# Mujer de 30 años que ingresa por episodio sincopal que presenta Enfermedad de Refsum – 2010

Dr. Edgardo Schapachnik

Queridos amigos:
Comparto con Ustedes el material correspondiente al próximo ateneo de nuestro Servicio, porque lo considero de sumo interés a los efectos de nuestro Foro

Un abrazo

Edgardo Schapachnik

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# HOSPITAL ARGERICH
# SERVICIO DE CARDIOLOGÍA
# ATENEO CLÍNICO

| | |
|---|---|
| **Paciente: A.R.** | **Sexo: Femenino** |
| **Edad: 30 años** | **Fecha de Ingreso: 29/08/10**<br>**Fecha de Egreso: 27/09/10** |

**MOTIVO DE INGRESO:** Síncope.

**ENFERMEDAD ACTUAL:** Paciente que consulta a guardia externa de este hospital por presentar episodio sincopal en reposo, sin pródromos, de un minuto de duración refiriendo palpitaciones y disnea CF II-III de 15 días de evolución. Se realiza ECG que evidencia bloqueo AV de tercer grado con escape ventricular a 30 latidos por minuto, por lo que se decide su internación en UCO.

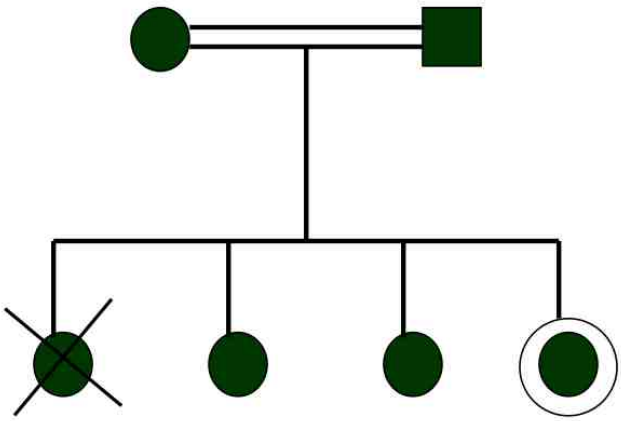
## ANTECEDENTES PERSONALES

FRC +: Dislipemia.

Hipoacusia neurosensorial congénita.

Retraso madurativo (secundario completo).

## ANTECEDENTES FAMILIARES



| | | | |
|---|---|---|---|
| **Fallecida en el nacimiento** | **S.R. (43) Portadora de MCP definitivo** | **V.R. (38) BCRD+HABI+ BAV 1'g** | **A.R. (30)** |

- Los padres poseen vínculo de consanguineidad.
- Las hermanas presentan hipoacusia congénita, retraso madurativo, alteraciones en la marcha e historia de convulsiones.

## EXAMEN FÍSICO

| TA: 140/85 | FC: 32 lpm | FR: 18 cpm | T: 36º |
|---|---|---|---|

**Ap. Cardiovascular:** Ingurgitación yugular 2/3 con colapso inspiratorio, choque de la punta palpable en 5º EII LMC. R1 y R2 en 4 focos, silencios impresionan libres, sin edemas, pulsos periféricos conservados.

**Ap. Respiratorio:** BMV, BEAB, sin ruidos agregados.

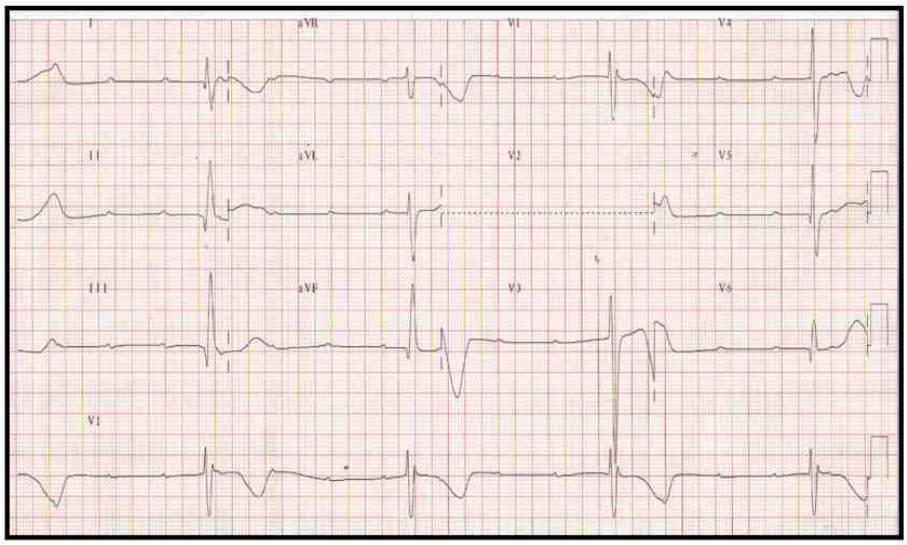
**Abdomen:** Blando, depresible, indoloro. RHA presentes. Sin visceromegalias.

**SNC:** Lúcida, pupilas isocóricas reactivas, estrabismo convergente. Hiporreflexia patelar y rotuliana, nistagmus espontáneo horizontal y vertical a predominio derecho.

**Ap. Genitourinario:** Mamas hipotróficas, escaso desarrollo de genitales externos. Tanner I. PPL - / PU -.

**Piel y TCS:** Palidez cutáneo-mucosa. Ictiosis generalizada.

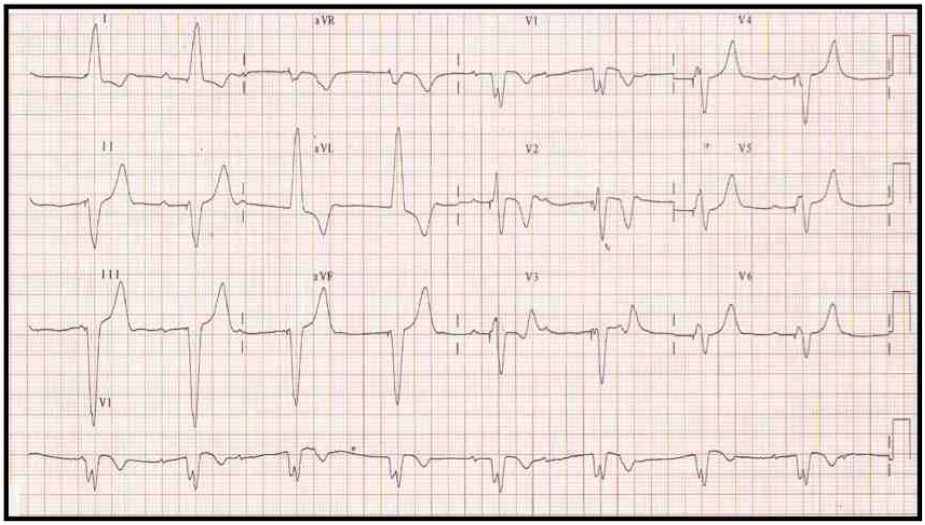
## ELECTROCARDIOGRAMA - INGRESO A UCO



## EVOLUCIÓN
## 29/08/10

- Al ingreso a UCO se realiza infusión de drogas cronotrópicas sin respuesta a las mismas, y al encontrarse la paciente sintomática (mareos) se decide la colocación de marcapasos transitorio.

## ELECTROCARDIOGRAMA POST-IMPLANTE DE MARCAPASOS TRANSITORIO




## ECOCARDIOGRAMA BIDIMENSIONAL

| DDVD | DDVI | DSVI | FAc | SIV | PP | AI | Ao |
|---|---|---|---|---|---|---|---|
| 2.4 | 5.05 | 3.60 | 29 | 0.90 | 0.95 | 3.15 | 2.75 |

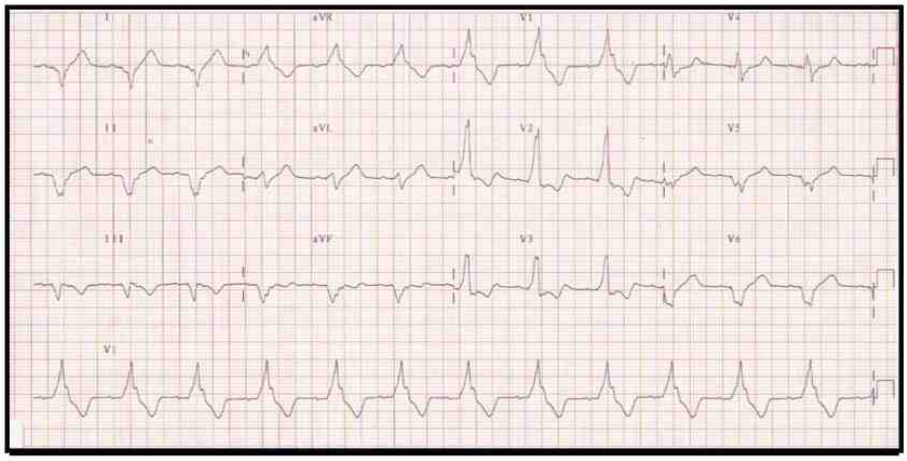
- Ventrículo izquierdo no dilatado con grosor parietal normal.
- Movimiento anormal del septum interventricular.
- Función sistólica normal.
- Diámetro de la aurícula derecha normal.
- Cavidades derechas normales. Se observa catéter de marcapasos.
- Válvulas morfológicamente normales.
- No se observa derrame pericárdico.

## EVOLUCIÓN

## 22/09/10

- Se realiza implante de marcapaso DDD definitivo.
- Se constata implante de catéter ventricular en seno coronario.

## ECG POST-IMPLANTE DE MARCAPASOS DEFINITIVO



## ECOCARDIOGRAMA POST-IMPLANTE DE MARCAPASOS DEFINITIVO

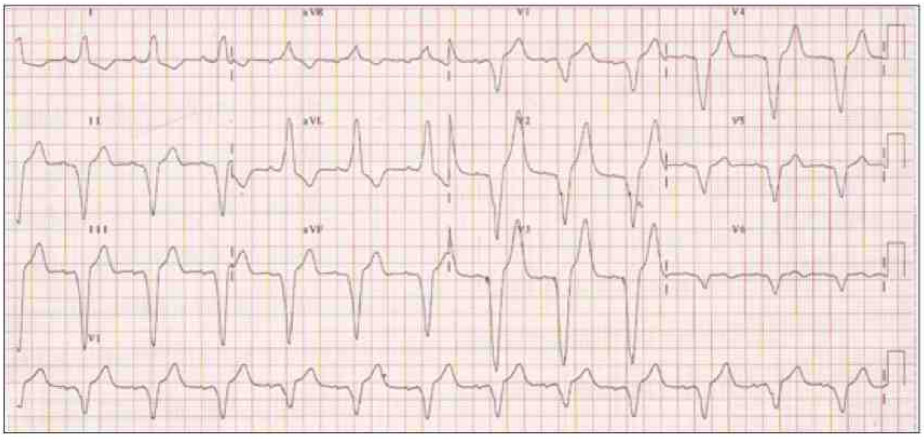
| DDVI | DSVI | FAc | SIV | PP | AI | Ao |
|---|---|---|---|---|---|---|
| 5.00 | 3.60 | 32 | 1.10 | 0.90 | 3.30 | 3.40 |

- Ventrículo izquierdo no dilatado con grosor parietal normal.
- Motilidad regional y función sistólica conservada.
- Aurícula izquierda no dilatada.
- Cavidades derechas normales.
- Válvulas morfológicamente normales.
- Se observan dos catéteres de marcapasos en aurícula derecha: uno a nivel del tercio medio del septum interauricular y el otro entrando a seno coronario. El mismo impresiona estar ubicado al menos hasta la región media en relación al anillo mitral.
- No se observa derrame pericárdico.

## EVOLUCIÓN

## 23/09/10

- Se decide la recolocación de de cable ventricular en forma exitosa.
- El 27/9/10 se otorga alta hospitalaria.



