Case Report

Morbidity and mortality in a family with Jervell and Lange-Nielsen Syndrome

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Introduction

Jervell and Lange-Nielsen syndrome (JLNS), originally described in 1957,[1] is a rare autosomal recessive channelopathy caused by pathogenic variants in genes encoding cardiac potassium channels, primarily *KCNQ1* and *KCNE1*. The syndrome is characterized by the association of congenital sensorineural deafness and marked QT interval prolongation and is frequently associated with high morbidity and mortality due to malignant ventricular arrhythmias and sudden cardiac death.[2]

Clinical diagnosis, together with genetic confirmation, is essential not only for individualized therapeutic management but also for family screening, genetic counseling, and prevention of fatal events. The original description of JLNS represented a milestone in the understanding of long QT syndrome, establishing the relationship between autonomic nervous system dysfunction and ventricular arrhythmogenesis.[1,3]

The present report describes a consanguineous family comprising five clinically evaluated individuals, four of whom underwent genetic testing and were found to carry the same pathogenic *KCNQ1* variant. The variant was identified in homozygosity in the proband and in heterozygosity in both parents and one sister. A second sister, who had previously died, presented a clinical phenotype highly suggestive of the homozygous form of the syndrome.

This report highlights the high morbidity and mortality associated with the homozygous form of JLNS, the marked phenotypic variability observed among heterozygous carriers, and the importance of genetic counseling. In addition to beta-blocker therapy, adjunctive therapeutic strategies, including left cardiac sympathetic denervation and implantation of cardiac electronic device, particularly implantable cardioverter-defibrillator (ICD), are discussed.

Keywords

Jervell-Lange Nielsen Syndrome; Long QT Syndrome; Mortality

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Case series description

The family underwent comprehensive clinical and genetic evaluation, including pedigree construction (Figure 1), allowing assessment of disease severity and progression across generations.

The index case (Case 1) was an 11-year-old boy with congenital deafness who was referred for cardiological evaluation after episodes of seizures during the first month of life and a positive family history of cardiac arrhythmia. Electrocardiography revealed a corrected QT interval (QTc) of 623 ms associated with macroscopic T-wave alternans (Figure 2A), resulting in a Schwartz score of 5.5 points.[4] The score was calculated based on the following findings: QTc >480 ms (3 points), T-wave alternans (1 point), congenital deafness (0.5 point), and one first-degree relative with a definite diagnosis of long QT syndrome (1 point).

Genetic analysis identified the *KCNQ1* variant c.778C>T (p.Gln260*) in homozygosity. This variant has previously been classified as pathogenic according to ACMG/AMP criteria[5] and is listed in the ClinVar database (ClinVar ID: 842276).[6] Treatment was initiated with propranolol, titrated to the full recommended dose (4 mg/kg/day divided into three daily doses), resulting in partial QTc reduction to 580 ms. Despite continuous therapy, the patient remained at high arrhythmic risk.

At eight years of age, he underwent left cardiac sympathetic denervation through video-assisted thoracoscopic surgery. Since then, he has remained asymptomatic, although QTc values have persistently exceeded 500 ms. Owing to the high risk of potentially lethal arrhythmic events, a dual-chamber transvenous implantable cardioverter-defibrillator (ICD) was implanted in December 2025 (Figure 3).

Both parents of the proband (Case 1), who were first cousins, were identified as heterozygous carriers of the same pathogenic variant. One sister died at 17 years of age after presenting with congenital deafness, exertional syncope, and a markedly prolonged QTc interval (Figure 2B), a phenotype highly suggestive of the homozygous form of the syndrome. At that time, diagnosis was based exclusively on clinical findings and phenotype, and propranolol therapy was initiated.

Another sister, who is heterozygous for the variant, remains asymptomatic and has a normal electrocardiogram. The father also has a normal ECG, whereas the mother presents with mild QTc prolongation (470 ms). All family members are currently receiving propranolol therapy. Exercise stress testing was not available. The demographic, clinical, genetic, and follow-up characteristics of all family members are summarized in Table 1.

