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Case Report

Borjeson-Forssman-Lehmann Syndrome: Clinical Features and Diagnostic Challenges

Marya Hameed, Fatima Siddiqui, Fahad Hassan Sheikh, Muhammad Khuzzaim Khan, Bushra Admani, Prasanna Kumar Gangishetti

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Correspondence to
Muhammad Khuzzaim Khan
Dow University of Health Sciences, Mission Rd, New Labour Colony Nanakwara, Karachi, Sindh 74200, Pakistan.
Email: khuzzaimkhan@yahoo.com

HIGHLIGHTS

- Borjeson-Forssman-Lehmann syndrome (BFLS): rare X-linked disorder from PHF6 mutations causing brain and mental issues.
- BFLS: facial, gonadal, brain, spine, ear issues. X-linked, PHF6 mutations.
- BFLS: supportive management, education, symptom treatment, surgery/hormones, genetic advice.

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Borjeson-Forssman-Lehmann Syndrome: Clinical Features and Diagnostic Challenges

Marya Hameed [1], **Fatima Siddiqui** [1], **Fahad Hassan Sheikh** [1], **Muhammad Khuzzaim Khan** [2], **Bushra Admani** [2], **Prasanna Kumar Gangishetti** [3]

[1]National Institute of Child health, Karachi, Pakistan
[2]Dow University of Health Sciences, Karachi, Pakistan
[3]University of Kentucky, Lexington KY, USA

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Muhammad Khuzzaim Khan
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Email: khuzzaimkhan@yahoo.com

ORCID iDs
Marya Hameed
https://orcid.org/0000-0002-1867-8755
Fatima Siddiqui
https://orcid.org/0000-0002-6203-6856
Fahad Hassan Sheikh
https://orcid.org/0000-0001-9380-0661
Muhammad Khuzzaim Khan
https://orcid.org/0000-0003-4586-8607
Bushra Admani
https://orcid.org/0000-0003-0859-7510
Prasanna Kumar Gangishetti
https://orcid.org/0000-0002-0204-6323

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ABSTRACT

Borjeson-Forssman-Lehmann syndrome (BFLS) is an X-linked recessive disorder resulting from mutations in the PHF6 gene. The syndrome is characterized by short stature, obesity, hypogonadism, hypotonia, intellectual disability, distinctive facial features, fleshy ears, and finger and toe abnormalities. However, the diagnostic challenge in identifying BFLS remains a topic of interest. In this case report, we present the clinical characteristics of a proband with BFLS, highlighting the additional features of hypotonia, intellectual disability, and distinctive facial features. While no definitive treatment exists for BFLS, patients benefit from specialized education and ongoing supervision from early childhood through adulthood. Symptomatic treatment, including close follow-up, may be necessary for complications such as seizures and hearing problems. Mastectomy or testosterone replacement therapy may be considered on a case-by-case basis. Genetic counseling for X-linkage should be offered to affected families.

Keywords: Genetic Counseling; Genetic Predisposition to Disease; Genetic Diseases, Inborn

INTRODUCTION

Borjeson-Forssman-Lehmann syndrome (BFLS) is a rare genetic disorder caused by pathogenic variants in the *PHF6* gene, which follows an X-linked recessive inheritance pattern [1]. Despite its rarity, BFLS poses significant challenges due to its diverse and complex clinical manifestations. Characteristic features of BFLS include short stature, obesity, hypogonadism, hypotonia, intellectual disability, learning disabilities, distinctive facial features, and abnormalities of the fingers and toes [2].

With fewer than 100 reported cases in the medical literature, BFLS remains a poorly understood syndrome [3]. The exact mechanisms by which pathogenic variants in the *PHF6* gene lead to the observed clinical phenotype are still under investigation. The *PHF6* gene plays a crucial role in various developmental processes, particularly in brain development and neuronal migration. Disruption of its function may contribute to the wide spectrum of symptoms observed in BFLS [4].

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Hameed M, Siddiqui F, Sheikh FH, Gangishetti PK; Data curation: Hameed M; Formal analysis: Siddiqui F, Sheikh FH, Khan MK, Admani B; Investigation: Siddiqui F, Sheikh FH, Khan MK, Admani B; Methodology: Hameed M, Khan MK, Gangishetti PK; Resources: Hameed M, Khan MK, Gangishetti PK; Supervision: Hameed M, Sheikh FH, Gangishetti PK; Writing - original draft: Siddiqui F, Sheikh FH, Khan MK, Admani B; Writing - review & editing: Hameed M, Siddiqui F, Khan MK, Admani B, Gangishetti PK.