## LABORATORIO

| | 29/08 | 01/09 | 10/09 | 20/09 |
|---|---|---|---|---|
| Hto. | 39 | 44 | 39 | 40 |
| G.B. | 8600 | 8800 | 6600 | 6500 |
| Plaq. | 264000 | 216000 | 180000 | 278000 |
| Glucemia | 0.95 | 0.94 | 0.76 | 0.83 |
| Urea | 0.30 | 0.37 | 0.30 | 0.30 |
| Creatinina | 1.10 | 0.83 | 0.72 | 0.70 |
| TP | 100 | | 99 | |
| KPTT | 32 | | 41 | |
| GOT/GPT | | | 21/23 | |
| Ionograma | 143/4.1/107 | 139/3.8/106 | 139/3.89/107 | |

| PERFIL LIPÍDICO | | | |
|---|---|---|---|
| CT | LDL | HDL | TAG |
| 394 | 301 | 48 | 227 |

# OPINIONES DE COLEGAS

Prezado Edgardo: a pessar de muito raro parece-me que o diagnóstico é claro: Síndrome cardio-auditiva ou surdocardíaco (surdez central sensoneural) de Jervell-Lange-Nielsen : autossômica recesiva. Em 1957 Hervell e Lange-Nielsen da Suécia Oslo, relatam pela primeira vez a variedade recessiva com surdez associada a QT longo e morte súbita(1).

Esta forma se conhece na língua inglesa com a sigla CSNHL (Congenital Sensory Neural Hearing Loss). [Cardioauditory Syndrome of Jervell and Lange-Nielsen; JLNS; Surdo-Cardiac Syndrome; Long QT Syndrome, Autosomal Recessive. Tem sido demonstrado que pode ocorrer como uma mutação homocigota em KCNQ1 ou KCNE1 com trato dominante e recentemente se identificou uma mutação heterocigota no C-terminal do KCNQ1 (2).
Do Jervell e Lange Nielsen 0,25 a 1% dos surdos-mudos. Uma em cada 300.000 pessoas. São Paulo deveria ter 30 a 40 casos e Bs As no mas de 20
O JTc encontra-se prolongado em crianças surdas mudas portadoras da variante Jervell e Lange-Nielsen de SQTL. Em 1997 Neyroud et al. mostram que a forma recessiva Jervell e Lange-Nielsen é causada por homocigose ou por mutações heterocigotas.

Esta forma recessiva é muitíssimo mais grave que a dominante de Romano Ward sem surdez autossômica dominante.
Na Itália Romano e col(3). descrevem a forma ausossômica dominante sem surdez descrita com arritmia rara que ocorre na idade pediátrica e conduz a fibrilação ventricular.
Ward em Israel em forma independente de Romano descreve em crianças a mesma forma sem surdez (4). Assim, fica conhecida como síndrome de Romano-Ward muito mais frequente que a forma com surdez de Hervell e Lange-Nielsen.

1) Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval, and sudden death, Am Heart J 1957; 54:59-68.
2) Ning L, Moss AJ, Zareba W, Robinson J, Rosero S, Ryan D, Qi M.Novel compound heterozygous mutations in the KCNQ1 gene associated with autosomal recessive long QT syndrome (Jervell and Lange-Nielsen syndrome). Ann Noninvasive Electrocardiol. 2003;8:246-250.

3) Romano C, Gemme G, Pongigglione R. aritmie cardiache rare dell’età pediatrica. Clin Pediatr 1963; 45:656-683.
4) Ward OC. A new familial cardiac syndrome in children. J Irish Med Assoc 1964; 54:103-106.

Andrés R. Pérez Riera

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Y yo que creia que el Sindrome Surdocardiaco, era el de aquel Cardiologo que NO queria escuchar a sus pacientes...o el de aquel cardiologo con predilección por las propuestas de Don Carlos Marx y Trotzsky.

En fin, como se aprende con el Potro...
Adrián Baranchuk

Querido Dr Edgardo: Comparto con el querido Maestro Perez Riera y me encanto su presentación, que impresiona un Síndrome de sordera congénita asociado a transtornos de la conducción y BAV completo en la evolución, me llama la atención no presente QT prolongado y la presencia de retraso madurativo, e hipercolesterolemia severa, las cuales no se encuadran en estos síndromes. Tal vez al finalizar el ateneo nos refiera la corroboración del diagnóstico.

El diagnóstico impresiona ser el referido, como diagnóstico diferencial se me ocurre el hipotiroidismo congénito no diagnosticado. Y el Síndrome de Turner que suele asociarse con hipotiroidismo y otras alteraciones.

Un abrazo y entiéndase lo planteo como diagnóstico diferencial.

Martin Ibarrola

Am Fam Physician.2007 Aug 1;76(3):405-10.Turner syndrome: diagnosis and management.Morgan T.

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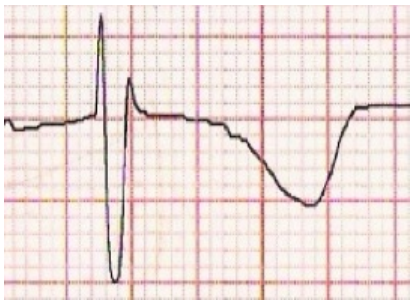
Querido Martín:

¿Te parece que NO tiene un QT prolongado?



Un abrazo

Edgardo Schapachnik

¡Qué caso más bonito! Me gustaría ver la Rx de tórax, porque si el electrodo estaba comandando bien en seno coronario, DI-AVL negativo con V1 positivo, porque decidieron llevarlo al ventriculo derecho, me imagino que tenía umbrales no deseados, abrazos desde el calor de Maracaibo.

Carlos Rodríguez Artuza

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Edgardinho e amigos esta es una forma grave Lhes mando uma revisão infelizemnte em English mas iremos a traduzir para ficar cientes da coisa

**Disease characteristics.**

Jervell and Lange-Nielsen syndrome (JLNS) is characterized by congenital profound bilateral sensorineural hearing loss and long QTc, usually greater than 500 msec. Prolongation of the QTc interval is associated with tachyarrhythmias, including VT, episodes of TdP, and VF, which may culminate in syncope or SD. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. 50% percent of individuals with JLNS had cardiac events before age three years. More than half of untreated children with JLNS die prior to age 15 years.

**Diagnosis/testing**. The diagnosis of JLNS is established in a child with congenital sensorineural deafness, long QT interval, and presence of two disease-causing mutations in either KCNQ1 or KCNE1, the only two genes known to be associated with JLNS. Such molecular genetic testing is clinically available.

**Management**. Treatment of manifestations: cochlear implantation to treat hearing loss; beta-adrenergic blockers for long QT interval; implantable cardioverter defibrillators for those with a history of cardiac arrest and/or failure to respond to other treatments.

**Agents/circumstances to avoid:** drugs that cause further prolongation of the QT interval; activities known to precipitate syncopal events in persons with long QT syndrome.

**Testing of relatives at risk**: hearing evaluation by standard newborn hearing screening programs and electrocardiograms for at-risk sibs; molecular genetic testing to confirm the diagnosis if the disease-causing mutations in an affected family member are known.

**Other:** Train family members in cardiopulmonary resuscitation; wear an ID bracelet explaining the diagnosis; notify local Emergency Medical Services of high-risk persons with JLNS.

**Genetic counseling**. JLNS is inherited in an autosomal recessive manner. Parents of a child with JLNS are usually heterozygotes; rarely, only one parent is a carrier and the other mutation is de novo. Parents may or may not have the long QT syndrome (LQTS) phenotype. At conception, each sib of an affected individual usually has a 25% chance of being affected with JLNS, a 50% chance of being a carrier of a JLNS disease-causing mutation and at risk for LQTS, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutations in the family are known.

## Diagnosis

### Clinical Diagnosis

The diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) is definitively established in individuals with all of the following:

**Congenital sensorineural deafness**

Long QT interval, often manifest as syncope, most often elicited by emotion or exercise

Presence of two disease-causing mutations in either KCNQ1 or KCNE1 [Priori et al 1999]

**Hearing loss**. All individuals with molecularly confirmed JLNS have profound congenital sensorineural deafness (see Deafness and Hereditary Hearing Loss Overview.)

**Long QTc**. Based on existing diagnostic criteria, all individuals with JLNS have a QTc interval greater than 500 msec (average 550 msec), indicating increased time for ventricular depolarization and repolarization [Tyson et al 2000]. Generally, the upper limit of normal for the QTc is 440 msec for males and 460 msec for post-pubertal females [Allan et al 2001, Priori et al 1999].

**Note:** (1) In the "pre-molecular" era, diagnosis of JLNS relied upon clinical criteria alone, and thus it is not currently known how many children with molecularly confirmed JLNS have a borderline QTc interval prolongation of 440 msec to 500 msec or how many children with molecularly confirmed JLNS have a QTc that falls within the "normal" range. This issue will be resolved as data on more affected individuals are gathered. A recent review [Schwartz et al 2006] gives a comprehensive summary of the natural history, molecular basis, and clinical characteristics of 186 affected individuals from 135 families,

in whom mutations were identified in 63 (47%). (2) Hearing loss commonly occurs in the setting of familial long QT syndrome (LQTS) (see Romano-Ward Syndrome). In this situation, the hearing loss may be entirely unrelated to the etiology of the LQTS, particularly if the hearing loss is moderate.

**Molecular Genetic Testing**
Genes. JLNS is caused by mutations in one of two genes: KCNQ1 and KCNE1 [Chen et al 1999, Duggal et al 1998, Neyroud et al 1997, Splawski et al 1997].

KCNQ1 (sometimes called JLN1) mutations account for more than 90% of individuals with JLNS. In a study of ten families, nine had mutations in KCNQ1 [Tyson et al 2000]. In a second study of 63 families, 57 (90.5%) had mutations in KCNQ1 [Schwartz et al 2006]. In a Norwegian study 12 out of 13 unrelated JLNS patients had four different Norwegian founder mutations [Berge et al 2008].

KCNE1 (sometimes called JLN2) mutations account for fewer than 10% of individuals with JLNS. Of 63 families, six (9.5%) had mutations in KCNE1 [Schwartz et al 2006]. None of the Norwegian patients with JLNS have been shown to have KCNE1 mutations [Berge et al 2008, Siem et al 2008, Tranebjaerg et al 1999].

**Clinical testing**

Sequence analysis/mutation scanning. Mutations have been found in either KCNQ1 or KCNE1 in 94% of individuals with clinical JLNS undergoing molecular testing [Schwartz et al 2006]. The mutations may be located in all coding exons. Current experience indicates that 33% are compound heterozygotes [Schwartz et al 2006].

Deletion/duplication analysis. Both deletion and duplication of exon(s) of KCNQ1 are known to cause long QT syndrome [Eddy et al 2008].

Summary of Molecular Genetic Testing Used in Jervell and Lange-Nielsen Syndrome

Gene Symbol / Locus Proportion of JLNS Attributed to Mutations in This Gene Test Method Mutations Detected Mutation Detection Frequency by Gene and by Test Method 1 Test Availability
KCNQ1 90% Deletion / duplication analysis 2 Partial- or complete-gene deletion Unknown Clinical

Sequence analysis / mutation scanning Sequence variants 94% 3
KCNE1 10% Sequence analysis / mutation scanning Sequence variants Clinical

Deletion / duplication analysis 2 Partial- or complete-gene deletion Unknown

Test Availability refers to availability in the GeneTests Laboratory Directory. GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate

directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. Testing that identifies deletions/duplications not detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), and array GH may be used.

3. Schwartz et al [2006]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy
To confirm/establish the diagnosis in a proband

1 Test KCNQ1, as mutations in this gene account for the majority of JLNS. In countries with founder mutations, like Norway, particular mutations should be tested first [Tranebjaerg et al 1999, Tranebjaerg 2004, Berge et al 2008, Siem et al 2008].

2 If no KCNQ1 mutation is identified, test KCNE1.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

**Genetically Related (Allelic) Disorders**
Heterozygosity for mutations in KCNQ1 and KCNE1 has been observed in children without hearing loss who have long QT syndrome (LQTS) inherited in an autosomal dominant manner [Towbin et al 2001] (also called Romano-Ward syndrome) (see Differential Diagnosis).

**Clinical Description**
Natural History
Homozygotes. Deafness is congenital, bilateral, profound, and sensorineural in all individuals with molecularly confirmed Jervell and Lange-Nielsen syndrome (JLNS) (see Deafness and Hereditary Hearing Loss Overview).

Abnormal cardiac depolarization and repolarization may result in prolongation of the QT interval and tachyarrhythmias (including ventricular tachycardia, episodes of torsade de pointes ventricular tachycardia, and ventricular fibrillation), which may culminate in syncope or sudden death. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright.

In the Schwartz et al [2006] study of 135 families with JLNS, the QTc was markedly prolonged (557±65 msec); 50% of individuals had cardiac events before age three years, with emotions and exercise being the primary triggers. Note, however, that selection bias for severely affected individuals cannot be excluded: individuals have been described with putative JLNS without any clinical manifestations other than deafness until adulthood, and to age 50 years in one case.

