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CASE REPORT

Attention-Deficit/Hyperactivity Disorder in a Patient with Lujan-Fryns Syndrome: A Case Report

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ABSTRACT

Introduction: Lujan-Fryns syndrome (LFS), a rare genetic anomaly first described in 1984, is characterized by a unique constellation of clinical features primarily attributed to mutations in the MED12 gene. These features include intellectual disability, behavioral complexities, and distinct somatic attributes. Although formal psychiatric criteria are lacking, numerous case studies have revealed a co-occurrence of LFS with psychological manifestations, including attention-deficit/hyperactivity disorder (ADHD). This case report explores the intricate relationship between LFS and ADHD, shedding light on potential diagnostic and therapeutic strategies.

Case Presentation: We present the clinical profile of a 13-year-old male diagnosed with LFS, who exhibited hyperactivity and inattention symptoms, leading to a diagnosis of ADHD. The patient's history included full-term birth, developmental delays, and speech challenges, necessitating special education. Treatment for ADHD included methylphenidate extended-release, behavioral modification techniques, and clonidine, resulting in significant symptom improvement. Marfanoid features were present, and LFS was confirmed through genetic testing. Comprehensive care with a multi-disciplinary approach addressed the associated medical concerns.

Conclusion: Recognizing and addressing the co-occurrence of LFS and ADHD is crucial. This complex interplay presents diagnostic and therapeutic challenges requiring a multidisciplinary approach. The absence of specific medications for LFS-associated ADHD highlights the need for customized treatments. This case report enhances our understanding of their relationship, paving the way for further research to improve clinical care for individuals with both these conditions.

Keywords: Lujan-Fryns Syndrome, ADHD, case report.

Introduction

The year 1984 marked the discovery of Lujan-Fryns syndrome (LFS), a remarkably rare genetic anomaly[1]. This syndrome is defined by a unique combination of clinical features, including intellectual disability, intricate behavioral manifestations, and distinctive somatic traits. Furthermore, it is rooted in mutations within the *MED12* gene located on the X chromosome, denoting an X-linked dominant mode of inheritance, resulting in a higher prevalence among men than among women[2-3].

Diagnostic criteria for LFS encompass a diverse amalgamation of defining attributes, which can manifest along a spectrum from mild to moderate intellectual impairment, often accompanied by marfanoid traits characterized by elongated extremities and digits. Simultaneously, generalized hypotonia, leading to reduced muscle tone, and distinctive craniofacial features significantly contribute to the diagnostic framework. Notably, while the formal diagnostic criteria do not include psychiatric symptomatology, an extensive body of case studies has highlighted the co-occurrence of LFS and psychological manifestations. This intricate fabric includes a range of phenotypic presentations, such as cognitive deficits, tendencies toward both aggressive and timid behaviors, hyperactivity, autistic traits, instances of psychotic symptomatology, and even challenges with eating behaviors[3]. In 1987, Fryns and Buttiens further enhanced our understanding of this landscape by providing additional clinical insights through the detailed exposition of two additional cases[4].

In the context of LFS, attention is focused on attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental condition diagnosed according to the criteria outlined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Furthermore, ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity, which significantly disrupts an individual's functioning and development. For this diagnosis, individuals must exhibit a minimum of six symptoms related to either inattention or hyperactivity-impulsivity, with these symptoms persisting for at least 6 months and being inconsistent with their age or developmental stage. For adolescents and adults aged 17 years and above, at least five symptoms are required. Inattention symptoms include careless mistakes, difficulty maintaining focus, failure to listen when directly addressed, challenges in task completion, organizational difficulties, unwillingness to engage in mentally demanding activities, tendency to lose items, susceptibility to distractions, and forgetfulness in daily tasks. Hyperactivity-impulsivity symptoms include fidgeting, leaving seat when expected to remain seated, engaging in inappropriate running or climbing, inability to participate quietly in leisure activities, a persistent sense of restlessness, excessive talking, giving answers before questions are completed, impatience, and interrupting or intruding on others[5].

