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CONGRESSO
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Unusual U-shaped QTc/RR relationship in a woman with Jervell and Lange-Nielsen syndrome related to KCNQ1 deletion

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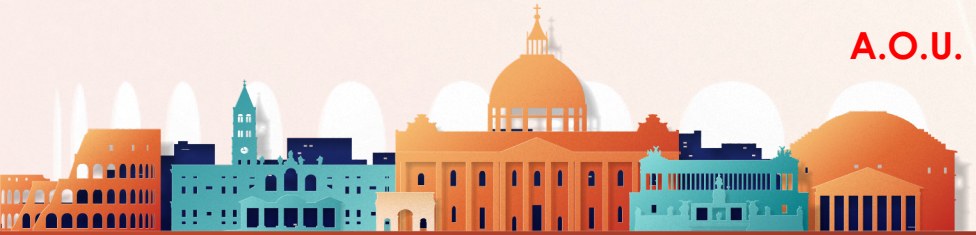
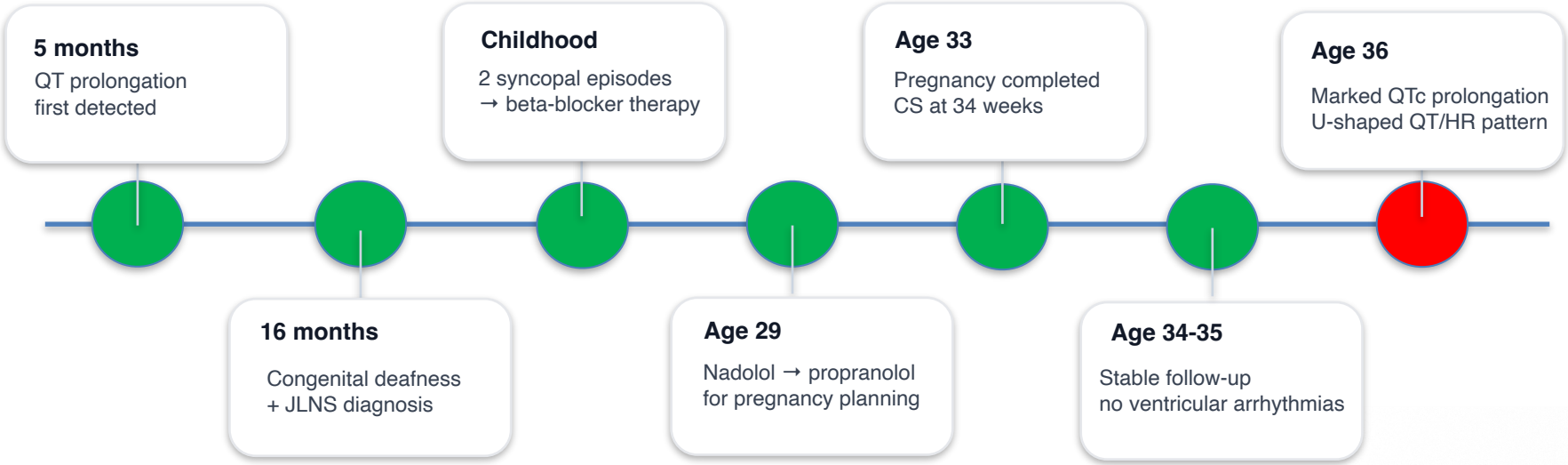


Longitudinal clinical course

A 36-year-old woman followed at our outpatient clinic, with genetically confirmed Jervell–Lange-Nielsen syndrome, congenital deafness, and long-standing beta-blocker therapy.



From genetics to phenotype

1. Genetic substrate

Homozygous KCNQ1 deletion

Region: intron 15–16 to 3'-UTR

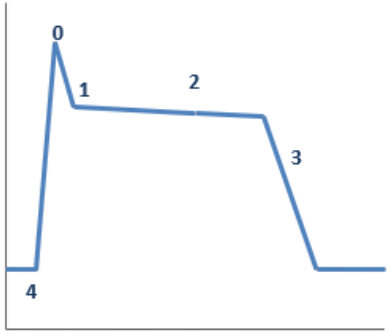
Biallelic loss-of-function phenotype

2. Channel effect

KCNQ1 -> α-subunit of IKs channel

↓ slow delayed rectifier K+ (Iks) current

↑ phase 3 of AP



3. Clinical phenotype

Marked QT prolongation

EAD/ TdP / VF risk

Congenital sensorineural deafness

Typical triggers: exercise, swimming, emotional stress, sudden immersion/ cold water

Reduced repolarization reserve

Phase 0 (rapid depolarization): fast Na+ inward current (INa)

Phase 1 (early repolarization): transient outward K+ current (Ito)

