The Jervell and Lange-Nielsen Syndrome
Natural History, Molecular Basis, and Clinical Outcome

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Background—Data on the Jervell and Lange-Nielsen syndrome (J-LN), the long-QT syndrome (LQTS) variant associated with deafness and caused by homozygous or compound heterozygous mutations on the KCNQ1 or on the KCNE1 genes encoding the \( I_{Ks} \) current, are still based largely on case reports.

Methods and Results—We analyzed data from 186 J-LN patients obtained from the literature (31%) and from individual physicians (69%). Most patients (86%) had cardiac events, and 50% were already symptomatic by age 3. Their QTcs was markedly prolonged (557±65 ms). Most of the arrhythmic events (95%) were triggered by emotions or exercise. Females are at lower risk for cardiac arrest and sudden death (CA/SD) (hazard ratio, 0.54; 95% CI, 0.34 to 0.88; \( P=0.01 \)). A QTc >550 ms and history of syncope during the first year of life are independent predictors of subsequent CA/SD. Most mutations (90.5%) are on the KCNQ1 gene; mutations on the KCNE1 gene are associated with a more benign course. \( \beta \)-Blockers have only partial efficacy; 51% of the patients had events despite therapy and 27% had CA/SD.

Conclusions—J-LN syndrome is a most severe variant of LQTS, with a very early onset and major QTc prolongation, and in which \( \beta \)-blockers have limited efficacy. Subgroups at relatively lower risk for CA/SD are identifiable and include females, patients with a QTc ≤550 ms, those without events in the first year of life, and those with mutations on KCNE1. Early therapy with implanted cardioverter/defibrillators must be considered. (Circulation. 2006;113:783-790.)

Key Words: arrhythmia ■ death, sudden ■ electrocardiography ■ heart arrest ■ long-QT syndrome

In 1957, Anton Jervell (see online-only Data Supplement) and his associate, Fred Lange-Nielsen, published the first report on a familial disorder characterized by the presence of a markedly prolonged QT interval, congenital deafness, and a high incidence of sudden cardiac death in childhood.1 Following the reports by Romano et al2 and Ward3 of an almost identical familial disease differing only in respect to normal hearing and the suggestion by Fraser et al4 of a genetic relationship between the two, the two syndromes were considered variants of one disease under the unifying name of long-QT syndrome, with the acronym LQTS.5 As we wrote 25 years ago, “There are not many instances in medical history of a single case report so critical for the development of the subsequent knowledge on a given disease.”6

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The progressive unraveling of the molecular basis of LQTS has disclosed that whereas the autosomal dominant Romano-Ward syndrome depends on mutations affecting at least 5 genes encoding sodium and potassium channels, the autosomal recessive Jervell and Lange Nielsen syndrome (J-LN) depends on homozygous or compound heterozygous mutations on either 1 of 2 genes, KCNQ1 and KCNE1.7-9 Proteins encoded by these 2 genes coassemble to form the channel encoded by these 2 genes coassemble to form the channel...
conducting the $I_{Ks}$ current. $KCNQ1$ is also the gene responsible for LQTI, the most common form of Romano-Ward syndrome.

Being a recessive disease, J-LN is far less common than the Romano-Ward syndrome, and the reports available are based primarily on either anecdotal observations or very small series of patients, which suggests a more severe clinical course than Romano-Ward syndrome. To achieve a more thorough and quantitative understanding of this life-threatening disorder and to foster a more rational management strategy, an international cooperative effort was initiated, and the results are presented here. The data now available on 186 J-LN patients also allow a meaningful comparison between the phenotypic aspects of J-LN and of 670 LQTS patients representing the 3 major genetic subgroups (LQT1, LQT2, LQT3), as previously reported.10

