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Jervell and Lange-Nielsen Syndrome (JLNS) in a 13-Year-Old Girl: A Rare Case Report

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ABSTRACT

JLNS is a rare genetic disorder characterized by congenital sensorineural hearing loss and a prolonged QTc interval, leading to life-threatening arrhythmias. Early diagnosis, beta-blocker therapy, lifestyle modifications, and consideration of ICD surgery are critical in managing sudden cardiac death risk.

1 | Introduction

Jervell and Lange-Nielsen syndrome (JLNS) was first identified in 1957 by Anton Jervell and Fred Lange-Nielsen, who described it in four children with both congenital deafness and recurrent episodes of syncope [1]. JLNS is a rare genetic disorder inherited in an autosomal recessive pattern. It is characterized by two primary features: congenital bilateral sensorineural hearing loss and a significantly prolonged QTc interval, typically over 500 milliseconds. This prolonged QTc interval predisposes individuals to dangerous arrhythmias, such as torsades de pointes (TdPs), and greatly increases the risk of sudden cardiac death. As a subtype of inherited long QT syndrome (LQTS), JLNS is particularly concerning due to its severe cardiac implications. Homozygous or compound heterozygous mutations in the KCNQ1 or KCNE1 genes most commonly cause the condition. However, other genetic loci may be involved, particularly in patients with a more severe course of the disease [2].

LQTS presents in two primary clinical forms. The more common autosomal dominant Romano-Ward syndrome affects about 1 in 2000 to 1 in 5000 individuals, manifesting primarily with cardiac symptoms [2]. In contrast, the autosomal recessive JLNS is exceptionally rare, affecting fewer than 1 in 4 million people. This extreme rarity underscores the unique challenges it presents, particularly with its combination of a severe cardiac phenotype and congenital bilateral sensorineural hearing loss, making it a particularly dangerous variant of LQTS [2, 3].

2 | Case History

A 13-year-old girl presented to the cardiology clinic with recurrent episodes of syncope and seizures. The episodes began when she was four and were often triggered by emotional stress, physical exertion, or sudden stimuli like loud noises or alarms. The syncopal episodes were occasionally accompanied by cyanosis

Abbreviations: ICD, Implantable Cardioverter–Defibrillator; JLNS, Jervell and Lange-Nielsen syndrome; LQTS, Long QT syndromesyndrome; QTc, Corrected QT interval; RWS, Romano-ward syndrome; TdPs, Torsades de Pointes.

and tonic-clonic fits, leading to earlier misdiagnoses of epilepsy and psychological disorders. Her parents reported that the episodes occurred unpredictably, sometimes during rest, causing significant anxiety for the family. The patient was diagnosed with profound bilateral sensorineural hearing loss shortly after birth and received a cochlear implant at the age of seven. She was attending school regularly, and neither she nor her parents reported any specific school-related triggers for her symptoms.

3 | Differential Diagnosis, Investigation, and Treatment

Neurological investigations, including electroencephalogram (EEG) and cranial imaging, had been performed earlier in her clinical course to rule out primary neurological causes, but the results were unremarkable. She had been treated with antiepileptic drugs for her seizure-like episodes, but without improvement. Over time, she exhibited behavioral changes, including irritability, aggression, and anxiety, which were attributed to the chronicity of her condition and the unpredictability of the syncopal episodes.

In addition to her cardiac symptoms, the patient had a history of idiopathic scoliosis and other connective tissue abnormalities. Her growth was also significantly delayed, with her height measured at 130 cm, placing her well below the average for her age. Her intellectual development was also affected, with an IQ of 75, indicating mild intellectual disability. These findings raised concerns about potential systemic involvement beyond her cardiac symptoms.

Upon referral to the cardiology service, an electrocardiogram (ECG) revealed a markedly prolonged corrected QT interval (QTc) of 610 ms. Given the combination of congenital sensorineural hearing loss and recurrent syncope, JLNS was considered a likely diagnosis. Genetic testing identified a pathogenic mutation in the KCNQ1 gene. It confirmed the diagnosis of JLNS, a rare autosomal recessive disorder that predisposes patients to life-threatening arrhythmias such as TdPs and ventricular fibrillation.

Following the diagnosis, the patient was initiated on high-dose beta-blocker therapy with propranolol at a dose of 2–3 mg/kg/day to reduce her risk of arrhythmias by limiting sympathetic stimulation of the heart. Her parents were counseled to minimize her exposure to potential triggers, such as emotional stress, physical exertion, and startling stimuli, which could precipitate further arrhythmic events. Lifestyle modifications, including stress management techniques and avoiding strenuous activities, are important in JLNS cases to reduce the risk of arrhythmic events. Additionally, given her history of scoliosis and connective tissue issues, she was referred to an orthopedic specialist for further evaluation and management.

4 | Outcome and Follow-Up

Despite optimal medical therapy, the patient continued to experience occasional episodes of near syncope, underscoring the importance of ongoing care and monitoring. Her parents were advised to monitor her symptoms closely and to return for regular follow-up appointments to assess the need for additional interventions. The option of an ICD was discussed, but no immediate decision was made. The family received counseling to attend a follow-up appointment, where further discussion would take place regarding the potential benefits and risks of ICD surgery.

The family was also referred for genetic counseling to discuss the implications of JLNS for other relatives. The need for psychological support was stressed to help them manage the emotional stress of living with a chronic condition. Additionally, the parents were reminded of the importance of regular cardiac checkups to monitor disease progression and reconsider the timing for potential ICD implantation.

