate interaction, solitary and stereotyped play, heightened anxiety toward strangers, hyperkinetic behavior, poor appetite with selective eating, lack of visual engagement and pointing behavior, no bladder or bowel control, and a regression of previously acquired language skills. Clinical evaluation led to a diagnosis of developmental encephalopathy with prominent communicative-language impairment and comorbid ASD level 3.

Between 6 and 8 years of age, the patient developed increasing behavioral disturbances, including impulsivity and both self- and other-directed aggression, accompanied by chronic insomnia.

At 9 years of age, he experienced two prolonged seizures characterized by reduced responsiveness, generalized hypotonia, pallor, perioral cyanosis, hypersalivation, and oxygen desaturation. The first episode resolved spontaneously after ~20 min but prompted hospital admission. The second one occurred during the hospital stay, and while ongoing, was recorded on EEG, showing a right posterior focal ictal discharge (Figure 3), interrupted by rectal diazepam about 20 min after the clinical onset. The patient was treated with valproate, resulting in seizure freedom at the 6-month follow-up. Interictal EEG showed generalized and focal posterior epileptiform discharges, in addition to a photoparoxysmal response. Whole-genome sequencing (WGS) confirmed the homozygous *NHLRC1* variant previously identified in his sister (p.Pro69Ala), consistent with LD, and revealed a de novo variant in *SHANK3* NM_0010804200 (c.3727dup, p.Ala1243Glyfs*69), supporting a dual diagnosis that includes PMS.

4 | DISCUSSION

We diagnosed LD with concomitant independent rare genetic conditions in two patients with developmental encephalopathy and superimposed clinical worsening.

Case 1 was initially diagnosed with ID due to a heterozygous loss-of-function pathogenic variant of *TRIO*. During adolescence, he developed seizures and behavioral issues, symptoms commonly encountered in *TRIO*-NDD.[6,7] However, the subsequent progressive course characterized by the emergence of highly drug-resistant seizures, myoclonus, ataxia, and cognitive deterioration prompted a comprehensive reassessment. A diagnosis of LD was ultimately confirmed through histopathological and clinically driven genetic analyses.

Case 2 had a severe developmental encephalopathy with ASD consistent with PMS,[8] and received the dual genetic diagnosis of *SHANK3* and *NHLRC1* pathogenic variants soon after the onset of epilepsy at 9 years of age, arguably related to LD. Indeed, although epilepsy can be present in up to 40% of patients with PMD, focal seizures and status epilepticus are infrequently noted, and photoparoxysmal response is not described, while these represent typical manifestations of LD.[1,9,10] In this case, NGS was driven clinically and by the genetic diagnosis of the patient's sister with LD.