Methods

The study population involves 186 patients from 135 families. These families originated from several countries, including Algeria, Canada, Finland, France, Germany, India, Iran, Italy, Japan, Lebanon, Morocco, Norway, Pakistan, Portugal, former Soviet Union, Spain, Sweden, Turkey, United Kingdom, United States, and former Yugoslavia. There were 2 sources of information: the international literature (31%) and individual physicians (69%). For the latter group, which also includes cases initially reported in the literature but with significant increases in follow-up, data were collected on specifically prepared forms, as previously described.10 Patients were considered affected by J-LN on the basis of the established diagnostic criteria for LQTS11 and on the presence of congenital neurosensorily deafness. Patients who died before diagnosis and without an analysis.10

Response to Therapy

Data on therapy were available for 172 patients (92%). This number also includes 36 patients who received no treatment (primarily those who died before diagnosis) and 12 patients who received therapy different from $\beta$-blockers. $\beta$-Blockers represent the most common treatment modality, involving 124 patients (91% of those being treated). The response to $\beta$-blockers was evaluated in 92 patients for whom precise information was available about both outcome and dosage. Our interest was in ascertaining whether actual treatment with $\beta$-blockers was effective; accordingly, and, as done previously,10 11 patients were not included in this analysis because either the dosage of $\beta$-blockers was <1.0 mg/kg per day propranolol (0.5 mg/kg per day for Japanese patients) or an equivalent dose of other $\beta$-blockers or because the therapy had been definitely discontinued. At this point the analysis was based on the intention-to-treat principle, and events occurring in relation to accidental or brief suspension of treatment were always included.

Statistical Analysis

Univariate analyses were performed by unpaired t test, ANOVA, and cross-tabulations, as appropriate. For continuous variables, data are presented as mean±1 SD or as median and interquartile range (IQR) whenever the distribution was skewed. Event-free survival was described with the use of the Kaplan-Meier life-table method. Time to first event (with birth used as time of origin) was determined by gender for any events (syncope, CA/SD, whichever occurred first) and for life-threatening events. The prognostic roles of QTc, history of syncope within the first year of life, genotype, and gender were analyzed. The proportional hazards assumption was checked by Schoenfeld residuals and/or by stratification. The proportional hazard model was used to compute hazard ratios (HRs) with their 95% CIs. The statistical significance level was set at $P<0.05$. All analyses were performed with SPSS software (version 11.5).
not significantly different between the 2 sources, with a median event-free survival time of 31 and 35 months ($P=0.89$) (Figure 1).

**Time to First Event**

The availability for 140 patients (88% of those with symptoms) of their age at first event has allowed the presentation of survival curves (interval from birth to first cardiac event). Among the J-LN patients, 15% becomes symptomatic within the first 12 months of life; the median time (50%) of survival free from cardiac events is 33 months, and by age 18 years 90% of them have had a first cardiac event (Figure 2A, 2B). This is in striking contrast to the Romano-Ward patients and especially the LQT2 and LQT3 subtypes, which manifest their symptoms much later in life (Figure 2C); of note, all of these Romano-Ward patients were symptomatic. Figure 2D shows how this difference in severity becomes even more striking when compared with a large group of unselected LQT1 patients referred to a single center.

**Triggers for Cardiac Events**

Figure 3 shows the prevalence of the various triggers for all cardiac events (Figure 3A) and for life-threatening cardiac events (Figure 3B). Exercise and emotions, which are both conditions associated with increased sympathetic activity, are equally important, and they account for 95% of cardiac events. Very few events (5%) were associated with rest or sleep. Among specific activities, swimming is notable because it is associated with events in 16% of all patients with known triggers.

When the analysis is limited to life-threatening events, it appears that 93% of them occur during exercise and emotions and only 7% during sleep/rest. In addition to those patients...
who had life-threatening events with the 3 main triggers, 15 (37%) suffered a CA/SD associated with “other conditions” (fever, pregnancy, anesthesia, normal daily activities, sepsis with low K⁺/H₁₁₀₀₁, diarrhea).

