

Lujan–Fryns Syndrome (LFS): A Unique Combination of Hypernasality, Marfanoid Body Habitus, and Neuropsychiatric Issues, Presenting as Acute-Onset Dysphagia

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ABSTRACT

BACKGROUND: Lujan–Fryns syndrome (LFS) is an extremely rare, X-linked disorder, for which the full clinical spectrum is still unknown. Usually, it presents with neuropsychiatric problems such as learning disabilities and behavioral issues in a typical combination with marfanoid features. Often, there is a positive family history for the disorder. However, sporadic cases have also been reported in males. More interestingly, there is no case of LFS presenting with acute-onset dysphagia in the English language medical literature.

CASE PRESENTATION: A 17-year-old Pakistani mentally normal school boy was admitted for the workup of acute-onset dysphagia, hypernasal speech, and nasal regurgitation of liquids. He had no neuropsychiatric issues, and his family history was unremarkable. An obvious nasal twang, facial dysmorphism, and marfanoid body habitus were found on examination. The genetic tests revealed a pathogenic missense mutation in the *MED12* gene on his X-chromosome.

CONCLUSION: LFS can present as acute-onset dysphagia and in the absence of any neuropsychiatric issues or positive family history of the syndrome.

KEYWORDS: Lujan–Fryns syndrome, marfanoid body habitus, Marfan syndrome, hypernasality, facial dysmorphism

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Introduction

Lujan–Fryns syndrome (LFS), which was first described in 1984, is a rare neuro-rheumatological disorder.¹ Marfanoid features, in association with mild–moderate mental retardation, and facial dysmorphism present a diagnostic challenge.² However, in the presence of family history, a typical combination of a varying degree of intellectual disability, marfanoid body habitus, and hypernasal speech makes the diagnosis of LFS more likely, if the alternative conditions have been excluded.^{3–5} Moreover, cases of LFS in the absence of any neuropsychiatric issues or positive family history for the disorder have also been reported.⁶ We searched the electronic medical database, including PubMed, MEDLINE, Web of Science, and Medscape for literature review (Table 1). We used the following keywords: “Lujan–Fryns syndrome”, “facial dysmorphism”, “marfanoid body habitus”, “hypernasal speech”, “X-linked mental retardation”, “*MED12*-related disorders”, and “dysphagia”. To the best of our literature search, no case of LFS presenting with acute-onset dysphagia has been reported previously. Herein, we report one such case of LFS,

presenting with acute-onset dysphagia, and in the absence of any neuropsychiatric issues or positive family history.

Case Presentation

A 17-year-old boy with unremarkable past history presented to the medical outpatient department (OPD) of Khyber Teaching Hospital (KTH), Peshawar, with a one-week history of dysphagia. He also reported hypernasal speech and nasal regurgitation of liquids. He denied any cough, headache, facial pain, or breathing problems. He did not have any paresthesias or weakness in any of his limbs. He had normal cranial nerve functions, including normal vision, hearing, and taste. He did not use any regular medications. He was a student of class 10, and his performance at school was satisfactory.

He had no family history of any similar medical problems. His parents were not related and had no medical or surgical issues. He had three brothers and one sister, and they were all normal. The rest of his history was unremarkable.

On examination, he appeared tall and thin. His vital signs were within reference range. He had an obvious nasal

Table 1. List of some of the published cases of LFS.

AUTHORS	PAPER	NUMBER OF CASES
Lujan et al	Am J Med Genet. 1984 Jan; 17(1):311–22.	4 (males)
Meinecke P et al	Clin Genet. 1985 Dec;28(6):516–20.	1 (female infant)
Fryns et al	Am J Med Genet. 1987 Oct;28(2):267–74.	4 (males)
Cunniff C et al	Pediatrics. 1990 Apr;85(4):499–504.	5
Gurrieri F et al	Am J Med Genet. 1991 Feb–Mar;38(2–3):290–1.	1 (female)
Lalatta F et al	Am J Med Genet. 1991 Feb–Mar;38(2–3):228–32.	4 (sporadic cases with no family history)
Stratton RF	Am J Med Genet. 1993 Apr 15;46(2):138–41.	1 (male)
Lacombe D et al	Genet Couns. 1993;4(3):193–8.	3 new cases and review of 20 previous case reports
Fryer A.	Am J Med Genet. 1994 Jul 1;51(3):277–8.	1
Wittine LM et al	Am J Med Genet. 1999 Oct 29;86(5):405–9.	2 (males)
Donders J	Am J Med Genet. 2002 Jan 22;107(3):243–6.	1 (male with no neuropsychiatric issues)
Lerma-Carrillo I et al	Am J Med Genet A. 2006 Dec 15;140(24):2807–11.	2 new cases and review of 32 previous case reports
Prescott TE et al	Eur J Med Genet. 2016 Aug;59(8):367–72	2
Prontera P et al	Am J Med Genet A. 2016 Sep;170(9):2377–82.	3 (2 males, 1 female)