QTc prolongation in JLNS, particularly when severe, appears to be associated with increased risk of death in infancy (SIDS). Although more than half of untreated children with JLNS die prior to age 15 years, some individuals are reported to have survived several syncopal episodes during adulthood.

The sex ratio among individuals with JLNS is even, but females are at lower risk for cardiac arrest/sudden death [Schwartz et al 2006].

Physical examination is unremarkable except for deafness.

Heterozygotes. Heterozygotes usually have normal hearing. In some individuals who are heterozygous for mutations associated with JLNS, QTc prolongation, fainting, and sudden death never occur. In contrast, some individuals heterozygous for mutations associated with JLNS may have QTc prolongation associated with fainting and death heritable in a dominant manner. This form of LQTS is called Romano-Ward syndrome (RWS). RWS can also be caused by mutations in several genes that do not cause deafness/JLNS in a homozygous form (see Differential Diagnosis.) These mutations may be associated with highly variable QTc intervals, from normal to markedly abnormal.

Histopathology of temporal bone. Histologic examination of a few temporal bones was performed prior to the availability of molecular genetic testing, but not since. In a mouse model with knock-out for the Kcnq1 gene (which can be considered an animal model for JLNS in humans), atrophy of the stria vascularis and collapse of the endolymphatic compartments and surrounding membranes are marked. Complete degeneration of the organ of Corti and associated degeneration of the spiral ganglion were found [Rivas & Francis 2005].

Genotype-Phenotype Correlations
Data to establish better predictors for a correlation between genotype and phenotype were provided from a large number of individuals with molecularly confirmed JLNS. Among 63 individuals who were genotyped, 33% were compound heterozygotes [Schwartz et al 2006]. No clinical difference was evident between persons with at least one complex mutation (insertion/deletion, splice mutation, truncation) and those with missense mutations.

Among six asymptomatic individuals in the study of Schwartz et al [2006], two had KCNQ1 mutations and four had KCNE1 mutations, further confirming the milder presentation of JLNS associated with KCNE1 mutations compared to JLNS associated with KCNQ1 mutations.

**Nomenclature**
Lange-Nielsen syndrome has also been called cardioauditory syndrome of Jervell and Lange-Nielsen and surdo cardiac syndrome.

JLNS is now appreciated to be a true syndrome with both the cardiac and the cochlear pathologies attributable to a common molecular etiology. Although there are several case reports in the older literature of individuals with long QT syndrome and non-profound hearing loss, in many of these reports it is likely that the hearing loss and prolonged QT interval have different etiologies (see Differential Diagnoses).

**Prevalence**
Prevalence varies depending on the population studied:

Norway has an unusually high prevalence of at least one in 200,000 [Tranebjaerg et al 1999]. This prevalence stems from four Norwegian founder mutations [Berge et al 2008, Siem et al 2008]

The syndrome is more common in cultures in which consanguineous marriage is common.

In a study of 350 children with congenital deafness in Turkey, one in 175 had JLNS [Ocal et al 1997].

A particular missense KCNQ1 mutation has been identified in the heterozygous state in autosomal dominant LQTS and in the homozygous state in JLNS in a few individuals from Finland; however, no clustering of JLNS was observed in Finland, in contrast to that observed in several other rare autosomal recessive disorders [Piippo et al 2001].

An overview of worldwide occurrence was published by Tranebjaerg [2004].

These data are the best available; however, diagnostic criteria using a QTc greater than 440 msec in children are likely to include some false positives, perhaps as many as 15%-20% [Allan et al 2001]. The design of the recent review by Schwartz et al [2006] did not allow refinement of prevalence estimates.

**Differential Diagnosis**
For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Deafness and prolonged QTc with or without long QT syndrome (LQTS) both have multiple etiologies, including genetic and environmental causes. In many individuals with both deafness and prolonged QTc (or LQTS), the deafness and prolonged QTc (or LQTS) have separate etiologies. All of these possibilities must be considered in each affected individual, particularly in the absence of parental consanguinity or an affected sib. The following considerations are relevant in an individual who has both deafness and prolonged QTc:

Prior to the availability of molecular genetic testing, the diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) was based on clinical criteria alone. RWS was commonly

diagnosed in persons with LQTS and normal hearing.

Some children with JLNS may be misdiagnosed with epilepsy and incorrectly treated with antiepileptic drugs before the correct diagnosis of JLNS is established [Tranebjaerg et al 1999].

Romano-Ward syndrome (RWS, long QT syndrome). The diagnosis of Romano-Ward syndrome (RWS) is made on the basis of a prolonged QT interval on the ECG or identification of a mutation in KCNQ1 (locus name LQT1), KCNH2 (locus name LQT2), SCN5A (locus name LQT3), KCNE1 (locus name LQT5), or KCNE2 (locus name LQT6) in the absence of profound congenital sensorineural deafness (the presence of which is highly suggestive of Jervell and Lange-Nielsen syndrome). Two other genes, ANK2 and KCNJ2, have been proposed as LQT4 and LQT7, respectively, but uncertainty exists as to whether the long QT syndrome (LQTS) designation is appropriate for these conditions and further study is underway. Diagnostic criteria have been established for the resting ECG QTc value in the absence of specific conditions known to lengthen the QTc interval. Table 2 summarizes the genes known to be associated with RWS. Only KCNQ1 and KCNE1 have been implicated in both RWS and JLNS.

Three families with autosomal recessive Romano-Ward syndrome without hearing loss have been well studied [Larsen et al 1999].

Table 2. Genes Associated with Autosomal Dominant Long QT Syndrome (Romano-Ward Syndrome)

| Locus Name | Gene | Protein Function | Proportion of Individuals with RWS |
|---|---|---|---|
| LQT1 | KCNQ1 | IKs K+ channel α subunit | 55%-60% |
| LQT2 | KCNH2 (HERG) | IKs K+ channel α subunit | 35%-40% |
| LQT3 | SCN5A | INa Na+ channel α subunit | 3%-5% |
| LQT4 | 1 | Unknown | Unknown |
| LQT5 | KCNE1 | IKs K+ β subunit | |
| LQT6 | KCNE2 | IKr K+ channel β subunit | |
| LQT7 | 1 | Unknown | Unknown |

From Keating & Sanguinetti [2001]

LQT = long QT

IKr = rapidly activating delayed rectifier potassium current

IKs = slowly activating delayed rectifier potassium channel

1. From Romano-Ward. Two other genes, ANK2 and KCNJ2, have been proposed as LQT4 and LQT7 respectively, but uncertainty exists as to whether the long QT syndrome (LQTS) designation is appropriate for these conditions; further study is underway.

Other genetic disorders considered to be cardiac channelopathies associated with LQTS

include the following [Ackerman 2005]:

Timothy syndrome

Andersen-Tawil syndrome

Brugada syndrome

Causes of hearing loss. The differential diagnosis for hearing loss includes consideration of other forms of syndromic and nonsyndromic disorders, as well as acquired disorders. For more information on hereditary hearing loss, see Deafness and Hereditary Hearing Loss Overview.

One disorder that should be noted specifically is DFNB1, the most common autosomal recessive form of nonsyndromic hearing loss. DFNB1 is characterized by congenital, non-progressive, mild-to-profound sensorineural hearing impairment. No other associated medical findings are present. Diagnosis of DFNB1 depends on identification of deafness-causing mutations in the GJB2 gene and/or the GJB6 gene, which alter the gap junction beta-2 protein (connexin 26) and the gap junction beta-6 protein (connexin 30), respectively. Molecular genetic testing detects more than 99% of mutations in these genes. JLNS should be suspected in any infant who has profound bilateral sensorineural hearing loss, no identifiable GJB2 or GJB6 mutations, and a normal physical examination.

Acquired causes of LQTS

Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia

Malnutrition or liquid protein diet

Drugs: vasodilators, tricyclic antidepressants, organophosphates, antihistamines, phenothiazines, procainamide, disopyramide, quinidine, and many others. For a complete, updated list seewww.azcert.org.

Primary myocardial problems: cardiomyopathy, myocarditis, ischemia

Central nervous or autonomic system injury; subarachnoid hemorrhage; stellate ganglion blockade

Sudden infant death syndrome (SIDS). Recent data from multicenter studies indicate that 9.5% of sudden infant death syndrome (SIDS) cases may be heterozygous for functionally significant mutations in one of the seven known LQTS genes (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CAV3) [Arnestad et al 2007, Berul & Perry 2007, Wang et al 2007]. Sudden arrhythmic death may thus be an important contributor to SIDS, and it is unknown which proportion of such cases have or would develop profound hearing impairment. Recent implementation of universal neonatal hearing screening, supplemented with early electrocardiography, may have the potential to identify high-risk children.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Jervell and Lange-Nielsen syndrome (JLNS), the following evaluations are recommended:

Formal audiologic evaluation for extent of hearing loss

Cardiac examination including calculation of QTc

A three-generation thorough family history on cardiac disease, syncope, and hearing

### Treatment of Manifestations

Hearing loss in JLNS may be treated successfully with cochlear implantation (CI), an intervention that does not interfere with bipolar pacemakers [Green et al 2000, Chorbachi et al 2002] (see Deafness and Hereditary Hearing Loss Overview). To date, the cumulative published experience is about 15 individuals with JLNS.

Of note, the diagnosis of JLNS was only verified with molecular genetic testing in four Norwegian patients, all of whom had mutations in KCNQ1.

Note: Although cochlear implantation seems safe, special precautions are necessary during anesthesia because of the increased risk of cardiac arrhythmia [Daneshi et al 2008, Siem et al 2008, Yanmei et al 2008].

The main goal in management of JLNS is prevention of syncope, cardiac arrest, and sudden death. Note that efficacy of beta-blocker treatment is only partial: 51% of treated individuals had cardiac events and 27% had cardiac arrest or sudden death. Even with additional therapies (e.g., pacemaker, implantable cardioverter/defibrillator, left sympathetic denervation), 18 of 32 (56%) individuals experienced additional symptoms, including sudden death in seven [Schwartz et al 2006].

Administration of beta-adrenergic blockers has been the traditional first-line medical therapy for cardiac events, but more aggressive immediate treatment may be appropriate. In contrast to Romano-Ward syndrome (RWS), cardiac events in JLNS frequently occur despite beta blockade [Schwartz et al 2006]. Goldenberg et al [2006] demonstrated markedly increased mortality in individuals with JLNS treated exclusively with beta blockers in comparison with individuals with RWS. A mortality rate of 35% over five years was observed for individuals receiving beta blockers exclusively; 86% of individuals treated exclusively with beta blockers experienced a cardiac event. The interactions of beta blockers with other medical conditions (e.g., asthma, diabetes mellitus, depression) should also be considered.

Implantable cardioverter defibrillators (ICDs) should be considered in individuals with a history of cardiac arrest or failure to respond to other treatments [Goel et al 2004]. More recent recommendations have strongly urged ICD placement for high-risk individuals, defined by the following criteria [Schwartz et al 2006]:

QTc interval >550 msec

Syncope before age five years

Male gender, older than age 20 years with KCNQ1 mutation

Sudden cardiac death appears to be low in individuals younger than age five years, but medical therapy should be administered early on in these high-risk individuals and ICD placement should be considered after age five years [Richter & Brugada 2006].

In certain cases, the availability of automated external defibrillators in the home, workplace, or school may be applicable, as is appropriate CPR training of family members and those who have regular contact with individuals with JLNS.

Left cardiac sympathetic denervation has been used with effect for some patients.

Prevention of Primary Manifestations
See Treatment of Manifestations regarding prevention of syncope, cardiac arrest, and sudden death.

Prevention of Secondary Complications
Special precautions during anesthesia are necessary because of the increased risk of cardiac arrhythmia [Daneshi et al 2008, Siem et al 2008, Yanmei et al 2008].

Agents/Circumstances to Avoid
The following should be avoided:

Drugs that cause further prolongation of the QT interval or provoke torsade de pointes; seewww.azcert.orgfor a complete and updated list.

Triggers for intense or sudden emotion; activities that are known to precipitate syncopal events in individuals with long QT syndrome, including:

Competitive sports

Amusement park rides

Scary movies

Jumping into cold water

A cardiologist should make recommendations for activity restrictions based on the effectiveness of medical intervention.