QT Interval Duration
QTc measurements were available for 160 patients (86%). The QTc of the J-LN patients was markedly prolonged (557±65 ms), with no difference between females and males (557±66 and 556±65 ms, respectively) (Figure 4A). Surprisingly, the QTc of symptomatic patients was not significantly longer than that of patients without symptoms (561±64 versus 535±71 ms; P=0.07). However, when the truly asymptomatic subjects (aged ≥15 years; n=10 aged 15 to 83 years) were compared with the younger asymptomatic subjects (n=16 aged 1 to 13 years), who still have a high probability of becoming symptomatic, an important finding emerged. The QTc of the very young asymptomatic subjects (561±64 ms) is similar to that of the symptomatic subjects (561±64 ms), which is significantly longer than that of the patients truly likely to remain asymptomatic (488±47 ms; P=0.004) (Figure 4B).

Figure 5 shows that the QTc is longer among J-LN symptomatic patients with CA/SD than among those with syncope (585±64 versus 545±58 ms; P<0.001) and that the same pattern (526±49 versus 494±45 ms; P<0.001) is present among symptomatic LQT1 patients. By contrast, no significant difference was present among LQT2 and LQT3 patients despite a trend in the same direction. When all QTTS patients (Romano-Ward and J-LN) are analyzed together, those with CA/SD have a longer QTc (545±65 versus 503±51; P<0.001).

Role of Gender
Females are at lower risk for life-threatening events (HR, 0.54; 95% CI, 0.34 to 0.88; P=0.01). Although a pattern (P=0.05) is already present when all cardiac events are considered (Figure 6A), this difference becomes more evident (P=0.01) when syncope is excluded and the analysis is limited to life-threatening events (CA/SD; Figure 6B) or to sudden death only (P=0.02; Figure 6C). These cumulative survival estimates do not take into account the potential confounding role of β-blocker therapy used in 63% and 70% of females and males, respectively.

Genetics
The genotype was known for 63 (47%) of the 135 families. In most families (57 of 63; 90.5%) the mutations were on the KCNQ1 gene, whereas in 6 (9.5%) they were on KCNE1. Among the genotyped probands, 33% were compound heterozygous. They and the homozygous subjects were not different for all the variables examined: QTc duration, prevalence of symptoms, gender, age at first episode, type of triggers, lethal episodes regardless of therapy, and response to β-blockers. These results also apply when the analysis is limited to the KCNQ1 subgroup.

In the KCNQ1 group, complex mutations (insertions/deletions, splice variants, truncations) in at least 1 allele were found in 74% of probands. There was no difference in QTc duration, symptoms, and life-threatening events between patients with at least 1 complex mutation and those with missense mutations.

Among the 77 symptomatic patients of known genotype, 73 (95%) have mutations on KCNQ1, and 4 (5%) have mutations on KCNE1. This distribution is significantly different (P=0.001) than that seen in the 6 truly asymptomatic successfully genotyped patients (aged ≥15 years), among
whom only 2 (33%) have mutations on \textit{KCNQ1}, whereas 4 (67%) have mutations on \textit{KCNE1}. In addition, a significantly longer QT interval was observed among patients with \textit{KCNQ1} mutations than among \textit{KCNE1} mutation carriers (556±55 versus 517±72; \(P=0.03\)). As shown in Figure 7, the cumulative probability of a first cardiac event is significantly lower for J-LN patients with \textit{KCNE1} mutations than for those carrying \textit{KCNQ1} mutations (\(P=0.0003\)). Even after we accounted for QTc and gender, \textit{KCNE1} mutations remain associated with a lower risk for arrhythmic events compared with \textit{KCNQ1} mutations, as shown in a Cox model by HR of 0.18 (95% CI, 0.06 to 0.50; \(P=0.001\)).

Prognostic Factors and Risk Stratification

After adjustment for gender, multivariate Cox regression analysis indicated that both a QTc \(\leq 550\) ms (ie, the median value of QTc in the entire J-LN population) and no history of syncope in the first year of life were significantly associated with a lower risk of a subsequent life-threatening event (HR, 0.36; 95% CI, 0.19 to 0.68; \(P=0.002\); HR, 0.44; 95% CI, 0.22 to 0.87; \(P=0.02\), respectively). In this multivariate analysis, gender was also an independent risk factor (\(P=0.03\)), with a lower risk for females than for males (HR, 0.51; 95% CI, 0.27 to 0.95).