ADHD is characterized by its triad of distinctive features: inattention, hyperactivity, and impulsivity. This condition affects approximately 5% of the pediatric population. Its origins are etiologically complex, involving a multifaceted interplay between genetic predisposition and environmental determinants. While the exact etiopathogenic mechanisms

remain partially unclear, it is believed that a combination of genetic predisposition and external triggers contributes to its clinical manifestation[6]. Notably, the existing literature has documented some cases suggesting a link between LFS and ADHD, implying the possible existence of ADHD as a prevalent phenotypic trait within the realm of LFS[3].

Within the intricate medical narrative, the present case study assumes a central role, shining a spotlight on an individual grappling with the complexities of LFS alongside ADHD. This clinical presentation offers an opportunity to delve into the depths of the nuanced interplay between LFS and ADHD, potentially yielding fresh insights into the intricate mechanisms that underlie their intersection. Such insights could lead to the development of more precise diagnostic approaches and customized therapeutic interventions.

The absence of specific medications for managing ADHD symptoms in individuals with LFS is evident from our research findings. Nonetheless, medications can still play a role in addressing symptoms such as hyperactivity and impulsivity often associated with ADHD. It is crucial, however, to approach medication with utmost caution in this specific population due to the potential for adverse effects. Consequently, the prescription of medication should be exclusively within the purview of qualified healthcare professionals who possess a comprehensive understanding of the individual's medical history and current symptoms. Moreover, individuals with both LFS and ADHD require specialized follow-up care, which includes neuro-psychological assessments, therapeutic strategies, and customized education plans. All these elements are aimed at diagnosing and proactively preventing psychiatric disorders and correlated behavioral challenges such as psychosis and instances of aggression.

In summary, the pivotal year of 1984 marked the significant recognition of LFS—a rare genetic condition encompassing intellectual challenges, intricate behavioral subtleties, and distinctive physical attributes. Emerging from disruptions in the *MED12* gene, the clinical landscape of this syndrome has evolved to encompass a spectrum of psychological expressions. Within this complex clinical narrative, the convergence of LFS and ADHD becomes a notable crossroads, prompting us to delve into the dynamic interplay governing these two conditions. This case study represents a step forward in elucidating the complexities characterizing the link between LFS and ADHD. It serves as a guide for further research, fostering a more comprehensive understanding and encouraging innovative therapeutic approaches[2-3].

Case Presentation

The patient's maternal history was unremarkable, and the pregnancy proceeded without complications. Both parents had no history of alcohol use. The patient was delivered via cesarean section at Prince Sultan Military Medical City in Riyadh, Saudi Arabia, following a full-term pregnancy, and had a birth weight of 3500 g and a body length of 49 cm. While the prenatal phase was unremarkable, developmental milestones were delayed. Independent walking did not commence until the age of 2 years, and speech initiation occurred around the age of 8 years with the support of dedicated speech

therapy. Persistent challenges in grammar and pronunciation were observed.

At the age of 5 years, the patient was referred to the Child and Adolescent Psychiatry clinic due to the emergence of hyperactivity and inattention symptoms. A diagnosis of ADHD was made based on DSM-5 criteria, as symptoms had persisted for over a year and had a negative impact on academic performance. Inattention symptoms included poor listening skills, misplacement of items, distractibility, a reduced attention span, difficulty completing tasks, and avoidance of activities requiring sustained concentration. Hyperactivity and impulsivity symptoms manifested as restlessness, motor-driven behavior, inability to engage quietly in leisure activities, restlessness in classroom, excessive talking, impatience, and intrusive behavior in social interactions.

The treatment plan began with the initiation of risperidone at a daily dose of 0.5 mg, followed by the incorporation of methylphenidate extended-release (Concerta) at 18 mg once daily to manage ADHD symptoms. As a result of this treatment adjustment, risperidone was discontinued. Further fine-tuning of the methylphenidate extended-release dosage resulted in a stable regimen of 54 mg once daily in the morning, which led to significant improvements in both hyperactivity and attention-related symptoms. Over the course of the preceding year, episodes of aggression and impulsivity, including physical confrontations with family members, had been noted. The implementation of behavioral modification techniques, along with clonidine administered at a daily dose of 0.1 mg, effectively reduced episodes of aggression without any adverse side effects.