This study was approved by the Research Ethics Committee of the Professor Edgard Santos University Hospital, Federal

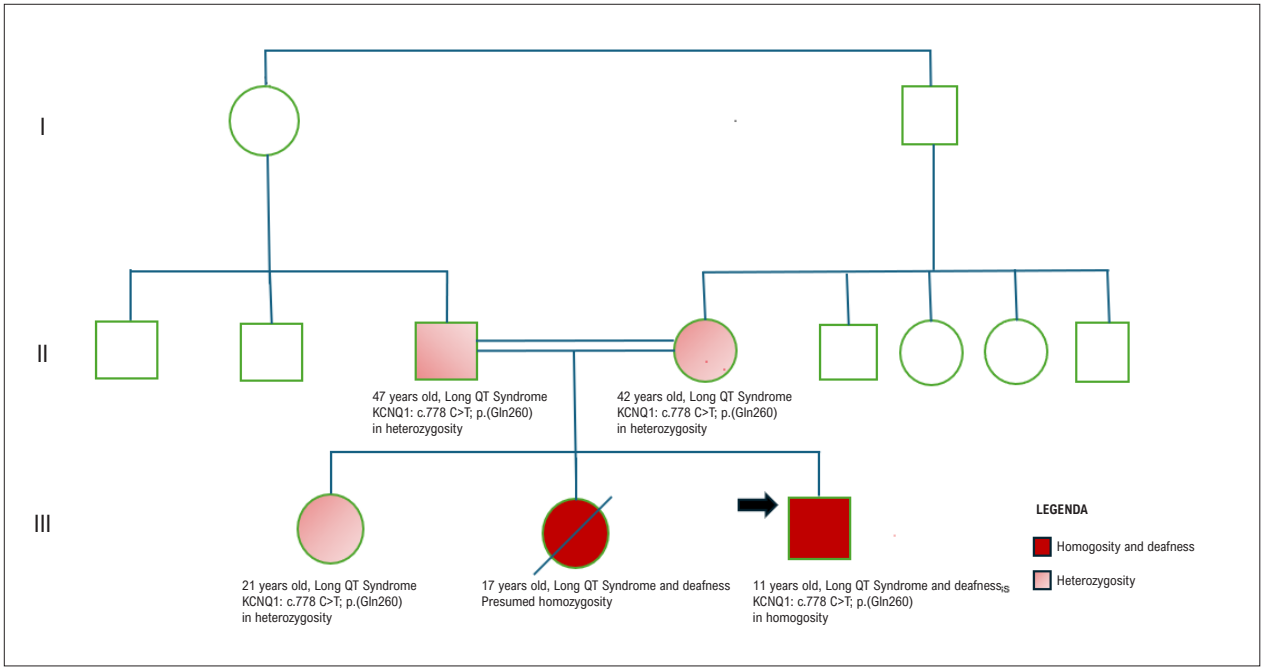

Figure 1 – *Pedigree of the family with Jervell and Lange-Nielsen syndrome. The proband carries the KCNQ1 c.778C>T (p.Gln260*) variant in homozygosity. Both parents and one sister were identified as heterozygous carriers. Another sister, who died at 17 years of age, presented a phenotype highly suggestive of the homozygous form of the syndrome.*