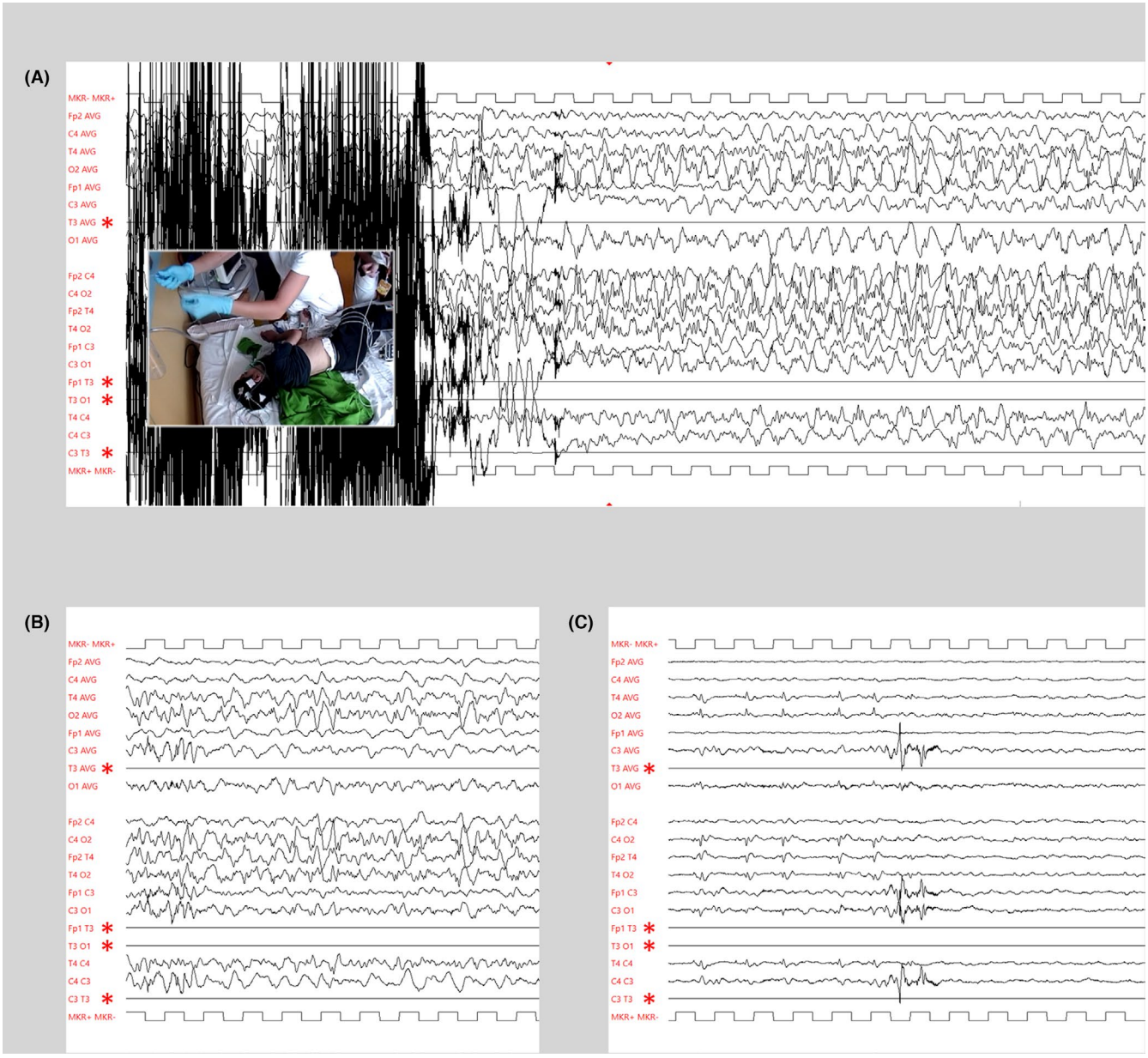

FIGURE 3 EEG (Case#2). Video-EEG recording started during a prolonged seizure (15 min after clinical onset with generalized hypotonia and loss of consciousness), showing (A) posterior rhythmic delta activity with superimposed fast discharge, prevailing on the right occipital channels. The ictal discharge attenuates two minutes following rectal diazepam administration (B), and is interrupted after 6 min (C). On the MKR channel the period of the square-wave corresponds to 1 s and its amplitude corresponds to 100 μV. Only a reduced number of electrodes are available; the montage is composed by eight referential channels (average reference) followed by eight longitudinal bipolar channels then three transverse bipolar channels; please note that due to technical issues electrode T3 is malfunctioning, so all related channels (asterisk) are flattened.

These cases highlight the importance of considering a differential diagnosis in patients whose clinical features deviate from the expected presentation associated with their genotypes, despite the difficulty of outlining the whole disease clinical spectrum of novel developmental and epileptic encephalopathy genes. As evidenced by this and prior reports, clinical features of multiple genetic disorders can overlap, mimic or obscure one another, thereby complicating diagnosis and delaying appropriate management.[11] Clinicians traditionally aim to identify a single explanation for the clinical manifestations of a patient and to attribute them to a single cause, especially when a rare disease is identified, according to the "single-disorder" paradigm. In fact, influenced by Occam's Razor principle, the finding of a pathogenic variant consistent with the majority of the patient's clinical features usually stops further genetic testing. However, when the clinical course is atypical or exhibits greater severity than

expected—scenarios in which clinicians may assert they are "widening the phenotype"—the possibility of a dual diagnosis contributing to the clinical picture should be considered.[11,12] The advent of NGS techniques, including WES and WGS, has revealed that dual molecular diagnosis are more common than previously assumed, occurring in up to 7% of syndromic cases[13]—a figure consistent with our findings in this cohort. In ultra-rare genetic disorders such as LD, phenotypic variability may be influenced by dual diagnosis that alter the disease trajectory,[5] as evidenced by the early-onset developmental delay, ID, and psychiatric features observed in these patients.

The dual diagnosis of a genetic disorder (i.e., the presence of pathogenic variants at two distinct and independently segregating loci that cause two different Mendelian conditions), colloquially known as "double trouble," may significantly impact genetic counseling and management strategies.[11,12] In fact, understanding the genetic basis of a given disorder could implement specific indications for correct follow-up and potential treatment, avoid ineffective medical care, provide prognosis information, and identify familial recurrence risk.

Notably, if genetic testing had been restricted to genes associated with progressive myoclonus epilepsies, both our patients might have been misclassified as atypical, early-onset forms of LD.[14] While LD has its typical onset around 13 years of age,[3] cases with onset in early childhood were described and suggested to be related to specific mutations.[14] In confirmed LD cases with early-onset presentations, comprehensive diagnostic workups, including NGS, are suggested to uncover additional contributing factors.[5] On the other hand, the presence of a preexisting diagnosis, such as *TRIO*-NDD in case 1, may significantly delay recognition of additional conditions like LD. This is particularly concerning given the development of clinical trials for disease-modifying therapies,[15,16] which require timely and accurate diagnosis for patient eligibility and better outcomes.

In conclusion, this report illustrates the complexity of diagnosing neurodevelopmental and neurodegenerative disorders when dual diagnoses coexist. It emphasizes the need for broad genetic testing and re-evaluation in patients with clinical attributes not aligning with the known phenotype and the evolution of a given genetic etiology, and suggests that phenotypical variability in ultra-rare disorders such as LD may, in part, be influenced by concurrent genetic conditions.

AUTHOR CONTRIBUTIONS

Lorenzo Muccioli: conceptualization; investigation; writing—original draft preparation. Francesca Bisulli: conceptualization; investigation; writing—original draft preparation. Raffaella Minardi: investigation; writing—review and editing. Maria Lucia Valentino: investigation; writing—review and editing. Micaela De Simone: investigation; writing—review and editing. Rodrigo Almeida Paroni: investigation; writing—review and editing. Edward Cesnik: investigation; writing—review & editing. Elisa Fallica: investigation; writing—review and editing. Luigi Bonan: investigation; writing—review and editing. Eleonora Pizzi: investigation; writing—review and editing. DEFEAT-LD Study Group: investigation; writing—review and editing. Gaetano Cantalupo: investigation; writing-review and editing; supervision. Laura Licchetta: investigation; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethics approval was not required for this study as it is a case series and does not involve research on human subjects requiring institutional review. Consent for publication could not be obtained for case # 1 as the patient is deceased. Efforts have been made to ensure that the report is anonymized and respects the patient's confidentiality. Consent for publication for case # 2 was obtained from the parents. Data generated or analyzed during this study are included in this article. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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APPENDIX A

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