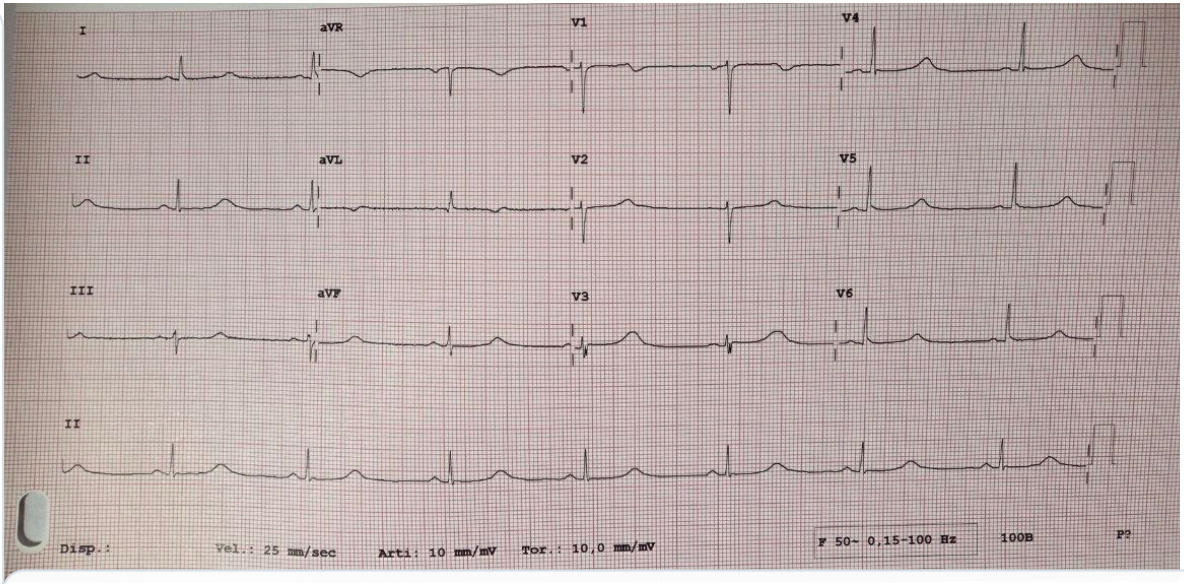
Phase 2 (plateau): L-type Ca2+ inward current (ICa-L) balanced by outward K+ currents

Phase 3 (final repolarization): IKr + IKs drive repolarization; in JLNS, ↓ IKs prolongs action potential duration

Phase 4: resting membrane potential

Index visit

- Asymptomatic outpatient follow-up
- On propranolol 160 mg/day, ≈2.8 mg/kg/day
- No new QT-prolonging drugs reported
- Electrolytes within normal range