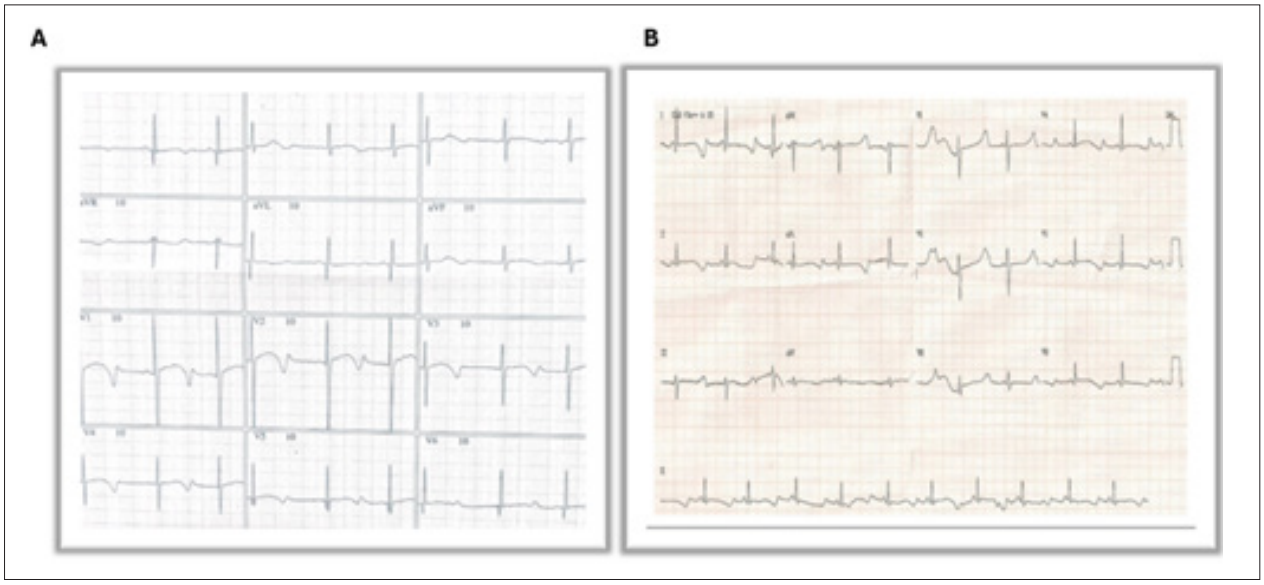

Figure 2 – *Electrocardiograms of the proband (A) and deceased sister (B). (A) Electrocardiogram of the proband showing visible macroscopic T-wave alternans in leads V3–V4 and a QTc interval of 623 ms. (B) Electrocardiogram of the deceased sister demonstrating marked QT prolongation and T-wave alternans in multiple leads, with a QTc interval of 618 ms.*

University of Bahia, Brazil, under approval number 6.304.113, dated September 15, 2023. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from the legal guardians for participation and publication of the clinical data.

Discussion

JLNS was first described by Anton Jervell and Fred Lange-Nielsen in 1957 in a Norwegian family in which four of six children presented congenital deafness and recurrent syncopal episodes, with three sudden deaths occurring during childhood. At that

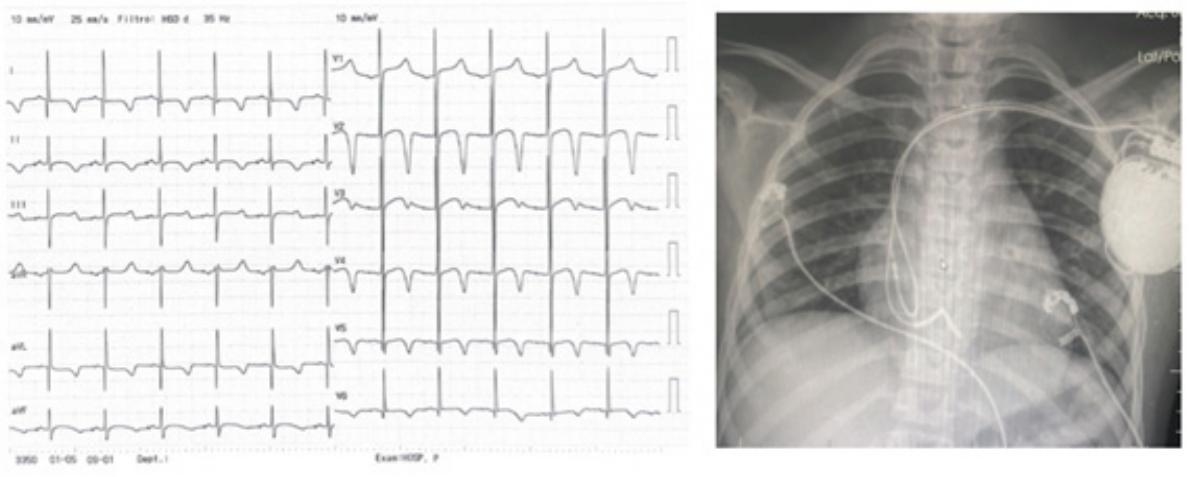

Figure 3 – *Electrocardiogram and chest radiograph of the proband following implantation of a dual-chamber transvenous implantable cardioverter-defibrillator (ICD).*