Testing of Relatives at Risk
Standard newborn screening programs are sufficient to identify hearing loss in children with JLNS.

Because of the relationship between JLNS and Romano-Ward syndrome, electrocardiogram should be considered for relatives at risk for JLNS even if they have

normal hearing.

If the JLNS disease-causing mutations in an affected family member are known, molecular genetic testing of a relative with congenital profound sensorineural hearing loss is recommended to confirm the diagnosis of JLNS.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation
SearchClinicalTrials.govfor access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other
Family members of individuals with JLNS should be trained in cardiopulmonary resuscitation (CPR) since up to 95% of individuals with JLNS have a cardiac event before adulthood [Schwartz et al 2006].

Affected individuals should wear an ID bracelet explaining their diagnosis.

It is appropriate to notify local Emergency Medical Services (EMS) of high-risk persons such as those with JLNS [Hazinski et al 2004].

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling
Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance
Jervell and Lange-Nielsen syndrome (JLNS) is inherited in an autosomal recessive manner.

Risk to Family Members
Parents of a proband

Parents of a child with JLNS are usually obligate heterozygotes. In rare cases, only one parent is a carrier and the other mutation is de novo [Schwartz et al 2000].

Parents may or may not have the LQTS phenotype. Studies have documented autosomal dominant inheritance of moderately prolonged QTc intervals in some, but not all, families in which one or more sibs have JLNS [Splawski et al 1997].

Recommendations for evaluation of the parents of a child with JLNS include comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Sibs of a proband

At conception, each sib of an individual with JLNS usually has a 25% chance of being affected with JLNS, a 50% chance of being heterozygous for a JLNS-associated mutation and at risk for LQTS, and a 25% chance of being unaffected and not a carrier. Thus, at conception, each sib of a proband with JLNS has a 3/4 chance of having either JLNS or LQTS.

Sibs with normal hearing have a 2/3 risk of being carriers of a mutation causing JLNS and being at risk for LQTS.

Sibs of a proband who has a de novo mutation are not at increased risk for JLNS but are at 50% risk for LQTS.

Recommendations for evaluation of sibs of a proband with JLNS include: audiologic evaluation, electrophysiologic evaluation for evidence of LQTS, molecular genetic testing if the disease-causing mutations in the proband are known, and comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Offspring of a proband

The offspring of an individual with JLNS inherit one abnormal allele; thus, 100% of the proband's offspring are at risk for LQTS.

In the event that the reproductive partner of the proband is also a carrier for a mutation in the same gene in which two mutations have been identified in the proband, the risk to offspring for JLNS is 50%.

Recommendations for evaluation of the offspring of an individual with JLNS include comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Other family members. Sibs of a proband's parents may also be at 50% risk of having a mutation in KCNE1 or KCNQ1 and at risk for LQTS.

Carrier Detection

Carrier testing is possible for family members once the mutations have been identified in the family.

Related Genetic Counseling Issues
Because prolonged QTc interval in families with JLNS may follow an autosomal dominant inheritance pattern, it is important that family members at risk undergo electrocardiographic testing for evidence of LQTS early in life. Individuals with LQTS are at increased risk for sudden death and thus require cardiologic intervention. The actual risk of LQTS is not known.

Carriers for JLNS have a single mutation in a gene for LQTS that may cause QTc prolongation or LQTS in either a clinically significant or clinically insignificant form. Whether the mutation is clinically significant or insignificant, it may be transmitted in a clinically significant fashion to future generations as either LQTS (i.e., Romano-Ward syndrome) or JLNS, a confusing phenomenon during pedigree evaluation.

Family planning

The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See for a list of laboratories offering DNA banking.

Prenatal Testing
Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements

Requests for prenatal testing for conditions such as LQTS that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see .

## Molecular Genetics

### Molecular Genetic Pathogenesis

Jervell and Lange-Nielsen syndrome (JLNS) is caused by an aberration in a potassium channel found in the stria vascularis of the cochlea (inner ear) and the heart.

KCNQ1 and KCNE1 encode the alpha and beta subunit proteins (KVLQT1/minK) for the slow potassium current, IKs of the cochlea and the heart.

When stimulated by sound, potassium from the scala media of the cochlea passes through the apex of the hair cells, depolarizing the hair cells and causing a calcium-channel-induced release of neurotransmitter onto the auditory nerve. Depolarizations of the auditory nerve are sent centrally where they are perceived as sound. The maintenance of high potassium concentration in the endolymphatic fluid of the inner ear is required for normal hearing. The potassium-rich fluid of the scala media is created by the IKs potassium channels (exclusively KVLQT1/minK) in the stria vascularis.

Malfunction in these channels in the cochlea causes deafness.

Malfunction in these channels in the heart results in abnormal ventricular electrical activity and LQTS.

#### KCNQ1

Normal allelic variants. The gene consists of 16 exons spanning approximately 400 kb. No benign polymorphisms have been identified in the coding region of the gene.

Pathologic allelic variants. At least 13 JLNS-causing mutations in KCNQ1 are known, ten resulting in frameshift and premature truncation [Tyson et al 2000, Wang et al 2002, Ning et al 2003, Zehelein et al 2006].

Normal gene product. The gene product is potassium voltage-gated channel subfamily KQT member 1 (also known as voltage-gated potassium channel protein KvLQT1); this alpha subunit has six transmembrane regions. It co-assembles with the protein encoded by KCNE1 to form the functional channel IKs.

Abnormal gene product. Mutations in the gene result in premature truncation and inability to co-assemble with the protein encoded by KCNE1 to form the functional channel IKs. In vitro, recessive mutations may exhibit a dominant negative effect that is not clinically observed in affected individuals, suggesting post-translational processing effects in vivo.

#### KCNE1

Normal allelic variants. The gene consists of three exons spanning approximately 40 kb. No normal variants have been identified in the coding region of the gene.

Pathologic allelic variants. Four JLNS-causing mutations have been identified in KCNE1, all of which are missense (see Table A).

Normal gene product. Potassium voltage-gated channel subfamily E member 1 (also

known as minK potassium channel protein beta subunit) is a protein of 130 amino acids with one transmembrane region. It co-assembles with the protein encoded by KCNQ1 to form the functional channel IKs.

Abnormal gene product. The specific effect of each mutation differs in the manner in which it impairs potassium channel function.

Resources
See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page.

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Prezado Edgardinho e amigos lhes mando um bom ressumo da entidade,. Mas tarde mando em Spanish.
Andrés R- Pérez Riera

The Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive form of LQTS with associated congenital deafness. It is caused specifically by mutation of the KCNE1 and KCNQ1 genes. In untreated individuals with JLNS, about 50 percent die by the age of 15 years due to ventricular arrhythmias.

This condition is an autosomal recessive disorder that affects an estimated 1.6 to 6 in 1 million children, and is responsible for less than 10 percent of all cases of long QT syndrome.

Mutations in the KCNE1 and KCNQ1 genes causeJervell and Lange-Nielsen syndrome. The proteins produced by these two genes work together to form a potassium channel that transports positively charged potassium ions out of cells. The movement of potassium ions through these channels is critical for maintaining the normal functions of the inner ear and cardiac muscle.

About 90 percent of cases of Jervell and Lange-Nielsen syndrome are caused by mutations in the KCNQ1 gene. KCNE1 mutations are responsible for the remaining 10 percent of cases. Mutations in these genes alter the usual structure and function of potassium channels or prevent the assembly of normal channels. These changes disrupt the flow of potassium ions in the inner ear and in cardiac muscle, leading to the hearing loss and irregular heart rhythm characteristic ofJervell and Lange-Nielsen syndrome.

Disease characteristics.Jervell and Lange-Nielsen syndrome (JLNS) is characterized bycongenitalprofound bilateral sensorineural hearing loss and long QTc, usu ally greater than 500 msec. Prolongation of the QTc interval is associated with tachyarrhythmias, including ventricular tachycardia, episodes oftorsade de pointesventricular tachycardia, and ventricular fibrillation, which may culminate in syncope or sudden death. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. Fifty percent of individuals with JLNS had cardiac events before age three years. More than half of untreated children with JLNS die prior to age 15 years.

Diagnosis/testing.The diagnosis of JLNS is established in a child withcongenitalsensorineural deafness, long QT interval, and presence of twodisease-causing mutationsin eitherKCNQ1orKCNE1, the only twogenesknown to be associated with JLNS. Suchmolecular genetic testingis clinically available.

Management.Treatment of manifestations:cochlear implantation to treat hearing loss; beta-adrenergic blockers for long QT interval; implantable cardioverter defibrillators for those with a history of cardiac arrest and/or failure to respond to other treatments.

Agents/circumstances to avoid:drugs that cause further prolongation of the QT interval; activities known to precipitate syncopal events in persons with long QT syndrome.

Testing of relatives at risk:hearing evaluation by standard newborn hearingscreeningprograms and electrocardiograms for at-risk sibs;molecular genetic testingto confirm the diagnosis if thedisease-causing mutationsin anaffectedfamily member are known.

Other:Train family members in cardiopulmonary resuscitation; wear an ID bracelet explaining the diagnosis; notify local Emergency Medical Services of high-risk persons with JLNS.

Genetic counseling.JLNS is inherited in anautosomal recessivemanner. Parents of a child with JLNS are usuallyheterozygotes; rarely, only one parent is acarrierand the othermutationisde novo. Parents may or may not have the long QT syndrome (LQTS)phenotype. At conception, each sib of anaffectedindividual usually has a 25% chance of beingaffectedwith JLNS, a 50% chance of being acarrierof a JLNSdisease-causing mutationand at risk for LQTS, and a 25% chance of beingunaffectedand not acarrier.Carrier testingfor at-risk relatives and prenatal testing for pregnancies at increased risk are possible if thedisease-causing mutationsi n the family are known.

**Clinical Diagnosis**

The diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) is definitively established in individuals with all of the following:

•Congenitalsensorineural deafness

•Long QT interval, often manifest as syncope, most often elicited by emotion or exercise

•Presence of twodisease-causing mutationsin eitherKCNQ1orKCNE1[Priori et al 1999]

Hearing loss.All individuals with molecularly confirmed JLNS have profoundcongenitalsensorineural deafness (seeDeafness and Hereditary Hearing Loss Overview.)

Long QTc.Based on existing diagnostic criteria, all individuals with JLNS have a QTc interval greater than 500 msec (average 550 msec), indicating increased time for ventricular depolarization and repolarization [Tyson et al 2000]. Generally, the upper limit of normal for the QTc is 440 msec for males and 460 msec for post-pubertal females [Allan et al 2001,Priori et al 1999].

Note: (1) In the "pre-molecular" era, diagnosis of JLNS relied upon clinical criteria alone, and thus it is not currently known how many children with molecularly confirmed JLNS have a borderline QTc interval prolongation of 440 msec to 500 msec or how many children with molecularly confirmed JLNS have a QTc that falls within the "normal" range. This issue will be resolved as data on moreaffectedindividuals are gathered. A recent review [Schwartz et al 2006] gives a comprehensive summary of the natural history, molecular basis, and clinical characteristics of 186affectedindividua ls from 135 families, in whommutationswere identified in 63 (47%). (2) Hearing loss commonly occurs in the setting offamiliallong QT syndrome (LQTS) (seeRomano-Ward Syndrome). In this

situation, the hearing loss may be entirely unrelated to the etiology of the LQTS, particularly if the hearing loss is moderate.

**Molecular Genetic Testing**

Genes.JLNS is caused bymutationsin one of twogenes:KCNQ1andKCNE1[Chen et al 1999,Duggal et al 1998,Neyroud et al 1997,Spla wski et al 1997].

•KCNQ1(sometimes calledJLN1)mutationsaccount for more than 90% of individuals with JLNS. In a study of ten families, nine hadmutationsinKCNQ1[Tyson et al 2000]. In a second study of 63 families, 57 (90.5%) hadmutationsinKCNQ1[Schwartz et al 2006]. In a Norwegian study 12 out of 13 unrelated JLNS patients had four different Norwegian foundermutations[Berge et al 2008].

•KCNE1(sometimes calledJLN2)mutationsaccount for fewer than 10% of individuals with JLNS. Of 63 families, six (9.5%) hadmutationsinKCNE1[Schwartz et al 2006]. None of the Norwegian patients with JLNS have been shown to haveKCNE1mutations[Berge et al 2008,Siem et al 2008,Tranebjaerg et al 1999].