\textbf{β-Blocker Therapy}

Among the 124 patients who were prescribed β-blockers, follow-up data were available for 103 (83%); however, 11 met the exclusion criteria and were considered off-therapy. Thus, 92 patients met the criteria for assessing β-blocker efficacy. Among them, 69 (75%) had experienced at least 1 cardiac event before the institution of β-blocker therapy, and 23 (25%) were asymptomatic before treatment was started. In total, 45 (49%) became or remained asymptomatic while on therapy, whereas the remaining 47 (51%) developed recurrences or experienced their first cardiac episode after initiation of therapy. There were 10 cardiac arrests and 15 sudden deaths, for a total of 27% of patients on therapy who suffered CA/SD. The median age at onset of therapy was 3.5 years (IQR, 1 to 7) (19 patients started on β-blockers soon after birth or within the first year), and the median duration of therapy was 8 years (IQR, 3 to 15). The median age at death on therapy was 8 years (IQR, 6 to 14).

\textbf{Additional Therapies}

In 32 of the 92 patients analyzed for the efficacy of β-blockers, 1 or more additional therapies were used, including pacemakers (n=12), implantable cardioverter/defibrillators (ICDs) (n=13), and left cardiac sympathetic denervation (LCSD) (n=16). In 18 of these 32 patients (56%), there were additional recurrences, including 7 sudden deaths. Recurrences occurred in 8 of 11 patients with pacemakers, in 9 of 16 patients with LCSD, and in 4 of 13 patients with an ICD (appropriate shocks).
Discussion

This cooperative study provides information on an unprecedented number of patients affected by the J-LN syndrome and allows for the first time a meaningful assessment of the main features of this intriguing disorder. The data show specific differences in terms of clinical manifestations and response to therapy with all subsets of LQTS. Even when compared with LQT1, the LQTS variant that shares with J-LN an impairment of the J wave, there are both similarities and important differences.

The J-LN syndrome has a special place in cardiology because it was its recognition by Anton Jervell,1 followed by his additional reports,13,14 which paved the way for the first absence of a history of syncope during the first year of life. A-V block16 and with syndactyly,17 the J-LN is the most exception of the very rare forms of LQTS with congenital deafness, the LQTS, which has been correctly described as a Rosetta stone for sudden cardiac death.15 Indeed, the identification of several of the LQTS genes has represented a major breakthrough for cardiology and for the study of cardiac arrhythmias by providing a previously unforeseen bridge between molecular biology and clinical cardiology.

The large numbers of the present study allow us to draw conclusions concerning the natural history of J-LN, the genotype-phenotype correlation, the risk factors for life-threatening cardiac events, and the response to therapy.

Natural History

As suspected from the early cases, and with the possible exception of the very rare forms of LQTS with congenital A-V block16 and with syndactyly,17 the J-LN is the most severe of the major variants of LQTS. This is exemplified by the fact that almost 90% of the patients become symptomatic and that sudden death exceeds 25% despite medical therapy. Furthermore, the J-LN patients begin to suffer cardiac events very early in life. During the first year of life 15% already had an event, by age 3 years 50% have had an event, and by age 18 years a staggering 90% had symptoms.

The uniquely early onset of symptoms is clearly illustrated by the comparisons with LQT1, LQT2, and LQT3 patients selected for having a severe form of LQTS because they were all symptomatic. This difference is further amplified when one compares all the J-LN patients not just with symptomatic LQT1 patients but especially with an unselected large group of LQT1 patients that, because of low penetrance,18 includes a significant proportion of silent mutation carriers and of asymptomatic individuals.