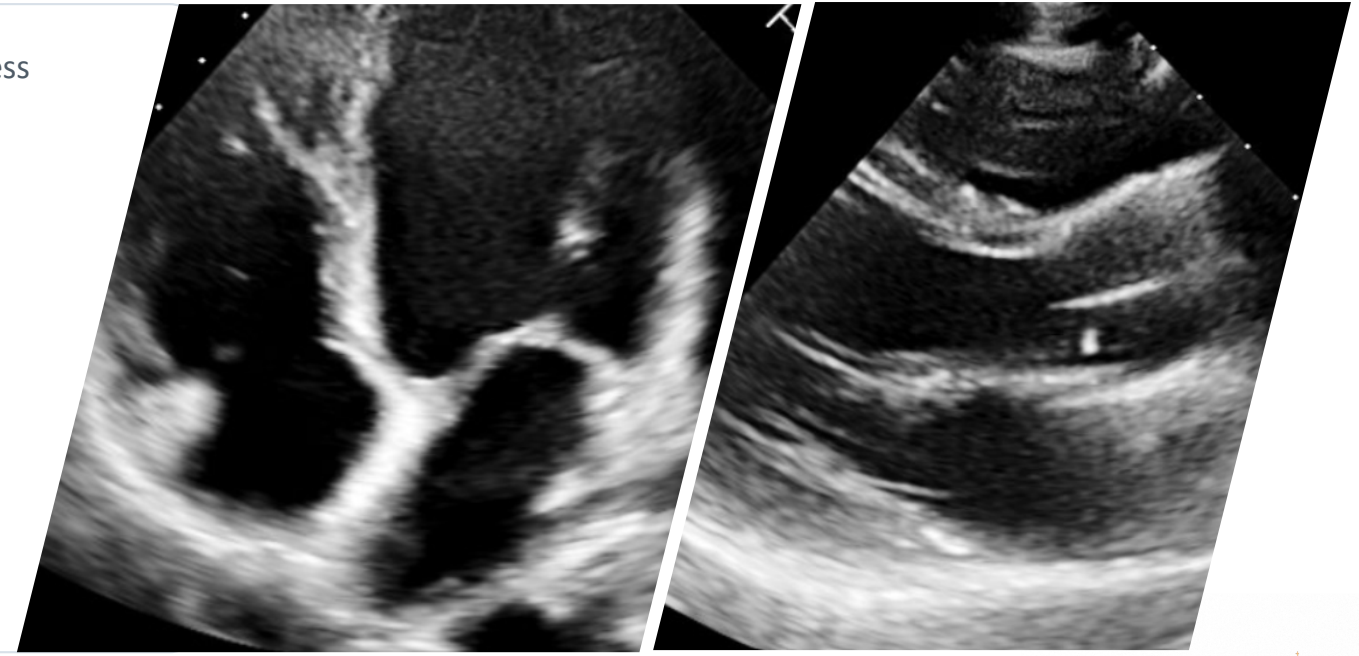


12-lead ECG: sinus bradycardia at 45 bpm | QT/QTcF/QTcB = 600/545/520 ms

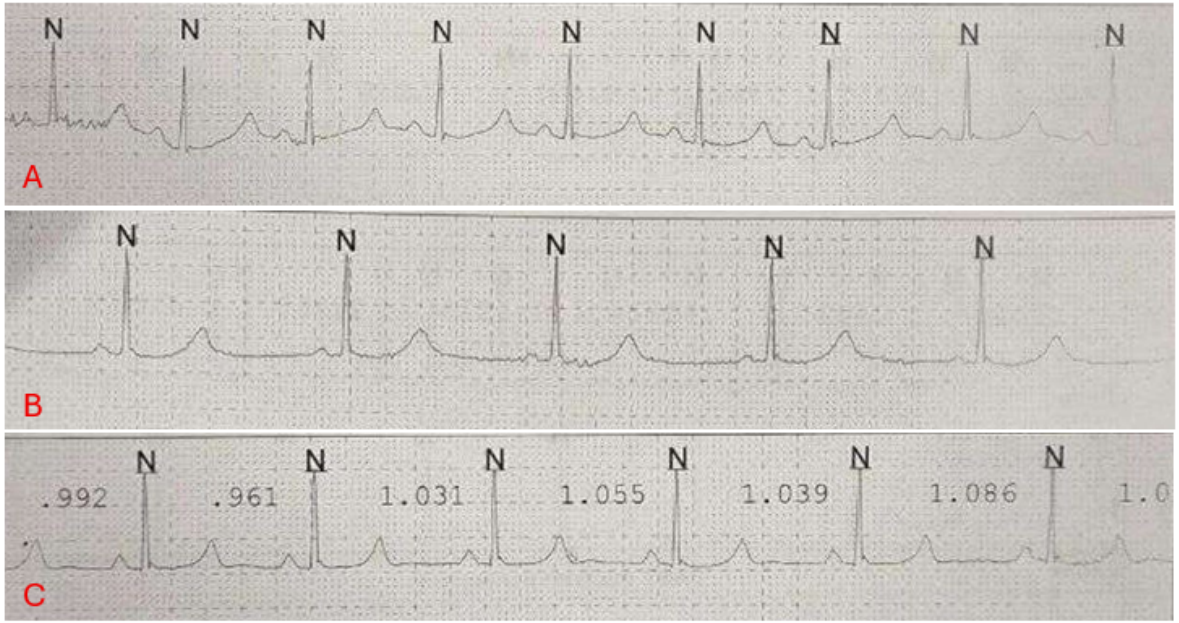
Unexpected QT prolongation under apparently stable clinical and pharmacological conditions

No structural substrate

- Normal LV size and wall thickness
- Preserved LVEF
- No regional wall motion abnormalities
- Normal RV size and function
- No significant valvular disease
- No pericardial effusion



Holter confirmation



Rhythm findings
• Sinus rhythm throughout (mean HR 55 bpm) • Rare isolated SV ectopy • No ventricular arrhythmias • No conduction disturbances

Minimum HR	Intermediate HR	Maximum HR
38 bpm	**60 bpm**	**79 bpm**
QT 670 ms QTcB 533 ms QTcF 575 ms	QT/QTc 510 ms lowest value	QT 586 ms QtcB 672 ms QTcF 642 ms