**Clinical testing**

•Sequence analysis/mutation scanning.Mutationshave been found in eitherKCNQ 1orKCNE1in 94% of individuals with clinical JLNS undergoing molecular testing [Schwartz et al 2006]. Themutationsmay be located in all codingexons. Current experience indicates that 33% arecompound heterozygotes[Schwartz et al 2006].

•Deletion/duplication analysis.Bothdeletionandduplicationofexon(s) ofKCNQ1are known to cause long QT syndrome [Eddy et al 2008].

Table 1. Summary ofMolecular Genetic TestingUsed in Jervell and Lange-Nielsen Syndrome

| Gene Symbol/Locus | Proportion of JLNS Attributed toMutationsin ThisGene | Test Method | MutationsDetected | MutationDetection Frequency byGeneand by Test Method[1] | Test Availability |
|---|---|---|---|---|---|
| *KCNQ1* | 90% | Deletion/duplicationanalysis[2] | Partial- or complete-genedeletion | Unknown | Clinical |
| | | Sequence analysis/mutation scanning | Sequence variants | 94%[3] | |
| *KCNE1* | 10% | Sequence analysis/mutation scanning | Sequence variants | | Clinical |
| | | Deletion/duplicationanalysis | Partial- or | Unknown | |

| | | |
|---|---|---|
| | $s^2$ | complete-genedeletion |

Test Availability refers to availability in theGeneTests Laboratory Directory.GeneReviewsdesignates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly wit h the laboratories to verify information.

1. The ability of the test method used to detect amutationthat is present in the indicatedgene

2. Testing that identifiesdeletions/duplicationsnot detectable bysequence analysisof genomicDNA; a variety of methods includingquantitative PCR, real-timePCR, multiplex ligation-dependentprobeamplification (MLPA), andarray GHmay be used.

3.Schwartz et al [2006]

Interpretation of test results.For issues to consider in interpretation ofsequence analysisresults, clickhere.

**Testing Strategy**

To confirm/establish the diagnosis in aproband

•1

TestKCNQ1, asmutationsin thisgeneaccount for the majority of JLNS. In countries with foundermutations, like Norway, particularmutationsshould be tested first [Tranebjaerg et al 1999,Tranebjaerg 2004,Berge et al 2008,Siem et al 2008].

•2

If noKCNQ1mutationis identified, testKCNE1.

Carrier testingfor at-risk relativesrequires prior identification of thedisease-causing mutationsin the family.

Note:Carriersareheterozygotesfor thisautosomal recessivedisorder.

Prenatal diagnosisand preimplantation genetic diagnosis (PGD)for at-risk pregnancies require prior identification of thedisease-causing mutationsin the family.

**Genetically Related (Allelic) Disorders**

Heterozygosity formutationsinKCNQ1andKCNE1has been observed in children without hearing loss who have long QT syndrome (LQTS) inherited in anautosomal dominantmanner [Towbin et al 2001] (also calledRomano-Ward syndrome) (seeDifferential Diagnosis).

## Clinical Description

### Natural History

Homozygotes.Deafness iscongenital, bilateral, profound, and sensorineural in all individuals with molecularly confirmed Jervell and Lange-Nielsen syndrome (JLNS) (seeDeafness and Hereditary Hearing Loss Overview).

Abnormal cardiac depolarization and repolarization may result in prolongation of the QT interval and tachyarrhythmias (including ventricular tachycardia, episodes oftorsade de pointesventricular tachycardia, and ventricular fibrillation), which may culminate in syncope or sudden death. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright.

In theSchwartz et al [2006]study of 135 families with JLNS, the QTc was markedly prolonged (557±65 msec); 50% of individuals had cardiac events before age three years, with emotions and exercise being the primary triggers. Note, however, that selection bias for severelyaffectedindividuals cannot be excluded: individuals have been described with putative JLNS without any clinical manifestations other than deafness until adulthood, and to age 50 years in one case.

QTc prolongation in JLNS, particularly when severe, appears to be associated with increased risk of death in infancy (SIDS). Although more than half of untreated children with JLNS die prior to age 15 years, some individuals are reported to have survived several syncopal episodes during adulthood.

The sex ratio among individuals with JLNS is even, but females are at lower risk for cardiac arrest/sudden death [Schwartz et al 2006].

Physical examination is unremarkable except for deafness.

Heterozygotes.Heterozygotesusually have normal hearing. In some individuals who are heterozygous formutationsassociated with JLNS, QTc prolongation, fainting, and sudden death never occur. In contrast, some individuals heterozygous formutationsassociated with JLNS may have QTc prolongation associated with fainting and death heritable in adominantmanner. This form of LQTS is calledRomano-Ward syndrome< /span>(RWS). RWS can also be caused bymutationsin severalgenesthat do not cause deafness/JLNS in a homozygous form (seeDifferential Diagnosis.) Thesemutationsmay be associated with highly variable QTc intervals, from normal to markedly abnormal.

Histopathology of temporal bone.Histologic examination of a few temporal bones was performed prior to the availability ofmolecular genetic testing, but not since. In a mouse model with knock-out for theKcnq1gene(which can be considered an animal model for JLNS in humans), atrophy of the stria vascularis and collapse of the endolymphatic compartments and surrounding membranes are marked. Complete degeneration of the organ of Corti and associated degeneration of the spiral ganglion were found [Rivas & Francis 2005].

**Genotype-Phenotype Correlations**

Data to establish better predictors for a correlation betweengenotypeandphen otypewere provided from a large number of individuals with molecularly confirmed JLNS. Among 63 individuals who were genotyped, 33% werecompound heterozygotes[Schwartz et al 2006]. No clinical difference was evident between persons with at least one complexmutation(insertion/deletion, splicemutation, truncation) and those withmissense mutations.

Among six asymptomatic individuals in the study ofSchwartz et al [2006], two hadKCNQ1mutationsand four hadKCNE1mutations, further confirming the milder presentation of JLNS associated withKCNE1mutationscompared to JLNS associated withKCNQ1mutations.

**Nomenclature**

Lange-Nielsen syndrome has also been called cardioauditory syndrome of Jervell and Lange-Nielsen and surdo cardiac syndrome.

JLNS is now appreciated to be a true syndrome with both the cardiac and the cochlear pathologies attributable to a common molecular etiology. Although there are several case reports in the older literature of individuals with long QT syndrome and non-profound hearing loss, in many of these reports it is likely that the hearing loss and prolonged QT interval have different etiologies (seeDifferential Diagnoses).

**Prevalence**

Prevalence varies depending on the population studied:

•Norwayhas an unusually high prevalence of at least one in 200,000 [Tranebjaerg et al 1999]. This prevalence stems from four Norwegian foundermutations[Berge et al 2008,Siem et al 2008]

•The syndrome is more common in cultures in which consanguineous marriage is common.

•In a study of 350 children withcongenitaldeafness in Turkey, one in 175 had JLNS [Ocal et al 1997].

•A particular missenseKCNQ1mutationhas been identified in the heterozygous state inautosomal dominantLQTS and in the homozygous state in JLNS in a few individuals from Finland; however, no clustering of JLNS was observed in Finland, in contrast to that observed in several other rareautosomal recessivedisorders [Piippo et al 2001].

•An overview of worldwide occurrence was published byTranebjaerg [2004].

These data are the best available; however, diagnostic criteria using a QTc greater than 440 msec in children are likely to include some false positives, perhaps as many as 15%-20% [Allan et al 2001]. The design of the recent review bySchwartz et al [2006]did not allow refinement of prevalence estimates.

**Differential Diagnosis**

For current information on availability of genetic testing for disorders included in this section, seeGeneTests Laboratory Directory.—ED.

Deafness and prolonged QTc with or without long QT syndrome (LQTS) both have multiple etiologies, including genetic and environmental causes. In many individuals with both deafness and prolonged QTc (or LQTS), the deafness and prolonged QTc (or LQTS) have separate etiologies. All of these possibilities must be considered in eachaffectedindividual, particularly in the absence of parental < /span>consanguinityor anaffectedsib. The following considerations are relevant in an individual who has both deafness and prolonged QTc:

•Prior to the availability ofmolecular genetic testing, the diagnosis of Jervell and Lange-Nielsen syndrome (JLNS) was based on clinical criteria alone. RWS was commonly diagnosed in persons with LQTS and normal hearing.

•Some children with JLNS may be misdiagnosed with epilepsy and incorrectly treated with antiepileptic drugs before the correct diagnosis of JLNS is established [Tranebjaerg et al 1999].

Romano-Ward syndrome(RWS, long QT syndrome).The diagnosis of Romano-Ward syndrome (RWS) is made on the basis of a prolonged QT interval on the ECG or identification of amutationinKCNQ1(locus nameLQT1),KCNH2(locus nameLQT2),SCN5A(locus nameLQT3),KCNE1(locus nameLQT5), orKCNE2(locus nameLQT6) in the absence of profoundcongenitalsens orineural deafness (the presence of which is highly suggestive of Jervell and Lange-Nielsen syndrome). Two othergenes,ANK2andKCNJ2, have been proposed as LQT4 and LQT7, respectively, but uncertainty exists as to whether the long QT syndrome (LQTS) designation is appropriate for these conditions and further study is underway. Diagnostic criteria have been established for the resting ECG QTc value in the absence of specific conditions known to lengthen the QTc interval.Table 2summarizes thegenesknown to be associated with RWS. OnlyKCNQ1andKCNE1have been implicated in both RWS and JLNS.

Three families withautosomal recessiveRomano-Ward syndrome without hearing loss have been well studied [Larsen et al 1999].

Table 2.GenesAssociated withAutosomal DominantLong QT Syndrome (Romano-Ward Syndrome)

| Locus Name | Gene | Protein Function | Proportion of Individuals with RWS |
|---|---|---|---|
| LQT1 | *KCNQ1* | $I_{Ks}$K+ channelαsubunit | 55%-60% |
| LQT2 | *KCNH2*(*HERG*) | $I_{Ks}$K+ channelαsubunit | 35%-40% |
| LQT3 | *SCN5A* | $I_{Na}$Na+ channel α | 3%-5% |

| | | |
|---|---|---|
| | | subunit |
| LQT4[1] | Unknown | Unknown |
| LQT5 | *KCNE1* | $I_{Ks}$K+ β subunit |
| LQT6 | *KCNE2* | $I_{Kr}$K+ channelβsubunit |
| LQT7[1] | Unknown | Unknown |

FromKeating & Sanguinetti [2001]

LQT = long QT

$I_{Kr}$= rapidly activating delayed rectifier potassium current

$I_{Ks}$= slowly activating delayed rectifier potassium channel

1.FromRomano-Ward. Two othergenes,ANK2andKCNJ2, have been proposed as LQT4 and LQT7 respectively, but uncertainty exists as to whether the long QT syndrome (LQTS) designation is appropriate for these conditions; further study is underway.

Other genetic disorders considered to be cardiac channelopathies associated with LQTS include the following [Ackerman 2005]:

•Timothy syndrome

•Andersen-Tawil syndrome

•Brugada syndrome

Causes of hearing loss.The differential diagnosis for hearing loss includes consideration of other forms of syndromic and nonsyndromic disorders, as well as acquired disorders. For more information on hereditary hearing loss, seeDeafness and Hereditary Hearing Loss Overview.

One disorder that should be noted specifically isDFNB1, the most commonautosomal recessiveform of nonsyndromic hearing loss. DFNB1 is characterized bycongenital, non-progressive, mild-to-profound sensorineural hearing impairment. No other associated medical findings are present. Diagnosis of DFNB1 depends on identification of deafness-causingmutationsin theGJB2geneand/or theGJB6gene, which alter the gap junction beta-2 protein (connexin 26) and the gap junction beta-6 protein (connexin 30), respectively.Molecular genetic testingdetects more than 99% ofmutationsin thesegenes. JLNS should be suspected in any infant who has profound bilateral sensorineural hearing loss, no identifiableGJB2orGJB6mutations, and a normal physical examination.

**Acquired causes of LQTS**

•Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia

•Malnutrition or liquid protein diet

•Drugs: vasodilators, tricyclic antidepressants, organophosphates, antihistamines, phenothiazines, procainamide, disopyramide, quinidine, and many others. For a complete, updated list seewww.azcert.org.