Table 1 – Demographic, genetic, and clinical characteristics of the five patients

Patient	Age	Genotype	Symptoms	Phenotype	Treatment	Outcome
Case 1 (Proband)	11 years	Homozygous KCNQ1 c.778C>T (p.Gln260*)	Seizures in the first year of life	Congenital deafness, QTc 623 ms	Propranolol + left cardiac sympathetic denervation + ICD	Asymptomatic, QTc > 500 ms
Case 2 (Sister 1)	17 years	Presumed homozygous	Exertional syncope	Congenital deafness, long QT	Propranolol	Death
Case 3 (Sister 2)	21 years	Heterozygous	Asymptomatic	Normal ECG	Propranolol	Asymptomatic
Case 4 (Mother)	42 years	Heterozygous	Asymptomatic	Mild QTc prolongation	Propranolol	Asymptomatic
Case 5 (Father)	47 years	Heterozygous	Asymptomatic	Normal ECG	Propranolol	Asymptomatic

ICD: implantable cardioverter-defibrillator; ECG: electrocardiogram.

time, the only remarkable clinical finding was marked QT interval prolongation, establishing the association between congenital long QT syndrome and sudden cardiac death.[1,3]

JLNS represents one of the most severe phenotypes within the spectrum of congenital long QT syndromes, characterized by very early disease onset, high arrhythmic burden, and substantial mortality. More than 50% of untreated children die before 15 years of age, and approximately half of affected individuals experience cardiac events before the age of three years. Even under beta-blocker therapy, mortality remains significant, with nearly 27% of patients experiencing cardiac arrest or sudden cardiac death despite treatment. Independent predictors of sudden cardiac death include: QTc duration greater than 550 ms, syncope during the first year of life, male sex, and pathogenic variants in *KCNQ1*.[7,8] Several of these high-risk features were present in the proband described in this report.

Notably, the present case was intentionally not evaluated using the 1-2-3-LQTS-Risk score.[9,10] This risk model was specifically developed and validated for patients with the three most common autosomal dominant forms of long QT syndrome, namely LQT1, LQT2, and LQT3. JLNS, in contrast, is a recessive and substantially more severe condition, characterized by an exceptionally high arrhythmic risk from early childhood. Consequently, affected individuals frequently require individualized management strategies and early implementation of advanced therapies, limiting the applicability of conventional risk prediction models.

The family reported herein illustrates the severe phenotype associated with homozygous JLNS and closely reflects the natural history described in classical cohorts. The proband presented with a QTc interval exceeding 600 ms, a finding consistently associated with an extremely high risk of life-threatening ventricular arrhythmias. Although non-selective beta-blockers such as nadolol and propranolol remain the cornerstone of therapy and constitute the standard first-line treatment for long QT syndrome, refractory patients frequently require additional interventions.[11,12] In Brazil, propranolol remains the only widely available non-selective beta-blocker within the public healthcare system. In contrast, nadolol

is generally preferred in several countries because of its longer half-life, once-daily administration, more stable pharmacological effect, improved adherence, and lower incidence of breakthrough arrhythmic events.

Within this context, left cardiac sympathetic denervation (LCSD) has emerged as an effective therapeutic strategy for reducing arrhythmic events, particularly as a bridge therapy in children who are not yet ideal candidates for implantable cardioverter-defibrillator (ICD) implantation. Observational studies have demonstrated a significant reduction in arrhythmic burden and, in some cases, shortening of the QT interval following LCSD, regardless of genotype.[13,14] The favorable clinical evolution observed in our patient after thoracoscopic LCSD supports the role of this intervention as an important adjunctive therapy in high-risk JLNS patients.