Even though these data include a number of patients identified many years ago when diagnosis was likely to be made only in the most severe cases, and indeed the QTc of patients reported from the literature is more prolonged, the difference in mortality is relatively modest compared with that of patients with direct information from the responsible physicians.

The conditions that trigger the cardiac events are, overall, very similar to those described for LQT1,10 as expected for mutations affecting the $I_K$ current. Most of these conditions (95%) involve sympathetic activation and are represented by exercise and emotions, and only 5% of the events occur at rest or during sleep. This observation confirms the specific relation between genotype and triggers for cardiac events that we postulated in 199519 and confirmed in 2001,10 QTc duration is also a major risk factor for J-LN patients, and it is much longer than in any other LQTS genetic group. This likely reflects the “double-hit,” the presence of 2 mutations, with the attendant greater loss in repolarizing current. QTc duration offers interesting insights for the possible prediction of those young patients more likely to remain asymptomatic throughout life. Indeed, analysis of the QTc of the still asymptomatic patients becomes informative when their age is taken into account. As Figure 2A shows that only 2% of patients become symptomatic after age 15 years, J-LN individuals without symptoms by this age can represent the group of “true asymptomatic” patients. The mean QTc of these individuals (488 ms) is significantly shorter than that of all the symptomatic patients (561 ms) and of patients who are still asymptomatic but aged <15 years (563 ms) who actually have a high probability of becoming symptomatic. The fact that QTc is not different between males and females, which is at clear variance with most LQTS patients, is surprising only at first glance because it is probably explained by the very young age of most patients. Even among normal individuals, the longer QTc associated with the female gender is absent at birth.20

The gender issue is more important in relation to the severity of the arrhythmic events. Indeed, the probability of a J-LN patient developing CA/SD is markedly higher for males. Besides gender, multivariate analyses identifies other 2 independent risk factors for the life-threatening events, namely, a QTc >550 ms and occurrence of syncope during the first year of life.

Molecular Basis

As expected on the basis of the distribution of genotypes in LQTS,20 most of the J-LN mutations are on the KCNQ1 gene. Although this distribution is replicated among the symptomatic patients, the pattern among the small group of genotyped asymptomatic patients is profoundly different because most of them are KCNE1 mutation carriers. Furthermore, a multivariate analysis shows that patients with KCNQ1 mutations have an almost 6-fold greater risk of arrhythmic events. Thus,
within the J-LN population it is possible to recognize a genetic subgroup at lower risk, namely, the patients with KCNE1 mutations. It follows that to genotype all J-LN patients should be regarded as correct management and not as a research objective.

A puzzling problem continues to be the reason why LQT1 patients are much more symptomatic and at risk for lethal events than the parents of the J-LN patients, despite the fact that they all are heterozygous for the same gene. The most obvious explanation suggests that J-LN mutations are “milder” and therefore, in the heterozygous form, do little harm. Some data support this concept. Indeed, most of the LQT1 genetic variants are missense mutations21,22 exerting a dominant negative effect because they can coassemble with normal subunits and interfere with channel function. On the other hand, the present data demonstrate that most (74%) of J-LN mutations on other hand, the present data demonstrate that most (74%) of J-LN mutations on KCNQ1 are complex mutations, likely to interfere with subunit assembly. This confirms, in a much larger and more heterogeneous group of J-LN families, observations previously published in small series.23–25 However, exceptions exist, including both dominant negative J-LN mutations23 and autosomal recessive Romano-Ward mutations with mild electrophysiological alterations.26,27 These still imperfect genotype-phenotype correlations point to the likely existence of additional factors, such as modifier genes,28 that alter the clinical severity resulting from specific mutations.

Consanguinity was reported in 41% of the J-LN probands’ parents, apparently in contrast with the finding that 67% of the successfully genotyped probands are homozygous. This might reflect a bias in reporting consanguinity but could also suggest that mild mutations spread more easily in close communities, thus increasing the chances to produce homozygous carriers.