Cognitively, the patient displayed below-average intellectual abilities, with an IQ test score of 86 at the age of 10 years, necessitating enrollment in special needs schools due to challenges in mainstream academic settings.

During the most recent clinical examination in December 2022, notable physical attributes were observed, including a height of 167.6 cm (2.37 standard deviations above average), weight of 74.4 kg (2.44 standard deviations above average), and head circumference of 56.5 cm (97th percentile). Additionally, the patient exhibited marfanoid features, such as tall stature, macrocephaly, a long narrow face with downslanting palpebral fissures, atypically folded ear helices bilaterally, a prominent nasal bridge, and the absence of pectus or joint hyperlaxity.

A comprehensive evaluation encompassing historical, physical, psychological, and behavioral aspects, along with investigative procedures, culminated in genetic testing conducted 1.5 years ago. This testing revealed a positive diagnosis of LFS, with whole exome sequencing identifying a hemizygous variant in *MED12*, specifically c.691C>T p.(Arg231Trp) (de novo).

Currently, the patient receives comprehensive care from various medical specialties, addressing conditions such as horseshoe kidneys, closure of an atrial septal defect through catheterization during early childhood, myopia, asthma, tympanostomy tubes, and scoliosis. Regular follow-ups across these specialties indicate the patient's ongoing medical stability. Furthermore, laboratory tests, as outlined in (Table 1), and brain magnetic resonance imaging (Figure 1) produced unremarkable results.

Table 1. Laboratory Data

Laboratory test	Result	Normal range
WBC	7.7 × 10^9 cells/L	4–11
RBC	5.07 × 10^{12} cells/L	4.2–6.2
Hemoglobin	149 g/L	125–180
Platelets	334 × 10^9 cells/L	150–450
Creatinine	56 mcmol/L	39–60
Bilirubin total	6 mcmol/L	2–8
Alanine aminotransferase	19 U/L	0–41
Alkaline phosphatase	171 U/L	129–417
Albumin	45 g/L	38–54
Sodium	139 mmol/L	136–160
Potassium	4.6 mmol/L	3.5–5.1
Calcium	2.32 mmol/L	2.1–2.55
Urea	3.9 mmol/L	2.8–8.1
25 Hydroxyvitamin D total	67.7 nmol/L	50–250
TSH	4.54 mIU/m	0.27–4.2
T4	19 pmol/L	12–22
Echocardiogarphy	- Trivial aortic valve insufficiency - Asymmetric interventricular hypertrophy - Mild mitral regurgitation - Good left ventricle systolic function	
CT Thoracolumbar spine	Thoracolumbar scoliotic deformity and horseshoe kidney	
Brain MRI	Unremarkable	

Abbreviations: WBC: white blood cells, RBC: red blood cells, TSH: thyroid-stimulating hormone, T4: thyroxine, CT: computed tomography, MRI: magnetic resonance imaging