•Primary myocardial problems: cardiomyopathy, myocarditis, ischemia

•Central nervous or autonomic system injury; subarachnoid hemorrhage; stellate ganglion blockade

Sudden infant death syndrome (SIDS).Recent data from multicenter studies indicate that 9.5% of sudden infant death syndrome (SIDS) cases may be heterozygous for functionally significantmutationsin one of the seven known LQTSgenes(KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CAV3) [Arnestad et al 2007,Berul & Perry 2007,Wang et al 2007].Sudden arrhythmic death may thus be an important contributor to SIDS, and it is unknown which proportion of such cases have or would develop profound hearing impairment. Recent implementation of universal neonatal hearingscreening, supplemented with early electrocardiography, may have the potential to identify high-risk children.

**Management**

**Evaluations Following Initial Diagnosis**

To establish the extent of disease in an individual diagnosed with Jervell and Lange-Nielsen syndrome (JLNS), the following evaluations are recommended:

•Formal audiologic evaluation for extent of hearing loss

•Cardiac examination including calculation of QTc

•A three-generation thoroughfamily historyon cardiac disease, syncope, and hearing

**Treatment of Manifestations**

Hearing loss in JLNS may be treated successfully with cochlear implantation (CI), an intervention that does not interfere with bipolar pacemakers [Green et al 2000,Chorbachi et al 2002Deafness and Hereditary Hearing Loss Overview). To date, the cumulative published experience is about 15 individuals with JLNS.

Of note, the diagnosis of JLNS was only verified withmolecular genetic testingin four Norwegian patients, all of whom hadmutationsinKCNQ1.

Note: Although cochlear implantation seems safe, special precautions are necessary during anesthesia because of the increased risk of cardiac arrhythmia [Daneshi et al 2008,Siem et al 2008Yanmei et al 2008].

The main goal in management of JLNS is prevention of syncope, cardiac arrest, and sudden death. Note that efficacy of beta-blocker treatment is only partial: 51% of treated individuals had cardiac events and 27% had cardiac arrest or sudden death. Even with additional therapies (e.g., pacemaker, implantable cardioverter/defibrillator, left sympathetic denervation), 18 of 32 (56%) individuals experienced additional symptoms, including sudden death in seven [Schwartz et al 2006].

•Administration of beta-adrenergic blockers has been the traditional first-line medical therapy for cardiac events, but more aggressive immediate treatment may be appropriate. In contrast toRomano-Ward syndrome(RWS), cardiac events in JLNS frequently occur despite beta blockade [Schwartz et al 2006].Goldenberg et al [2006]demonstrated markedly increased mortality in individuals with JLNS treated e xclusively with beta blockers in comparison with individuals with RWS. A mortality rate of 35% over five years was observed for individuals receiving beta blockers exclusively; 86% of individuals treated exclusively with beta blockers experienced a cardiac event. The interactions of beta blockers with other medical conditions (e.g., asthma, diabetes mellitus, depression) should also be considered.

•Implantable cardioverter defibrillators (ICDs) should be considered in individuals with a history of cardiac arrest or failure to respond to other treatments [Goel et al 2004]. More recent recommendations have strongly urged ICD placement for high-risk individuals, defined by the following criteria [Schwartz et al 2006]:

- QTc interval >550 msec
- Syncope before age five years
- Male gender, older than age 20 years withKCNQ1mutation

Sudden cardiac death appears to be low in individuals younger than age five years, but medical therapy should be administered early on in these high-risk individuals and ICD placement should be considered after age five years [Richter & Brugada 2006].

•In certain cases, the availability of automated external defibrillators in the home, workplace, or school may be applicable, as is appropriate CPR training of family members and those who have regular contact with individuals with JLNS.

•Left cardiac sympathetic denervation has been used with effect for some patients.

**Prevention of Primary Manifestations**

SeeTreatment of Manifestationsregarding prevention of syncope, cardiac arrest, and sudden death.

**Prevention of Secondary Complications**

Special precautions during anesthesia are necessary because of the increased risk of cardiac arrhythmia [Daneshi et al 2008,Siem et al 2008,Yanmei et al 2008].

**Agents/Circumstances to Avoid**

The following should be avoided:

•Drugs that cause further prolongation of the QT interval or provoketorsade de pointes; seewww.azcert.orgfor a complete and updated list.

•Triggers for intense or sudden emotion; activities that are known to precipitate syncopal events in individuals with long QT syndrome, including:

- Competitive sports

- Amusement park rides
- Scary movies
- Jumping into cold water

A cardiologist should make recommendations for activity restrictions based on the effectiveness of medical intervention.

**Testing of Relatives at Risk**

Standardnewborn screeningprograms are sufficient to identify hearing loss in children with JLNS.

Because of the relationship between JLNS and Romano-Ward syndrome, electrocardiogram should be considered for relatives at risk for JLNS even if they have normal hearing.

If the JLNSdisease-causing mutationsin anaffected< /span>family member are known,molecular genetic testingof a relative withcongenitalprofound sensorineural hearing loss is recommended to confirm the diagnosis of JLNS.

SeeGenetic Counselingfor issues related to testing of at-risk relatives forgenetic counselingpurposes.

**Therapies Under Investigation**

SearchClinicalTrials.govfor access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

**Other**

Family members of individuals with JLNS should be trained in cardiopulmonary resuscitation (CPR) since up to 95% of individuals with JLNS have a cardiac event before adulthood [Schwartz et al 2006].

Affectedindividuals should wear an ID bracelet explaining their diagnosis.

It is appropriate to notify local Emergency Medical Services (EMS) of high-risk persons such as those with JLNS [Hazinski et al 2004].

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment,mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resou rces. See theGeneTests Clinic Directory.

SeeConsumer Resourcesfor disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

**Genetic Counseling**

Genetic counselingis the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with geneticrisk

assessmentand the use offamily historyand genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a gene tics orprenatal diagnosisclinic, see theGeneTests Clinic Directory.

**Mode of Inheritance**

Jervell and Lange-Nielsen syndrome (JLNS) is inherited in anautosomal recessivemanner.

**Risk to Family Members**

Parents of aproband

•Parents of a child with JLNS are usuallyobligate heterozygotes. In rare cases, only one parent is acarrierand the othermutationisde novo[< /span>Schwartz et al 2000].

•Parents may or may not have the LQTSphenotype. Studies have documentedautosomal dominantinheritance of moderately prolonged QTc intervals in some, but not all, families in which one or more sibs have JLNS [Splawski et al 1997].

•Recommendations for evaluation of the parents of a child with JLNS include comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Sibs of aproband

•At conception, each sib of an individual with JLNS usually has a 25% chance of beingaffectedwith JLNS, a 50% chance of being heterozygous for a JLNS-associatedmutationand at risk for LQTS, and a 25% chance of beingunaffectedand not acarrier. Thus, at conception, each sib of aprobandwith JLNS has a 3/4 chance of having either JLNS or LQTS.

•Sibs with normal hearing have a 2/3 risk of beingcarriersof amutationcausing JLNS and being at risk for LQTS.

•Sibs of aprobandwho has ade novomutationare not at increased risk for JLNS but are at 50% risk for LQTS.

•Recommendations for evaluation of sibs of aprobandwith JLNS include: audiologic evaluation, electrophysiologic evaluation for evidence of LQTS,molecular genetic testingif thedisease-causing mutationsin theprobandare known, and comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Offspring of aproband

•The offspring of an individual with JLNS inherit one abnormalallele; thus, 100% of theproband's offspring are at risk for LQTS.

•In the event that the reproductive partner of theprobandis also acarrierfor amutationin the samegenein which twomutationshave been identified in theproband, the risk to offspring for JLNS is 50%.

•Recommendations for evaluation of the offspring of an individual with JLNS include comprehensive electrocardiographic testing for evidence of QTc prolongation by a physician familiar with LQTS.

Other family members.Sibs of aproband's parents may also be at 50% risk of having amutationinKCNE1orKCNQ1and at risk for LQTS.

**Carrier Detection**

Carrier testingis possible for family members once themutationshave been identified in the family.

**Related Genetic Counseling Issues**

Because prolonged QTc interval in families with JLNS may follow anautosomal dominantinheritance pattern, it is important that family members at risk undergo electrocardiographic testing for evidence of LQTS early in life. Individuals with LQTS are at increased risk for sudden death and thus require cardiologic intervention. The actual risk of LQTS is not known.

Carriersfor JLNS have a singlemutationin agenefor LQTS that may cause QTc prolongation or LQTS in either a clinically significant or clinically insignificant form. Whether themutationis clinica lly significant or insignificant, it may be transmitted in a clinically significant fashion to future generations as either LQTS (i.e.,Romano-Ward syndrome) or JLNS, a confusing phenomenon duringpedigreeevaluation.

**Family planning**

•The optimal time for determination of genetic risk, clarification ofcarrierstatus, and discussion of the availability of prenatal testing is before pregnancy.

•It is appropriate to offergenetic counseling(including discussion of potential risks to offspring and reproductive options) to young adults who areaffected, arecarriers, or are at risk of beingcarriers.

DNA bankingis the storage ofDNA(typically ex tracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding ofgenes,mutations, and diseases will improve in the future, consideration should be given to bankingDNAofaffectedindividuals. Seefor a list of laboratories offeringDNA banking.

**Prenatal Testing**

Prenatal diagnosisfor pregnancies at increased risk is possible by analysis ofDNAextracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causingallelesof anaffectedfamily member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements

Requests for prenatal testing for conditions such as LQTS that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD)may be available for families in which thedisease-causing mutationshave been identified. For laboratories offering PGD, see.

**Molecular Genetics**

**Molecular Genetic Pathogenesis**

Jervell and Lange-Nielsen syndrome (JLNS) is caused by an aberration in a potassium channel found in the stria vascularis of the cochlea (inner ear) and the heart.

•KCNQ1andKCNE1encode the alpha and beta subunit proteins ($K_V$LQT1/minK) for the slow potassium current, $I_{Ks}$of the cochlea and the heart.

•When stimulated by sound, potassium from the scala media of the cochlea passes through the apex of the hair cells, depolarizing the hair cells and causing a calcium-channel-induced release of neurotransmitter onto the auditory nerve. Depolarizations of the auditory nerve are sent centrally where they are perceived as sound. The maintenance of high potassium concentration in the endolymphatic fluid of the inner ear is required for normal hearing. The potass ium-rich fluid of the scala media is created by the $I_{Ks}$potassium channels (exclusively $K_V$LQT1/minK) in the stria vascularis.

•Malfunction in these channels in the cochlea causes deafness.

•Malfunction in these channels in the heart results in abnormal ventricular electrical activity and LQTS.

***KCNQ1***

Normal allelic variants.Thegeneconsists of 16exonsspanning approximately 400 kb. No benignpolymorphismshave been identified in thecoding regionof thegene.

Pathologic allelic variants.At least 13 JLNS-causingmutationsinKCNQ1are known, ten resulting in frameshift and premature truncation [Tyson et al 2000,Wang et al 2002,Ning et al 2003,Zehelein et al 2006].

Normalgene product.Thegene productis potassium voltage-gated channel subfamily KQT member 1 (also known as voltage-gated potassium channel protein KvLQT1); this alpha subunit has six transmembrane regions. It co-assembles with the protein encoded byKCNE1to form the functional channel $I_{Ks}$.

Abnormalgene product.Mutationsin thegeneresult in premature truncation and inability to co-assemble with the protein encoded byKCNE1to form the functional channel $I_{Ks}$. In vitro,recessivemutationsmay exhibit adominantnegative effect that is not clinically observed inaffectedindividuals, suggesting post-translational processing effects in vivo.

***KCNE1***

Normal allelic variants.Thegeneconsists of threeexonsspanning approximately 40 kb. No normal variants have been identified in thecoding regionof thegene.

Pathologic allelic variants.Four JLNS-causingmutationshave been identified inKCNE1, all of which are missense (seeTable A).

Normalgene product.Potassium voltage-gated channel subfamily E member 1 (also known as minK potassium channel protein beta subunit) is a protein of 130 amino acids with one transmembrane region. It co-assembles with the protein encoded byKCNQ1to form the functional channel $I_{Ks}$.

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Fijate bien Edgardinho el LQT3

**CARACTERÍSTICAS DA VARIANTE SQT3**

Dr Andrés Ricardo Pérez Riera
Professor da Faculdade de Medicina do ABC. Chefe do Setor de Eletrovetrocardiografia -Fundação Santo André – Santo André – São Paulo – Brasil.

NOME: SQT3;

GENE AFETADO: SCN5A

CROMOSSOMO: 3. Mapeado pela primeira vez em 1994 por Jiang e col1. Mais tarde se detecta no gene SCN5A uma mutação p21-24 no cromossomo 3 por Wang e col2.