Despite the absence of a definitive cure for BFLS, early recognition and symptomatic management are crucial for optimizing the quality of life for affected individuals. Prompt diagnosis allows for appropriate interventions and support tailored to the specific needs of individuals with BFLS. Special education programs, therapeutic interventions, and psychosocial rehabilitation can help address the learning disabilities, intellectual challenges, and social difficulties often experienced by affected individuals [5].

In this report, we present the case of a 12-year-old male who presented with gynecomastia, adding to the growing body of knowledge on BFLS. Through sharing this case, our aim is to raise awareness among healthcare professionals about the diverse clinical features associated with BFLS and emphasize the importance of early diagnosis and management. By understanding the underlying genetic basis and the spectrum of clinical manifestations, healthcare providers can contribute to improving the lives of individuals with BFLS and their families.

CASE DESCRIPTION

A 12-year-old male presented to the outpatient department of a large tertiary care hospital in Karachi with a complaint of gynecomastia. The parents reported that their son had limited sociability and found it challenging to interact with others. The parent also reported that he had language delay and learning disabilities. He was born at 38^{+7} weeks gestation with a birth weight of 3,140 g, which falls within the normal range. On further questioning, it was revealed that the patient's parent had a history of minor learning disabilities. There was no known consanguinity in the parents' relationship, and no other family members had a history of genetic diseases.

On physical examination, the patient exhibited truncal obesity, dysmorphic face, including large ears and fleshy earlobes, and shortened toes (**Fig. 1**). Notably, gynecomastia and small testes were observed (**Fig. 2**). Ocular examination findings were positive for nystagmus. Subsequent cognitive assessment, based on standardized tests such as the Wechsler Intelligence Scale for Children, confirmed the presence of intellectual disability. The results indicated that he has an intellectual disability, as his Full-Scale IQ score was 55, which falls in

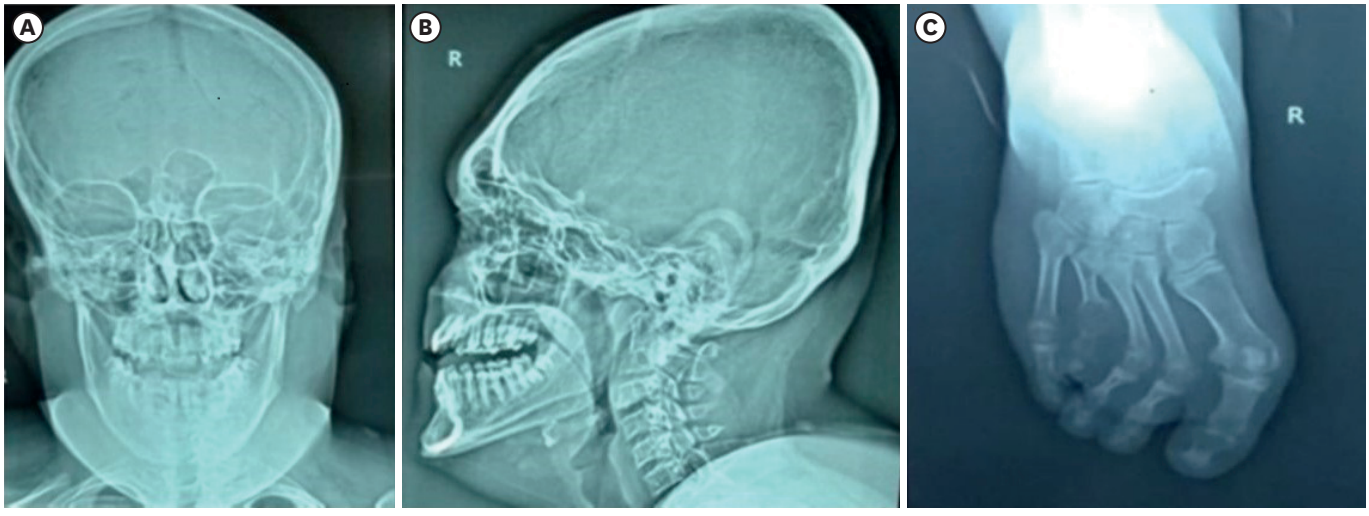

Fig. 1. X-ray views of prominent dysmorphic facies (A and B), and shortened toes (C), commonly seen in Borjeson-Forssman-Lehmann syndrome.