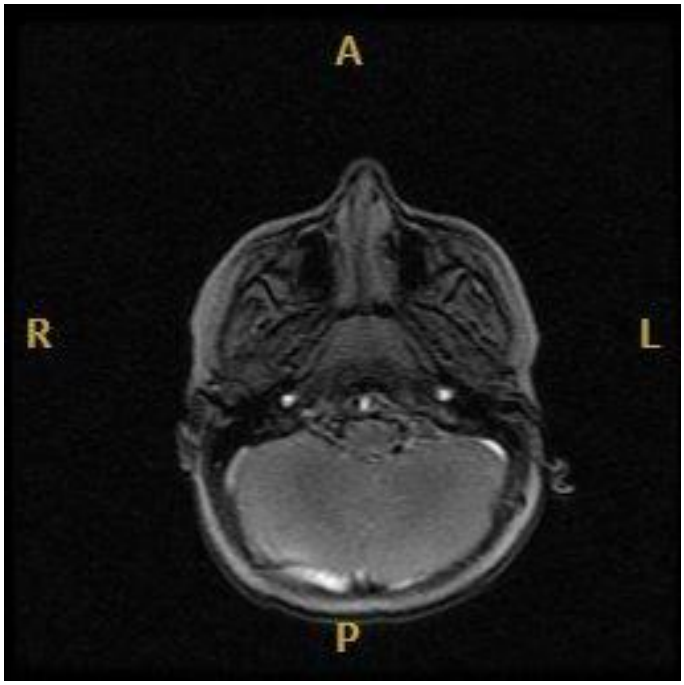

Figure 1. Horizontal plane of brain magnetic resonance imaging

Discussion

In 1984, LFS emerged as a rare genetic anomaly characterized by a unique constellation of clinical features. This syndrome, primarily associated with mutations in the *MED12* gene located on the X chromosome, encompasses intellectual disability, behavioral nuances, and distinctive somatic attributes[2-3]. The case study presented here highlights a 13-year-old male with LFS who concurrently presented with ADHD. The co-existence of these conditions warrants an investigation into the intricate interplay between LFS and ADHD, shedding light on potential diagnostic and therapeutic strategies.

In comparison, previous cases of LFS have demonstrated a wide spectrum of psychiatric manifestations, encompassing hyperactivity, autistic-like behavior, shyness, and, in some instances, symptoms reminiscent of schizophrenia. Common physical features associated with LFS include tall stature, maxillary hypoplasia, a high-arched palate, and craniofacial anomalies. Additionally, cardiac abnormalities, cortical malformations, and genetic variations have been observed in various cases[2]. Behavioral and psychiatric disorders are frequently linked with LFS, with some cases exhibiting milder forms of these symptoms. The genetic basis of LFS may involve mutations in the *MED12* gene, which is believed to contribute to the observed clinical spectrum. Furthermore, ongoing research explores the relationship between LFS and other X-linked mental retardation syndromes, as well as the potential genetic mechanisms of behavioral manifestations[3]. This case underscores the clinical heterogeneity of LFS and emphasizes the importance of thorough evaluation and multidisciplinary care for individuals affected by this syndrome.

Prior case reports have demonstrated the co-occurrence of ADHD and LFS, akin to our present case. In the majority of these previous reports, patients consistently exhibited IQ

scores below the average range[1,2,7,8,9,10,11], a finding consistent with our own observations, where the recorded IQ score stood at 86. It is noteworthy that an exception to this trend emerged in one report, wherein a patient exhibited an IQ level of 99, situating them within the average range[12]. Regarding treatment options, existing literature offers limited direction on how to manage ADHD symptoms in individuals with LFS. Only two articles have detailed pharmacological interventions. According to study by (Stathopulu et al., 2003) demonstrated using Methylphenidate in such case showed good response. According to another case report by (Elyasi et al., 2019) detailed trial of Ritalin for aggression and learning difficulties. As far as we are aware, there are limited pharmacological interventions demonstrated in the literature. However, we are reporting Clonidine as a potential management approach to address aggression in cases similar to ours.

This case report provides unique insights into the co-occurrence of LFS and ADHD, highlighting the rarity of this combination and the immediate need for comprehensive understanding. Its strengths lie in presenting a distinctive clinical scenario, employing a multidisciplinary approach that covers historical, physical, psychological, and genetic aspects, and offering valuable treatment insights for managing ADHD symptoms in individuals with LFS. However, it is important to acknowledge the limitations, primarily its focus on a single patient, which may restrict its ability to capture the full spectrum of LFS and its intersections with ADHD. Additionally, the absence of long-term data and consideration of genetic heterogeneity underscores the necessity for future research to enhance our understanding and broaden therapeutic approaches for this complex co-occurrence.

Conclusion

Our case study highlights the significance of recognizing and addressing the co-occurrence of LFS and ADHD. This intricate intersection poses diagnostic and therapeutic challenges that necessitate a multidisciplinary approach. The lack of specific medications for managing ADHD symptoms in individuals with LFS underscores the importance of developing personalized treatment strategies.

Future research should focus on expanding the case pool to accumulate data from multiple cases with LFS and concurrent ADHD, conducting long-term follow-up studies to monitor developmental trajectories, investigating the genetic heterogeneity of LFS, and exploring alternative therapeutic interventions. This case report represents a step forward in understanding the complexities of the relationship between LFS and ADHD and encourages further research to advance clinical care for individuals facing these dual challenges.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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