Implications for Therapy

LQT1 patients are at high risk during sympathetic activation and are very well protected by β-blockers, as shown by the incidence of only 1.6% and 1.1% of CA/SD in 2 large studies performed in referral centers29,30 and also among children.31 This is in striking contrast to the 27% of J-LN patients who suffered CA/SD despite being treated with β-blockers. In addition, an impressive 51% of patients remained or became symptomatic while on therapy. The figures of this clear failure of β-blockers to provide adequate protection from arrhythmic events are even worse than those previously reported for LQT3 patients, namely, 17% and 14% for combined CA/SD.10,29

These grim figures are compounded by the fact that a high incidence of recurrences is recorded even when β-blockers are associated with additional therapies such as pacing or LCSD. The limited efficacy of LCSD is at variance with the encouraging results obtained even in the difficult-to-manage LQT3 group.32

The very limited efficacy of β-blockers for J-LN patients is alarming and indicates the need for more aggressive therapy in at least half of them. Risk stratification including genotype, age at diagnosis, symptoms at presentation, degree of QT-interval prolongation, and gender may help identify patients at higher risk of life-threatening events. Neither LCSD nor antibradycardia pacing was protective against life-threatening events in patients known to be at increased risk, which suggests that ICD implantation may be required. Young J-LN children are at particularly high risk for cardiac events, as 50% of them experienced events by 3 years of age. These data suggest that J-LN children with high-risk characteristics should be considered for defibrillator implantation. Young J-LN children and infants without identified high-risk characteristics should have an external defibrillator available in addition to medications. Improvements in defibrillator technology that allow implantation of smaller epicardial systems are needed. LCSD, given its efficacy in LQTS patients with storms of shocks by the ICD,33 has a place in all J-LN patients, with the goal of minimizing the probability of an ICD shock, which, especially in young children, has a high potential to trigger storms of shocks as a result of pain, fright, and further release of catecholamines.

The present study offers the first possibility of selecting for these young children more or less aggressive therapies on the basis of data-driven risk stratification. Indeed, because a J-LN child with a QTc <550 ms and without syncope in the first year of life has ~90% probability of not suffering CA/SD events before age 8 to 10 years, in this group it would be possible to wait a few years before the decision is made to implant an ICD. The presence of female gender and/or of KCNE1 mutations can also usefully contribute to individually tailored management of this life-threatening disease.

For J-LN patients, aggressive efforts to risk-stratify and to provide tiered therapy based on risk are absolutely essential.

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Disclosures

None.

References

The Jervell and Lange-Nielsen syndrome (J-LN) is the long-QT syndrome variant associated with congenital deafness. It was first described by Jervell and Lange-Nielsen in 1956. The syndrome is caused by mutations in the genes encoding the β-subunits of the slow component of the delayed rectifier potassium channel, which are involved in the repolarization phase of the cardiac action potential.

Over the past few decades, the understanding of the molecular basis of J-LN has significantly advanced. Mutations in the KCNQ1 and KCNH2 genes have been identified as the most common causes of J-LN. These mutations result in a loss of function for the potassium channel, leading to a prolongation of the QT interval and increased risk of life-threatening arrhythmias.

In addition to the genetic basis, environmental factors and interactions with other congenital conditions can also influence the clinical presentation of J-LN. For example, the presence of congenital deafness is a hallmark of the Jervell and Lange-Nielsen syndrome. However, individuals with J-LN may also present with other symptoms such as photophobia, nystagmus, and cognitive delays.

Risk stratification in J-LN is critical to identify patients who are at higher risk for life-threatening arrhythmias. This involves the careful evaluation of clinical features, family history, and genetic testing. The use of implantable cardioverter-defibrillators (ICDs) is often considered in high-risk individuals, although the decision to implant an ICD should be made on an individualized basis, taking into account the patient’s overall clinical picture, quality of life, and other medical considerations.

In summary, J-LN is a serious congenital disorder that requires a multidisciplinary approach for diagnosis and management. Continued research is needed to further refine risk stratification strategies and improve outcomes for patients with J-LN.
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