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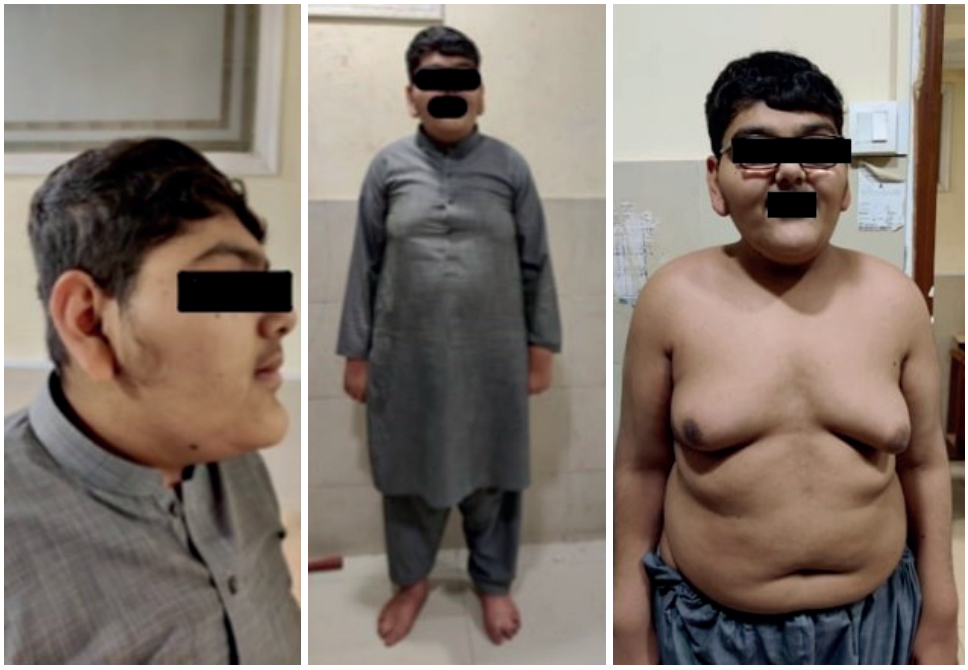

Fig. 2. Illustration of the characteristic obese body habitus and gynecomastia seen in Borjeson-Forssman-Lehmann syndrome.

the extremely low range of intellectual functioning. His Verbal Comprehension Index score was 58, his Perceptual Reasoning Index score was 54, his Working Memory Index score was 56, and his Processing Speed Index score was 53. All of these scores are also in the extremely low range, suggesting that he has significant difficulties in verbal and nonverbal reasoning, memory, and speed of information processing.

Further diagnostic workup was conducted on an outpatient basis. Laboratory findings revealed low levels of testosterone (0.5 nmol/L; normal range: 9.2–31.8 nmol/L). Brain magnetic resonance imaging (MRI) showed no structural abnormalities or signs of neuronal migration defects. The patient's karyotype analysis confirmed a gender-appropriate 46, XY result.

Genetic testing using next-generation sequencing (NGS) identified a pathogenic variant in the *PHF6* gene, which is associated with BFLS. The specific variant identified in our patient was a frameshift mutation (c.569_570del), resulting in a premature termination codon (p.Glu190Aspfs*9). This variant was confirmed to be de novo, as parental genetic testing revealed no evidence of the mutation. Multiple lines of evidence support the pathogenicity of this variant, including its absence in large-scale population databases, its location in a functionally important region of the gene, and the presence of other pathogenic *PHF6* variants in individuals with BFLS. Based on the ACMG guidelines, the variant can be assigned a pathogenic classification with strong (PVS1) and moderate (PM2) evidence for pathogenicity and supporting (PP3) evidence for pathogenicity.

Based on the characteristic physical appearance, clinical features, laboratory findings, brain MRI results, and genetic testing results, the patient was diagnosed with BFLS.

As there are currently no curative treatments available for BFLS, the parents were advised to enroll their son in a special education program tailored to his learning disabilities.

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Symptomatic treatment, including counseling for psychosocial rehabilitation, was initiated to address the specific needs of the patient. Regular follow-up visits were recommended to monitor his development and manage any emerging symptoms. Written and signed consent from the patient's guardian was obtained for publication purposes. Informed and written consent for the publication of this case report and accompanying data has been obtained from the guardian of the patient. The case report was approved by the National Institute of Child Health's Institutional Review Board (NICH/2023/042).

DISCUSSION

The presented case of BFLS is a rare X-linked disorder with incomplete recessive inheritance [6,7]. BFLS was initially described by Borjeson et al. [8] in 1962 as an X-linked intellectual disability syndrome primarily affecting males. While BFLS cases in males typically manifest with dysmorphic physical features, hypogonadism, intellectual disability, and epilepsy, the clinical presentation in females is rare and was initially reported without genetic confirmation. It is important to note that in this discussion, the focus will primarily be on the case of the male patient. In this case, the significance lies in the unique clinical features observed, which provide valuable insights into the phenotypic variability of BFLS. Furthermore, the identification of additional critical features not previously reported adds to the understanding of the disease progression.