MUTAÇÃO: 3p21-24

NÚMERO OMIM: 600163

CANAL AFETADO: Canal de Na+

FASE DO PA AFETADA: Platô, dome ou fase 2

TRANSMISSÃO: Autossômica dominante. Em 1998 a Dra. Silvia Priori et al. mostra a primeira evidência que a síndrome de Romano-Ward (SRW) pode ser recessiva3. Observação: Todas as SQT3 correspondem a SRW, porém, a recíproca não é verdadeira porque a SRW pode ser tipo 4 (SQT4), SQT2 7(HERG) e SQT5 21q22.1 (Mink) 4;

DEFLAGRADORES ("Triggers"): Sono, vagotonia noturna. A maioria dos eventos ocorrem durante o sono ou no repouso (61%) 5. Contrariamente na do que na SQT1 ocorrem quase exclusivamente durante o esforço ou estresse;
FENÓTIPO

A) Clínico: Há referência que SQT3 pode estar associada a sindactilia6;

B) Eletrocardiográfico:

1) Freqüência cardíaca: tendência a bradicardia em relação à idade e em alguns casos se ha observado diminuição durante os rising efforts. Quando a FC aumenta o intervalo QT encurta mais na SQT3 do que nas SQT1e SQT2;

2) Intervalo PR: Usualmente normal. Porém, nos encontramos uma família com PR curto.

3) Segmento ST: prolongamento significativo. Conseqüência: aparecimento tardio da onda T. A mutação delta KPQ ocasiona entrada pequena e persistente Na+ em fase 2 com reabertura tardia o que explica o prolongamento do intervalo QT.

4) Dependência do intervalo QT da freqüência cardíaca: significativa.

5) Intervalo QT: Na variante SQT3 costuma ser mais longo do que nas SQT1 e SQT2.

6) Onda U: pode ser proeminente em muitos casos como conseqüência de repolarização mais longa da célula M. Aumenta nas bradicardia e nas pausas e pode apresentar polaridade alternante.

7) Dispersão do intervalo QT: acentuada7. Por sua vez este fato é um marcador de risco para o aparecimento de arritmais8.

RESPOSTA À PROVA DE ESFORÇO ("Exercise Stress Testing"): ocasionalmente pode ser observada normalização das alterações da repolarização ventricular. Nas variantes SQT1 e SQT2 pode desencadear os eventos taquiarrítmicos.

INCIDÊNCIA RELATIVA: quando comparado às formas SQTL1 e SQT2. A menos freqüente 1%.

NÚMERO DE EVENTOS: menor do que na SQT1 eSQT2;
LETALIDADE DOS EVENTOS: maior do que na SQT1 eSQT2

LETALIDADE CUMULATIVA: Semelhante nas três variantes

ALELOS:

1) Enfermidade de Brugada;

2) Formas mistas com a doença de Brugada;

3) Fibrilação ventricular idiopática genuína (FVIG).

4) Doemça de Lenègre
ENFERMIDADE DE BRUGADA: Esta variante considera-se alélica com a doença de Brugada. Por isso se diz que é a “imagem em espelho” da SQT3 porque ambas afetam a subunidade alfa do canal de Na+ e são autossômicas dominantes. Aproximadamente 2/3 dos casos do Brugada são esporádicos (síndrome de Brugada) e apenas 1/3 há herança autossômica dominante com historia familiar positiva. A demonstração genética é possível em apenas 15% a 20% dos casos (enfermidade de Brugada).
FORMAS MISTAS COM A DOENÇA DE BRUGADA O canal de Na+ no gene SCN5A está envolvido tanto na doença de Brugada quanto na SQT3. Estes síndromes resultam de efeitos opostos sobre o canal. Assim, no Brugada a mutação ocasiona redução da entrada de Na+ ao passo que na SQTL3 está associada a ganho na função com entrada lenta do cátion na fase 2.
Pesquisas assinalam a existências de formas mistas caracterizada por sobreposição de manifestações fenotípicas com intervalo QTc prolongado e supradesnivelamento do segmento ST de V1 a V2 ou V3.
Flecainide droga empregada para desmascarar a doença de Brugada pode ocasionar supradesnivelamento do segmento ST em alguns pacientes com SQT39.
FIBRILAÇÃO VENTRICULAR IDIOPÁTICA GENUINA (FVIG): A FVIG, a variante SQT3 e a enfermidade de Brugada afetam o mesmo gene SCN5A, ocupam o mesmo número OMIM (600163) e o mesmo loco (3p21-p24).

DROGAS QUE MELHORAM A REPOLARIZAÇÃO

1) Mexiletina;

2) Flecainamida

1) Mexiletina: um antiarrítmico da classe 1B denominado lidocaina-like – resulta ser muito eficaz para encurtar o QT apenas na SQT3. Esta variedade apresenta uma onda T de aparecimento tardio por prolongamento do segmento ST como conseqüência da entrada permanente de Na+. Nestes pacientes, mexiletine encurta significativamente o QTc evitando o aparecimento das TdP. Curiosamente, a droga não encurta o QT longo da síndrome do QT congênita que afeta o canal de K+ (defeito HERG do canal de K+) denominada SQT210-11.
A droga não encurta o QT longo da síndrome do QT congênita que afeta o canal de K+ (defeito HERG do canal de K+) ou SQT212.
2) Flecainide: esta droga tem sido proposta e parece promissora para o tratamento via oral a baixas na SQT3 em pacientes com a mutação DeltaKPQ no gene of SCN5A. Ocasiona bloqueio na entrada tardia de Na+13.
DROGAS QUE PIORAM A REPOLARIZAÇÃO
Os beta-bloqueadores possuem efeito protetor nas SQT1 e SQT2, mais podem desencadear TdP na SQT314.

DROGA QUE SIMULA A VARIANTE SQT3
A droga conhecida como ATX-II ocasiona aumento da entrada de Na+ tardia INa podendo assim simular a situação da SQT3 prolongando a duração do segmento ST e ocasionando onda T tardia e QT longo. Este prolongamento do ST por aumento na entrada tardia de Na+ parece mais intenso nas células M do que nas endocárdicas e epicárdica o que aumenta a dispersão da repolarização. Este maior aumento nas células M obedece a que as mesmas possuem um canal tardio de Na+ maior15.

TRATAMENTO
Na SQTL1 e SQT2 se beneficiam mais com os beta-bloqueadores. Na SQT3 estas drogas podem ser prejudiciais. Esta é a variante que melhor responde ao marcapasso. Alguns pacientes podem apresentar pausas súbitas do ritmo sinusal que ultrapassam os 1,2 segundos não precedidas por alterações na freqüência cardíaca. Elas podem ser importante no início das arritmias em pacientes com SQTL e freqüentemente precedem o início das TdP assinalando a indicação do marcapasso como escolha terapêutica;
Eventualmente pelo Holter pode-se registrar as características do começo dos surtos das TdP, isto é se são bradicárdico dependente o que ajuda na escolha do método terapêutico a ser empregado. Assim, TV desencadeadas por pausas ou bradiarritmias tem indicação de marcapasso permanente. Várias publicações preconizam como tratamento de escolha, nos casos em que se constata que a bradicardia inapropriada é o fator gerador principal dos episódios taquiarrítmicos implante de marcapasso a freqüências entre 70 e 90/bpm. O marcapasso permanente está claramente indicado em aqueles pacientes com bradicardia inapropriada e evidencia de arritmia maligna pausa-dependenteou bradicardia-dependente. O recurso não deve realizar-se como terapêutica única e sim complementar da terapia antiadrenérgica. Resumindo o marcapasso está indicado quando há demonstração que as TdP são bradicardia ou pausa-dependentes. Freqüências superiores a 110 batimentos por minuto, podem conduzir a miocardiopatia dilatada.
O implante do marcapasso permanente a freqüências maiores pode ser de maior beneficio nos pacientes portadores da SQT3 porque este tem maior risco de arritmias a baixas freqüências quando comparados a SQT2 HERG. Com aumento da FC há maior encurtamento do QT na SQT3 do que na SQT216.
O cardiodesfibrilador deveria ser cogitado em aqueles pacientes com arritmias recorrentes a pesar de adequada terapia antiadrenérgica. Alguns subtipos genéticos como SQT3 pode não responder a terapia antiadrenérgica ou ainda responder adversamente necessitando um ICD17.

Até 10% dos pacientes assintomáticos de qualquer variedade de SQTL apresentam MS ou parada cardiorrespiratória no primeiro episódio de arritmia, particularmente os portadores da variante 3 que tem menor número de eventos porém de maior mortalidade em cada episodio. Devido a esse elevado risco, o tratamento é recomendado em todos os pacientes assintomáticos com SQTL, à exceção dos membros da família portadores da anormalidade genética, assintomáticos, acima de 20 anos e com intervalo QTc normal18.
Uma ferramenta de grande utilidade para a tomada de decisão na escolha terapêutica é o ECG de longa duração (Holter) porque permite:

1) Eventualmente registrar as características do começo dos surtos das TdP, isto é, se são bradicárdico dependente fato particularmente freqüente na variante 3 o que ajuda na escolha do método terapêutico a ser empregado. Assim, TV desencadeadas por pausas ou bradiarritmias tem indicação de marcapasso permanente a freqüência maior.

2) Alternância da onda T: este parâmetro é um marcador de instabilidade elétrica e de heterogeneidade regional de repolarização e identifica os pacientes com SLQTL de alto risco. Estes pacientes possuem um risco aumentado de eventos cardíacos, porém, a onda T alternante não se constitui um marcador independente de risco19.
A Terapêutica inicial de escolha é “Over drive atrial pacing”. Várias publicações preconizam como tratamento de escolha, nos casos em que se constata que a bradicardia inapropriada é gerador de episódios taquiarrítmicos malignos pausa-dependente ou bradicardia-dependente o implante de marcapasso a freqüências entre 70 e 90/bpm. O marcapasso na Prevenção da pausa tem sido referido empregando um algoritmo do marcapasso (rate smoothing) o qual aumenta temporariamente a freqüência do

marcapasso na ocorrência de:

1) Extra-sístole espontâneas;

2) Diminuição da FC abaixo de 18% da freqüência base;

3) Pausas relacionadas a mudança no T-U e;

4) Pausas recorrentes que induzem a TdP.

O algoritmo “rate smoothing” parece ser uma boa ferramenta na prevenção das TdP da SQTL20.

Freqüências superiores do marcapasso a 110 batimentos por minuto podem conduzir a miocardiopatia dilatada.

O implante do marcapasso permanente a freqüências maiores pode ser de maior beneficio nos pacientes portadores da variante SQTL3 porque este tem maior risco de arritmias a baixas freqüências (VAGOTONIA) quando comparados a variante SQTL2 HERG. Com o aumento da FC há maior encurtamento do QT na variante SQTL3 do que na SQTL216.

Khan sugere que todo paciente diagnosticado assintomático e menor de 40 anos devem ser tratado21. No arsenal terapêutico farmacológico na SQT3 temos 2 drogas: Mexiletine e flecainide.

Mexiletine MexitilR (Boeringer Ingenheim) pela via oral Cápsulas: 100 e 200mg. Posologia: 3 vezes dia. máximo 1200mg x dia. com ( antiarrítmico bloqueador dos canais de Na+ da classe IB), diminui o intervalo QT e normaliza a morfologia da onda T apenas na variante SQTL3. O mesmo não ocorre em pacientes com SQTL2 e SQTL1. Esta variedade de SQTL é secundária a uma alteração genética que afeta o canal de Na+ localizada no cromossômo 3p21 especificamente na subunidade alfa do canal do gene SCN5A, o mesmo atingido na síndrome de Brugada. Nestes pacientes, mexiletine encurta significativamente o QTc evitando o aparecimento das TdP. A droga não encurta o intervalo QT longo da síndrome do QT congênita que afeta o canal de K+ (defeito HERG do canal de K+) ou SQTL26. As drogas da classe IB, tem cinética rápida de união e liberação e assim, reduzem apenas levemente a Vmáx.. sem afetar o complexo QRS e o intervalo JT. No modificam ou encurtam a duração do PA. O bloqueio do canal de Na+ com flecainide droga via oral tem sido proposto para o tratamento da variante SQTL3. Em alguns pacientes de SQTL3 a droga ocasiona supradesnivelamento do segmento ST tipo “Brugada like” (fenótipo intermediário12.)