5 | Discussion

JLNS is a rare autosomal recessive disorder that affects 1/200,000–1/1,000,000 children, characterized by a high incidence of potentially fatal cardiac events in children and congenital bilateral hearing loss [4]. Reports have recently demonstrated that secondary hypochromic anemia and gastrointestinal symptoms and indications are also present in this disease [5]. Although in our case the patient was anemic, with hemoglobin 9.8 g%, there weren't any symptoms of gastrointestinal disturbance.

Failure of KCNQ1-encoded voltage-gated potassium ion channels, which support the maintenance of salt and water balance in various epithelial tissues, including the heart, inner ear, and gastrointestinal tract, accounts for these disparate symptoms [6].

The KCNQ1 and KCNE1 genes have homozygous or compound heterozygous loss-of-function mutations that lead to JLNS [4]. The same mechanisms that generate the previously identified congenital hearing loss—disruption of inner ear endolymph homeostasis based on loss of KCNQ1/KCNE1 function—also contribute to the vestibular dysfunction that is a core component of JLNS [4].

Both males and females are equally likely to develop JLNS [7]. Most patients with JLNS experience symptoms by age three, when their QT interval is markedly prolonged to more than 550 ms. A low-risk form of JLNS occurs in children who do not have syncope [4]. Children with syncope, sudden cardiac death, and interrupted cardiac arrest fall into the high-risk category for JLNS and require ICD implantation between 8 and 10 years of age [7].

The most severe type of long QT syndromes, known as JLNS, was described by Schwartz et al. as follows: 15% of children have a heart attack before one year, 50% develop symptoms before the age of three, and the median heart attack–free survival time is 33 months [8].

The most common triggers of a cardiac event in JLNS include physical activity, swimming, emotion in adults, and prolonged sobbing in children [7]. Besides diarrhea, sepsis, and hypokalemia, fever is the most common cause of cardiac events in

children [7]. JLNS protects the female gender from serious cardiac events [7].

A study conducted by Faridi, R. et al., in Pakistan describes a detailed analysis of three families in which JLNS was found, highlighting the importance of cardiac evaluation in deaf individuals without a molecular genetic diagnosis. Initially, families PKDF461, 4410, and 4502 were presumed to have nonsyndromic deafness due to the absence of symptoms such as vertigo, dizziness, syncope, or sudden deaths. However, detailed genetic analysis revealed a variant of the KCNE1 gene in family PKDF461, prompting further cardiology consultations and ECG evaluations. These investigations confirmed prolonged QT intervals in affected individuals, uncovering a syndromic association that was previously overlooked. Additionally, the study reported that among 104 Pakistani children with moderate to severe sensorineural hearing loss, four were diagnosed with long QT syndrome after detailed family histories and screening ECGs. Importantly, the evaluation extended to family members of these children, revealing that one hearing individual also exhibited LQTS. This finding underscores the silent nature of arrhythmias and the genetic risk carried by relatives, even those without hearing loss [8]. This study by Faridi, R., specifically highlights the need for comprehensive screening of such rare diseases.

As mutation screening finds only 70%–80% of cases, diagnosis is still made using clinical criteria [9]. Genetic screening has two primary functions in JLNS. The first step is to identify the gene that causes each case of JLNS. Because KCNQ1 mutation confers a sixfold higher risk of arrhythmias than KCNQ2 mutation, this could directly influence clinical decision-making. Finding family members who carry the mutation and may still be at risk of unexpected death is a second purpose of genetic testing [9].

According to Crotti et al., beta-blockers are the first-line treatment for JLNS and other types of long QT syndromes because they reduce the likelihood of arrhythmias during sympathetic stimulation events. At a dose of 2–3 mg/kg per day, propranolol is the most commonly used and well-tolerated drug [10]. Beta-blockers are significantly less protective in JLNS compared to other types of long QT syndrome; 51% of patients still experience symptoms after treatment, and the risk of cardiac arrhythmias and sudden death is tenfold higher overall [9]. Unfortunately, other therapies, such as left-sided sympathetic denervation (LCSD) and pacemakers that prevent bradycardia, are less successful in preventing cardiac arrest.

As a result, ICDs for treating JLNS are growing in popularity. They have gained popularity since the late 1990s and are considered safe for children [10–12]. When extremely young children have an activated ICD, it can cause them great discomfort and fear, which can trigger further activation of the ICD and a "storm" of shocks. They are, therefore, reserved for situations involving cardiac arrest or situations refractory to beta-blockade [10].

6 | Conclusion

This case emphasizes the importance of early recognition of JLNS in patients with congenital hearing loss and recurrent syncope. Misdiagnoses can delay lifesaving treatments. The diagnosis of JLNS confirmed through ECG and genetic testing led to beta-blocker therapy and lifestyle modifications to reduce arrhythmia risk. However, persistent symptoms highlight the potential need for an ICD to prevent sudden cardiac death. Early diagnosis, genetic counseling, and regular follow-up are essential for managing this rare but serious condition.

Author Contributions

Masab Ali: conceptualization, formal analysis, project administration, supervision, validation, visualization, writing – original draft, writing – review and editing. **Sana Javeriya:** conceptualization, data curation, resources, writing – original draft, writing – review and editing. **Muhammad Husnain Ahmad:** validation, visualization, writing – original draft. **Ilsa Babar:** methodology, methodology, validation, validation, visualization, visualization, writing – original draft, writing – original draft. **Muhammad Maaz Bin Rehan:** validation, visualization. **Hafiza Iman:** validation, visualization. **Humza Saeed:** validation, visualization, writing – original draft.

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Consent

Written informed consent was obtained from the patient to publish this report per the journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data and materials are available upon request from the corresponding author.

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