Clinical phenotypes associated with BFLS have been reported in previous case studies (**Table 1**) [9-11]. In comparison to these reports, the present case exhibited distinct characteristics. The patient demonstrated fleshy ear lobes, deep-set eyes, prominent supra-orbital ridges, and thick facial connective tissues, which are consistent with the classic facial features observed in BFLS patients. Additionally, ocular abnormalities such as nystagmus, retinal, and optic nerve abnormalities were noted, along with the development of hyperopia and cataracts at an early age. Skeletal abnormalities, including scoliosis, kyphosis, and tapered and malleable fingers, were also observed. Furthermore, less commonly reported findings such as generalized polyneuropathy, epilepsy, and Perthes disease were present in the patient.

Table 1. Clinical features of BFLS reported in previous cases.

Clinical features	Case 1 [9]	Case 2 [10]	Case 3 [11]	Present case
CNS	Intellectual disability, seizures, hypotonia, ataxia, behavioral problems	Intellectual disability, seizures	Intellectual disability, seizures	Language delay, learning disabilities, limited sociability, initial resistance to consent, intellectual disability
Skeletal	Short stature, tapered fingers, short toes, broad feet, scoliosis, kyphosis	Short stature, tapered fingers, short toes, broad feet	Short stature, tapered fingers, short toes, broad feet	Truncal obesity, shortened toes
Endocrine	Obesity, hypogonadism, underdeveloped genitalia, gynecomastia	Obesity, hypogonadism, underdeveloped genitalia, gynecomastia	Obesity, hypogonadism, underdeveloped genitalia, gynecomastia	Gynecomastia, small testes, low levels of testosterone
Facial phenotypes	Coarse facial features, large ears, deep-set eyes, prominent supraorbital ridges, broad nasal bridge, thick lips	Coarse facial features, large ears, deep-set eyes, prominent supraorbital ridges, broad nasal bridge, thick lips	Coarse facial features, large ears, deep-set eyes, prominent supraorbital ridges, broad nasal bridge, thick lips	Dysmorphic facies, large ears, fleshy earlobes
Eye	-	Strabismus, nystagmus, myopia, astigmatism	Strabismus, nystagmus	Nystagmus
Dental	-	Malocclusion, crowded teeth	-	-
PHF6 variant	c.1000C>T (p.Arg334*)	c.1024G>A (p.Gly342Arg)	c.1024G>A (p.Gly342Arg)	c.569_570delGA (p.Glu190Aspfs*9)

CNS, central nervous system.

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The pathogenesis of BFLS results from dysregulated neuronal positioning due to defective *PHF6* gene signaling during proper neuronal migration [12]. Pathogenic variants of *PHF6* that cause BFLS include nonsense, frameshift, splice site and missense mutations, as well as deletions of one or more exons [13]. These variants result in loss or reduction of *PHF6* expression or protein stability, leading to impaired transcriptional regulation of genes involved in neurodevelopment and hematopoiesis [14]. BFLS mainly affects males, who present with intellectual disability, obesity, hypogonadism, developmental delay, and distinctive facial features. Females can also be affected by de novo heterozygous variants in *PHF6*, but they show a different phenotype with moderate to severe intellectual disability, characteristic facial dysmorphism, dental, finger and toe anomalies and linear skin pigmentation [15]. The phenotypic variability in females may be influenced by the severity of the variant, the pattern of X-inactivation and the presence of functional mosaicism [16,17]. The *PHF6* gene mutations have been associated with BFLS, as well as their involvement in certain cancers, such as T-cell acute lymphoblastic leukemia and acute myelogenous leukemia [18]. Further exploration of the *PHF6* gene mutations, including variant hot spots and protein-related contents, contributes to the understanding of the biomolecular perspective of BFLS.

As of now, there is no definitive treatment for BFLS. However, symptomatic management is essential for addressing specific symptoms such as seizures, Perthes disease, and hearing problems, with close monitoring for timely intervention [19]. In some cases, mastectomy or testosterone replacement therapy may be considered as supportive adjuncts. Genetic counseling for X-linkage is highly recommended for affected families [20].

This case report enhances our understanding of the variable manifestations observed in BFLS and emphasizes the significance of elucidating the underlying molecular mechanisms associated with *PHF6* gene mutations. The presence of gynecomastia, language delay, learning disabilities, truncal obesity, dysmorphic facies, shortened toes, and low testosterone levels in this patient expands the clinical spectrum of BFLS. These findings underscore the need for further research aimed at identifying targeted treatments for this rare disorder. Additionally, investigating the functional consequences of the specific *PHF6* variant identified (p.Glu190Aspfs*9) may provide valuable insights for the development of novel therapeutic strategies.

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