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 \( \text{KCNQ1} \) or on the \( \text{KCNE1} \) 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 QTc 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 \( \text{KCNQ1} \) gene; mutations on the \( \text{KCNE1} \) 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 \( \text{KCNE1} \). 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

Clinical Perspective p 790

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, \( \text{KCNQ1} \) and \( \text{KCNE1} \).7–9 Proteins encoded by these 2 genes coassemble to form the channel...
conducting the \(I_{Ks}\) current. \(KCNQ1\) is also the gene responsible for LQTS1, 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 J-LN\(^11\) and on the presence of congenital sensorineural deafness. Patients who died before diagnosis and without an ECG (n\(^s\)) were considered affected by J-LN on the basis of a history and in 41% of the successfully genotyped families. Genotyping information is available for only a few of the literature cases, largely because several patients had died or because they relate to the premolecular era; of the 97 families reported by individual physicians, 57 (59%) were successfully genotyped, mutations were not identified in 4, and the remaining families have not yet been tested.

Whenever appropriate, the data of the J-LN patients will be compared with those of 670 genotyped and symptomatic LQTS patients\(^10\) or those of 355 LQT1 patients from the Pavia database.\(^12\)

### Cardiac Events and Triggers

Patients were considered symptomatic if they had suffered either syncope, aborted cardiac arrest, or sudden death. We also distinguished between syncope and life-threatening events (cardiac arrest and sudden death [CA/SD]).

The analysis of the triggers for cardiac events focused on 3 main conditions: exercise, emotion, and rest or sleep without arousal, as previously described.\(^10\) We also considered the occurrence of cardiac events under “other conditions,” which include all the situations different from the first 3. This reflects the fact that these other conditions are well described and often associated with cardiac events and also that the extremely young age of many patients makes the appropriate definition of intense physical exercise or of strong emotion more difficult. To avoid selection bias, whenever multiple triggers were operant in a single patient, they were all included in the 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.

### Characteristics of 186 Subjects With J-LN Syndrome

<table>
<thead>
<tr>
<th>Characteristics of 186 Subjects With J-LN Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families/probands, n</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
</tr>
<tr>
<td>Family history of J-LN, n (%)</td>
</tr>
<tr>
<td>Consanguinity, %</td>
</tr>
<tr>
<td>History of cardiac events, n (%)</td>
</tr>
<tr>
<td>Median age at first event, y (IQR)</td>
</tr>
<tr>
<td>LQTS-related death, n (%)</td>
</tr>
<tr>
<td>Median age at death, y (IQR)</td>
</tr>
<tr>
<td>Asymptomatic patients, n (%)</td>
</tr>
<tr>
<td>Age (\geq)15 y, n (%)</td>
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<td>Median time of follow-up, y (IQR)*</td>
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</table>

*35% for all families and 41% for genotyped families only.

### 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 evaluated by a Cox model, and hazard ratios (HRs) were reported with their 95% CIs. Probability values <0.05 were considered statistically significant. SPSS software (version 11.5) was used for computation.

### Results

#### Patient Population

The clinical characteristics of the 186 J-LN patients are summarized in the Table. In 38 of the 135 families (28%), 1 or more affected individuals were identified in addition to the proband. Consanguinity was reported in 35% of these families and in 41% of the successfully genotyped families. Females (52%) and males are equally represented. Life-threatening events (CA/SD) occurred in 72 patients (39%), and among these there were 50 sudden deaths (27%); the median age at death was 8.5 years (IQR, 3.6 to 14).

The overwhelming majority of the patients (n=160; 86%) are symptomatic; among the few patients still asymptomatic (n=26), only 10 are aged \(\geq\)15 years. Thus, only 5% of this entire population approaches adulthood without having suffered cardiac events.

When patients reported by the literature were compared with those reported by individual physicians, few differences emerged. The former group showed a more prolonged QTc (592±58 versus 543±63 ms; \(P<0.001\)), but the prevalence of symptomatic patients and the mortality (CA/SD) rate was
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.10 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.12

**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 only in the J-LN patients (Figure 2B). 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

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**Figure 1.** Kaplan-Meier curves of event-free survival according to the source of information.

**Figure 2.** Kaplan-Meier curves of event-free survival. A, All J-LN patients; B, all J-LN patients with a magnified view of the events occurring in the first 15 years of life; C, J-LN patients vs Romano-Ward symptomatic patients of known genotype;10 D, J-LN patients vs LQT1 symptomatic patients and an unselected LQT1 population.12

**Figure 3.** Conditions (triggers) associated with the occurrence of all cardiac events (A) and of life-threatening cardiac events only in the J-LN patients (B). Numbers in parentheses indicate numbers of triggers.
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⁺/H⁺, 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 (563±70 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 LQTS patients (Romano-Ward and J-LN) are analyzed together, those with CA/SD have a longer QTc (545±65 vs 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 KCNQ1, whereas 4 (67%) have mutations on KCNE1. In addition, a significantly longer QT interval was observed among patients with KCNQ1 mutations than among 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 KCNE1 mutations than for those carrying KCNQ1 mutations (P = 0.0003). Even after we accounted for QTc and gender, KCNE1 mutations remain associated with a lower risk for arrhythmic events compared with 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 ≥ 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).

**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).

**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).
The J-LN syndrome has a special place in cardiology because it was its recognition by Anton Jervell, followed by the absence of a history of syncope during the first year of life. As suspected from the early cases, and with 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.

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 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, 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 mutations 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 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. However, exceptions exist, including both dominant negative J-LN mutations and autosomal recessive Romano-Ward mutations with mild electrophysiological alterations.

These still imperfect genotype-phenotype correlations point to the likely existence of additional factors, such as modifier genes, 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 centers and also among children. 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.

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.

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, 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

Clinical Perspective

The Jervell and Lange-Nielsen syndrome (J-LN) is the long-QT syndrome variant associated with congenital deafness. It is caused by homoygous or compound heterozygous mutations on the KCNQ1 or the KCNE1 genes encoding the β-subunit of the slow component of the delayed rectifier potassium channel.

In J-LN patients, the QT interval is prolonged; most arrhythmic events (95%) are triggered by emotional or physical stress, and 27% had cardiac arrest or sudden death (CA/SD). The severity of the clinical manifestations, early occurrence of life-threatening arrhythmias, and poor response to medical therapy indicate the need to resort to use of an implantable cardioverter/defibrillator (ICD).

We found that 4 factors (QTc > 65 ms), female gender, and mutations on the KCNQ1 gene were associated with a significantly lower risk for CA/SD. This novel information allows, for the first-time, physicians managing J-LN patients to make therapeutic choices based on a data-driven individualized risk stratification.
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