**Figure 1.** Facial dysmorphism in our patient showing micrognathia, low-set small ears, depressed nasal base, maxillary hypoplasia, and so forth (permission obtained from the patient).**Figure 2.** Relatively tall thin appearance of our patient, with a degree of hyper-flexibility at wrist and fingers (permission obtained from the patient).

twang. Moreover, he had relatively low-set, normal-shaped smaller ears, micrognathia, short mandible, relatively flat nasal bridge, and maxillary hypoplasia. He had high-arched palate, thin long fingers and digits, sandal gap, hyper-flexible joints, relative hypotonia, and positive wrist and thumb signs (Figs. 1–4). The ratio of his arm span to height was increased [1.18 (normal = 1.05)]. Moreover, the ratio of his upper body (measured from head to pubis) to lower limb was reduced [0.65 (normal = >0.85)]. He had mild pectus excavatum and pes cavus. However, there was no scoliosis, pneumothorax, or murmur of aortic regurgitation (AR). A slit-lamp examination by a senior ophthalmologist excluded any lens dislocation or any other ocular abnormality. He was examined by a senior otolaryngologist, who excluded any evidence of velopharyngeal insufficiency (VPI) or any other ear, nose, and throat (ENT)-related functional abnormality. He performed normally on the mini-mental state examination (MMSE), the learning disability assessment test, and Woodcock-Johnson IV (WJ IV).

The patient's baseline investigations, including full blood count, renal, liver, and thyroid function tests, serum electrolytes, blood sugar, urinalysis, chest X-ray, and abdominal ultrasound, were all normal. His specialized investigations, including nerve conduction studies (NCS), electromyography (EMG), and MRI brain plus cervical spine, were also



Figure 3. Hyper-flexibility at right hand (permission obtained from the patient).



Figure 4. Mild–moderate pectus excavatum (permission obtained from the patient).

unremarkable. He had normal lumbar puncture and plasma homocysteine levels. An echocardiogram showed normal heart function and structure, except for a mild AR and minimal mitral valve prolapse (MVP). Moreover, there was no evidence of any aortic root dilatation. Finally, his genetic assessment was done. Polymerase chain reaction (PCR) was used to amplify the DNA prior to sequence analysis for *MED12* gene on the X-chromosome. The sequence analysis revealed a pathogenic missense mutation (pN1007S) in the *MED12* gene. For the sake of clarity, the sequence analysis for *MED12* gene was repeated from another reputable center. However, the results remained the same. His karyotype was 46-XY. Sequence analysis preceded by a PCR was done to screen his parents, younger sister, and brother for similar mutations in *MED12* gene. However, the results were negative. His elder brother was not screened, as he was working abroad and was thus inaccessible.

Considering his marfanoid features, facial dysmorphism, and positive genetic test results for *MED12* gene, a diagnosis of LFS was made. He and his family were counseled regarding

the X-linked pattern of inheritance of his disease. The patient was referred to the speech, swallowing, and language assessment team for physiotherapeutic sessions. He was discharged home on a beta blocker (propranolol 10 mg thrice daily).

The patient was reviewed again after three months. His speech had become normal after multiple sessions with the speech therapist. His swallowing difficulties had improved remarkably, and his nasal regurgitation of fluids had subsided. His repeat echocardiogram was unchanged. Moreover, his repeat slit-lamp ophthalmologic and ENT examination was as normal as before his discharge from the hospital. He will be reviewed again in three months' time. His follow-up plan will include detailed clinical assessment, slit-lamp ophthalmologic and ENT examination, as well as echocardiography.