ICD implantation in children with long QT syndrome, including severe forms such as JLNS, is an established strategy for secondary prevention and, in selected circumstances, primary prevention of sudden cardiac death.[15,16] Age alone should not be considered a contraindication; rather, the indication should be based on clinical severity, response to medical therapy, anatomical considerations, and anticipated long-term outcomes. Current recommendations generally favor transvenous systems in larger children with suitable anatomy, whereas epicardial or subcutaneous approaches may be considered in younger patients or when venous preservation is desirable.

In patients with long QT syndrome, particularly those with beta-blocker-induced bradycardia, dual-chamber transvenous ICD systems may provide additional functional advantages. Atrial pacing can prevent excessive bradycardia while minimizing unnecessary ventricular pacing, thereby avoiding ventricular dyssynchrony and potential repolarization changes.

Nevertheless, ICD implantation in pediatric patients remains associated with considerable complication rates. Contemporary studies have reported early complication rates approaching 20% in epicardial systems, with lower rates in transvenous devices. Late complications occur in approximately 20–30% of patients during long-term follow-up.[17,18] Lead dysfunction may affect up to 20% of cases, depending on patient age and device type. Similarly, inappropriate shocks occur in approximately 10–20% of patients over medium- to long-term follow-up, findings that are consistent across pediatric cohorts and long QT syndrome registries.[19] Furthermore, repeated interventions during somatic growth are common and represent a major limitation of device therapy.

Beyond technical considerations, the psychosocial impact of ICD implantation in childhood should not be underestimated. Anxiety, fear of shocks, restrictions on physical activities, and concerns regarding social integration may substantially affect quality of life. These considerations reinforce the importance of careful patient selection, individualized device choice, and multidisciplinary long-term follow-up. In the present case, ICD implantation was deliberately postponed until optimization of medical therapy and achievement of more favorable anthropometric conditions. Importantly, the patient and his parents actively participated in the decision-making process after a thorough discussion of the potential risks and benefits.

Finally, parental consanguinity played a crucial role in the occurrence of the pathogenic variant in homozygosity, emphasizing the importance of reproductive genetic counseling in affected families.[20] Although heterozygous carriers generally exhibit a milder phenotype, residual arrhythmic risk is not negligible, and lifelong clinical follow-up remains warranted.

Conclusion

JLNS represents a recessive syndromic form of congenital long QT syndrome type 1, resulting predominantly from biallelic pathogenic variants in *KCNQ1* and, less frequently, *KCNE1*. It is a rare channelopathy associated with a markedly increased risk of ventricular arrhythmias and sudden cardiac death, particularly in homozygous individuals.

This case series highlights the substantial morbidity and mortality associated with the disease, the phenotypic variability observed among heterozygous carriers, and the therapeutic challenges imposed by pediatric age. The present report reinforces the importance of early diagnosis, a stepwise therapeutic approach—including beta-blocker therapy, left cardiac sympathetic denervation, and implantable cardiac devices—and comprehensive genetic counseling in consanguineous families.

Despite significant advances in diagnosis and treatment, JLNS remains a major clinical challenge, requiring individualized decision-making and multidisciplinary management involving electrophysiologists, geneticists, pediatricians, and specialized inherited arrhythmia teams.

Author Contributions

Conception and design of the research: Duarte JOP, Nascimento SUCN, Magalhães LP, Aras R; Data collection: Duarte JOP, Aragão PHS, Andrade VV, Chiaretti ALS, Guabiru AT; Data analysis and interpretation: Duarte JOP, Aras R; Manuscript drafting: Duarte JOP, Nascimento SUCN, Guabiru AT; Critical revision of the manuscript for important intellectual content: Duarte JOP, Nascimento SUCN, Magalhães LP, Aras R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital Universitário Professor Edgard Santos (UFBA) under the protocol number 6.304.113. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used Gemini for grammatical error correction and translation into English. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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