The unusual QT/HR pattern

Healthy subjects

QT shortens progressively as heart rate increases

Relationship is broadly monotonic

Only mild hysteresis during spontaneous HR changes

Classical LQT1

QT shortening with HR acceleration is blunted

This is clearer during exercise and recovery

Most QT/HR data come from heterozygous LQT1 patients

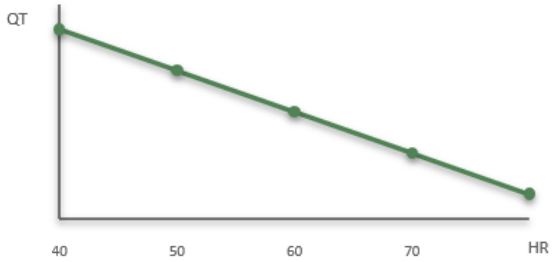
Our JLNS patient

QT/QTc reached a minimum around 60 bpm

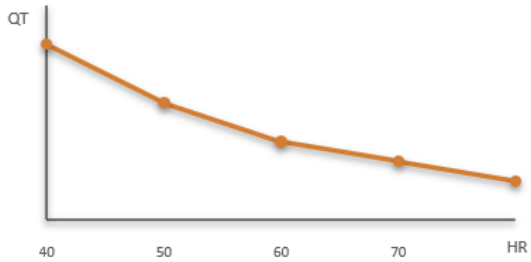
QT/QTc remained prolonged at lower and higher HR

This creates a U-shaped QTc/HR relationship

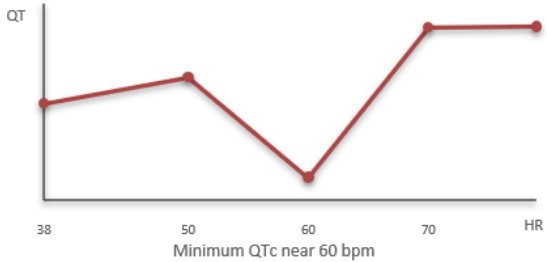
Expected: healthy QT/HR behavior



Expected: classical LQT1



Observed: JLNS case



Malik et al. Heart 2002; Aziz et al. Circ Arrhythm Electrophysiol 2011; Horner et al. Heart Rhythm 2011; Harvey et al. Eur J Prev Cardiol 2022.

QT dynamicity

QT dynamicity is the overall behavior of the QT interval in response to changes in RR interval or heart rate. Several parameters have been proposed to characterize this relationship.

QT/RR slope

Magnitude of adaptation

It estimates how much QT changes when RR changes.

QT/RR hysteresis

Delay of adaptation

Captures the delayed adaptation of the QT interval after HR changes. QT depends on current RR interval and recent RR history.

Individualized QT (QTi)

Patient-specific correction

QT is corrected using the individual patient's QT–RR relationship, often estimated from Holter data.

QT clock

24-hour burden and timing

A visual map of QT duration across the day, based on Holter data.

Zareba & Bayés de Luna. Ann Noninvasive Electrocardiol 2005; Gravel et al. Ann Noninvasive Electrocardiol 2018; Page et al. Heart Rhythm 2016; Robyns et al. Front Cardiovasc Med 2023.

Literature gap

Well established evidence

- JLNS is a severe recessive LQTS phenotype
- Usually related to biallelic **KCNQ1/KCNE1** dysfunction
- Early onset, marked QT prolongation, high arrhythmic risk
- Beta-blocker protection may be incomplete
- Most dynamic QT/HR data come from heterozygous Romano-Ward patients

Evidence from dynamic studies

- QT adaptation to HR appears to be genotype-specific
- Exercise/recovery and standing tests can unmask abnormal repolarization
- Holter-derived QT/RR metrics may outperform single resting QTc
- QT/RR slope, QT clock, and hysteresis are emerging tools

Poorly characterized

- Dynamic QT/HR behavior in **JLNS**, especially biallelic **KCNQ1** disease
- Whether JLNS behaves as “severe LQT1” or as a distinct dynamic phenotype
- Non-linear QTc/HR patterns and their clinical meaning in rare congenital LQTS phenotypes with severe IKs dysfunction

JLNS may not simply be “more severe LQT1”; it may show distinct dynamic repolarization behavior

Schwartz et al. Circulation 2006; Aziz et al. Circ Arrhythm Electrophysiol 2011; Horner et al. Heart Rhythm 2011; Waddell-Smith et al. J Cardiovasc Dev Dis 2022; Gravel et al. Ann Noninvasive Electrocardiol 2018.

Take-home messages

Static QTc captures a moment; QT dynamicity captures behavior.

Resting ECG may miss **dynamic** repolarization abnormalities.

JLNS may represent a distinct dynamic phenotype, not only the severe end of LQT1.

Severe IKs dysfunction may produce less predictable **QT/HR adaptation**.

Non-linear QT/HR behavior challenges standard correction formulas and linear QT/RR metrics.

Marked electrical abnormality can coexist with normal echocardiography. Future evaluation may need Holter-derived **QT/HR mapping**.

This case reframes JLNS follow-up from measuring QTc to characterizing repolarization behavior.

Thank you