Discussion

LFS is an X-linked disorder, which is characterized by a combination of a varying degree of mental retardation, behavioral problems, marfanoid body habitus, facial dysmorphism, and hypernasal speech.⁷ There is still some controversy regarding the type of X-linked inheritance, X-linked dominant, and X-linked recessive. However, it is generally said to be X-linked dominant.^{4,5,7,8} Moreover, sporadic cases without any family history of the disease have also been reported.^{9,10} Our patient appeared to be one of the sporadic cases, without any syndromal family history.

LFS is more common in males. However, neither the exact etiology nor the prevalence rates in general population are known.¹¹ It must be specifically considered in the differential diagnoses of mentally retarded and psychiatric patients and in those with marfanoid body habitus and facial dysmorphism with hypernasal speech. Moreover, the diagnosis needs clinical features, as well as confirmation with the genetic tests.^{5,11} It is worth mentioning that recently, mutations of three genes (*MED12*, *UPF3B*, and *ZDHHC9*) have been reported in the broadly defined LFS. However, currently, there is no antenatal test available.^{6,12,13} *MED12*, one of the members of the large Mediator complex, has a central role in RNA polymerase II transcription. As a multiprotein complex, the Mediator complex is responsible for cell growth, development, and differentiation.¹⁴ Although *MED12* is important for structural protein synthesis, it still needs to be found why our patient had MVP only and no other structural cardiac or cerebral lesions.

Clinical presentation of LFS is highly variable. Most patients have mild–moderate mental retardation and learning difficulties. Neuropsychiatric and behavioral issues can be variable and include emotional lability, aggressive and hyperactive attitude, shyness and/or autistic behavior, and even extreme psychiatric problems such as psychotic disturbances, hallucinations, and schizophrenia.¹⁵ However, our patient had none of these neuropsychiatric problems.

Facial dysmorphism includes, but is not limited to, features such as prominent forehead, long narrow face,



maxillary hypoplasia, small mandible, high-arched palate, small or receding chin, and low-set, normal-shaped ears. The marfanoid body habitus entails a tall stature, arachnodactyly, long limbs, short halluces, long second toes, and sandal gap, increased arm span to height ratio, and reduced trunk to lower limb ratio. The marfanoid stature usually becomes obvious after puberty.^{5,10,16} Usually, there is accompanying hypotonia and hypernasality, in the absence of any VPI or mucosal/submucosal cleft palate. Although our patient presented with acute-onset dysphagia, the reasons cannot be clearly stated. Moreover, as our patient's dysphagia improved with physiotherapy and swallowing/speech exercises, there is a possibility that it might have been because of the relative hypotonia of the pharyngeal muscles. Other clinical features of LFS may include cardiac abnormalities such as atrial septal defect (ASD) and ventricular septal defect (VSD).¹⁷ Lens dislocation is not a feature of LFS and is a key feature to distinguish this from Marfan syndrome or homocystinuria.^{5,10,16}

Genetic testing for *MED12*, *UPF3B*, and *ZDHHC9* is necessary for confirming the diagnosis of LFS. Nevertheless, additional laboratory investigations should be done to rule out the differential diagnoses. They should include an echocardiogram, ultrasound, ophthalmologic examination, serum and urinary homocystine levels, chromosomal analysis, and biochemical analysis of aminoacids in plasma and urine.^{12,14}

There is no specific treatment for LFS. Patients need to be educated about its diagnosis. Moreover, they should be regularly followed up at the neuropsychiatric clinic to detect, and then treat any neuropsychiatric issues, as early as possible. Similarly, patients with predominant rheumatologic issues must be followed up at the rheumatology or orthopedics clinic, for the early detection and treatment of any resulting complications. Those having cardiac issues such as ASD and MVP need to be evaluated by the cardiologist on a regular basis. Most importantly, the patient must be informed about the X-linked mode of inheritance.^{5,15}

Conclusion

LFS must be considered in the differential diagnoses of intellectual disability, marfanoid body habitus, facial dysmorphism, and/or hypernasal speech. Rarely, it can present as an acute-onset dysphagia and in the absence of any neuropsychiatric issues or positive family history. The associated dysphagia and hypernasality may improve with the speech and swallowing exercises.

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Ethics Approval and Consent to Participate

The study was approved by the ethics review committee of Khyber Teaching Hospital (KTH), Peshawar, Pakistan. An informed written consent was obtained from the patient for the publication of this case report.

Author Contributions

Made the diagnosis and drafted the manuscript: AK, MH, MA. All the authors read and approved the final manuscript. Helped in revising the manuscript: IH. All the authors read and approved the revised version before resubmission.

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