Treze pacientes portadores da variante SQTL3 foram testados com flecainamide EV na dose preconizada para a prova farmacológica da síndrome de Brugada. Em 12 observou-se encurtamento do intervalo QTc e em 6 dos 13 supradesnivelamento do segmento ST de V1 a V3 ≥do que 2mm9.

No gene SCN5A a mutação no canal de Na+ DeltaKPQ ocasiona SQTL3 e a mutação 1795ins D provoca ambas: a síndrome de Brugada e SQTL3. Esta última mutação com o emprego de flecainida do modo uso-dependente demora 4 vezes a recuperação desde o estado inativado por realçar a inativação intermediária. Ambas mutações com o uso de flecainide ocasionam modificações nas comportas de inativação desde o estado fechado, com inativação rápida e intermediária22.

Uma dose baixa de flecainida oral encurta o intervalo QTc e normaliza o padrão de repolarização de onda T em pacientes com a variante SQTL3 com mutação DeltaKPQ de SCN5A. A mutação Delta KPQ apresenta reaberturas repetitivas do canal de Na+ e uma corrente lenta e prolongada de entrada do cátion em fase 223. Esta corrente manifesta-se no ECG por prolongamento do intervalo QT as custas do segmento ST e aparecimento tardio da onda T. Flecainide atuando no canal de Na+ com a mutação DeltaKPQ ocasiona bloqueio preferencial na corrente de entrada tardia de Na+ com recuperação lenta o que

explica o encurtamento do intervalo QT da variante SQTL324.
Assim, flecainida em baixas pela via oral dose é um agente terapêutico prometedor para pacientes com SQTL com a mutação DeltaKPQ de SCN5A no canal de Na+. Verificou-se que apenas a flecainida, (e não a lidocaina) corrige o fenótipo da variante SQTL3 em portadores da mutação DG.
Estes resultados demonstram que esta mutação confere uma resposta farmacológica única na expressão dos canais e sabe-se que o bloqueio dos canais DG pela flecainida atua no C-terminal da subunidade alfa do canal de Na+ por una interação flecainida/canal. Existem fenótipos intermediários.

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Querido Carlos, que gusto nuevamente tener noticias tuyas, como fue turquia? conta la experiencia por favor. Yo creo que no hubo intención de ir al seno, lo que maperece raro es que se haya desplazado desde el VD hacia ahi, no digo que no pase, pero es poco frecuente, otra opción por la juventud del pacientes es que el ostium esté más horizontal y anterior que lo habitual, con una gran vena que discurre por la cara diafragmática del cuore, y en realidad hayan pensado que estaban el VD ojo esto no es una crítica, y está descripto y alguna vez nos ha pasado (en nuestro servicio tenemos más de 9000 marcapasos implantados), y en esta región los umbrales suelen ser muy buenos, no podes dejar el electrodos ahí Carlos, porque no esté diseñado para el seno, y en realidad se termina dislocando, con respecto a este tema, me imagino que el electrodo, Edgardo no seria

fijación activa, ya que acá se hubieran dado cuenta ya que no solo produce dolor tipo pericardítico agudo sino aparece derrame pericárdico, siendo raro el taponamiento porque generalmente la lesión no es perforación sino un profusión de un milímetro o menos, y si se retira con cuidado, la reflexión muscular, cierra la mínima lesión.

Volviendo al caso, Edgardo hermosa presentación, y Martin ¿no mediste el QT? en estos casos de QT largo, los trastornos de conducción son de mal pronóstico, y en muchos casos se relacionan con tormentas eléctricas, al igual que la severa alternancia de la onda T, la que traduce una gran dispersión de la repolarización. Tiene indicación de marcapasos definitivo, e intentaría dejarlo estimulando entre 80 y 90 latidos/min, para homogeneizar la repolarización, agregaría betabloqueadores y estudiar a toda la familia. ¿Se podrá realizar test genético?

Finalmente, un comentario y después de muchos años de debate, especialmente con nuestros amigos gringos del norte, no existen diferencias en implantar un marcapasos VVI vs DDD, en bloqueo AV completo, con respecto al desarrollo de cardiopatía por estimulación preferencial en ápex o síndrome de marcapasos. En las personas muy jóvenes, esto puede ser discutido y hay controversia. Pero en estos pacientes siempre hay que detenerse a pensar en la cantidad de recambios que pueden llegar a tener, y en la posibilidad de lesión de uno o mas electrodos.

Saludos y no me disculpo por lo extenso,  Edgard, hermoso caso y presentación, un lujo.

Francisco Femenia

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Muy buena tu análisis Francisco, pero la dispersión duele a los ojos

DISPERSIÓN!!!!! Si Cervantes se levantara de la tumba te manta!

Fijate antes de mandar el recado que a los que no vemos español por años y a los Brasileños aprenderemos errado.

Andrés R. Pérez Riera.

Bueh, el tuerto se ríe del degollado...Análisis es masculino, por lo tanto debiera ser: Muy BUENO tu análisis.

Cervantes se tendria que llevar a mas de uno...

Adián Baranchuk

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Francisco concuerdo contigo parcialmente, nosotros hemos tenido casos por aquí que inadvertidamente se han implantado en el seno coronario y han evolucionado bien, aún cuando estos electrodos no están diseñados para eso, yo también asociaría nadolol. En relación a Turquía, todavía tengo dolor de no haber ido a presentar mi poster ya que el gobierno no me liberó dólares para poder viajar, hasta les pasé una carta de la aceptación del manuscrito, recuerda que tenemos un control de cambio en este país y no somos dueños ni siquiera de nuestro propio dinero, que tal.....pero bueno seguimos firmes y luchando, mejor no hablo más porque se me suelta la lengua y es peligroso, jajajajaj. Te cuento que sigo el foro todos los días del mundo, lo único es que casi no opino, hoy el caso me gustó tanto que no me lo aguanté. Recuerda que el próximo año tienes una invitación con nosotros a Maracaibo, te digo la fecha pronto, te adelanto que es para las Jornadas de la Facultad de Medicina de la Universidad del Zulia, única escuela de medicina de Maracaibo, me dieron parte de la tarde con 4 conferencias y tú eres invitado internacional, bueno abrazos y seguimos en contacto.

Carlos Rodríguez Artuza

Gracias Carlos y no te enojes, la próxima vez, usamos la cuenta de Adrian en Suiza, y nos vamos los tres con un poster tuyo, que a nivel internacional siempre te los aceptan,
igual quiero comentar al foro el excelente caso que mando Carlos al Congreso Internacional de Pediatria, que se realizó en Turquia, el cual fue aceptado, sobre repolarización precoz y otras yerbas, un orgullo para el foro tener tan querido amigo y representante, un abrazo y que no decaigas
Francisco Femenia

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La verdad es que este juego es duro

Carlos Rodríguez Artuza

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Querido Andrés, vos con la excusa que estás en la intersección de que no sabemos si sos brasileño, argentino, angloparlante, cordobés, zafas!! por eso te perdonamos, igual te queremos porque además de Maestro sos un gran amigo, por otro lado yo debo estar en el top five de errores gramaticales y de puntuación, pero el que creo que tiene todas las fichas para que Cervantes lo

mate, es nuestro querido Samuel, acá estamos en el horno, ademas lo mejor es que ni él entiende lo que escribe, abrazo

Francisco Femenia

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Estimado Dr Edgardo y Francisco:

Perdón, no me exprese correctamente, el QT es prolongado, el diagnostico impresiona claro a primera vista.

Saben soy vazco y cabeza dura aparte de burro.

No me convence totalmente, refiere hipoacusia no sordera congénita. El QT prolongado no lo refieren en los demás familiares eso era lo que quería notar.

Llama la atención:la asociación de hipoacusia, retraso madurativo, el nistagmus horizontal y vertical espontáneo, estrabismo, hiporreflexia muscular, y los valores de colesterol LDL en sangre, la ictiocitosis , escaso desarrollo de órganos genitales con hipotrofia mamaria y la asociación familiar no es con sordera sino que refiere hipoacusia, alteraciones en la marcha y convulsiones. Además de los trastornos de la conducción, no refiere muerte súbita familiar ni QT prolongado familiar, si trastornos de conducción obviamente.

Impresiona una enfermedad heredofamiliar pero muchos mas síntomas asociados que los referidos para el Síndrome de Jervell-Lange-Nielsen como nos deleitó el Maestro Pérez Riera.

Por eso me referí a hipotiroidismo como principal diagnóstico diferencial, y menos probablemente enfermedades como lipodisfrofias como la de **Enfermedad de Refsum**, por los demás síntomas y signos mencionados.

Por dicho motivo querido Dr Edgardo es que me referí que nos comente el diagnostico luego del ateneo. ¿O Ud ya la conoce antes de la presentación?

Le envió un cordial saludo queridos Dr Edgardo y Francisc

Martin Ibarrola

**Atrial Lead Dysfunction: An Unusual Feature of Hypothyroidism**

KRISTEN K. PATTON M.D., MATTHEW LEVY M.D., MOHAN VISWANATHAN M.D.

Pacing and Clinical Electrophysiology Volume 31,Issue 12,pages 1650–1652, December 2008

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É VERDADE OBRIGADO PELA CORREÇÃO

Andrés R. Pérez Riera

Estimado Edgardo,
Interesante caso y veo que hay discusión al respecto.
De acuerdo a lo que leo, en la flia. hay un fallecido al nacer, otro con marcapasos, otro con bloqueo trifascicular y la paciente con BAVC. Todos con trastornos de conducción posiblemente sodio dependientes. La sordera tal vez nos confunda. No recuerdo que JLN curse con BAVC. El BAVC es una causa adquirida de QTL y generación de TdP. Dessertenne hace más de 40 años hizo la primera descripción de TdP y particularmente en un BAVC. El QTL del JLN está ligado a mutaciones en los canales de K. La pregunta que me hago, ¿este caso no estará ligado a una mutación de los canales de sodio (Lenegre) ya que hay antecedentes de trastornos de conducción en sus hermanos?
Por lo tanto
1. ¿El QTL no estará asociado al BAVC?
2. ¿La sordera y los otros trastornos, tendrán que ver con el BAVC y el QTL?
3. Seguramente alguien del foro nos va a explicar y unirá todos los datos en una sola teoría o patología.
Saludos.

Oscar Pellizzón.

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Ña paciente es muy joven. Necesita DDD para disminuir el riesgo de FA. También, algunos pacientes con bloqueo AV tienen conductión VA y pueden terminar con síndrome de marcapaso.

Dardo Ferrara

Queridos amigos:
Hoy se realizó el Ateneo al que por razones personales no pude concurrir.
Según me comentan mis colegas, las opiniones predominantes coincidieron con el razonamiento que hizo Martín y los diagnósticos finales a los que arribó el ateneo fueron el de **ENFERMEDAD DE REFSUM**, y en segundo lugar se planteó el diagnóstico de **Síndrome de Kearns Sayre.**
Clínicamente eran muy evidentes las manifestaciones neurológicas y el síndrome cutáneo, de allí que surgieran aquellos diagnósticos

Propongo que Martín nos haga un resumen de estas enfermedades y el compromiso cardíaco que ambas presentan.
Buena oportunidad para aprender.

Un abrazo

Edgardo Schapachnik

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La **enfermedad de Refsum** pertenece al grupo de las lipidosis, enfermedades por almacenamiento de lípidos, trastorno familiar autosómico recesivo que se presenta usualmente en la infancia, con polineuropatía, sordera, ictiosis, ataxia, retinitis pigmentaria y cardiomiopatía, Las proteinas del lcr y el ac fitánico están aumentados, es una leucodistrofia que afecta el crecimiento de la envoltura de la mielina, fue descripta por el neurólogo Sigval D Refsum de Noruega.

Manuel Salvador Cano

Estimado Dr Edgardo: el reconocimiento no es para mí, mi admiración a los médicos de su Hospital. Por la dedicación a sus pacientes. En otros centros simplemente se hubiera ido con un marcapasos simplemente.

¿Por que la propuse? es similar a lo por Ud referido, el hipotiroidismo no encajaba en algunas cosas, comencé por asociación de enfermedades neuromusculares, con ictiocitosis y saltaron las leucodistrofias, lo único que no refirió en el EF era la retinitis, pero dentro de este grupo de enfermedades la única que cursa con LDL elevado es la enfermedad de Refsum por este motivo la mencioné.

El tratamiento es la restricción dietética de determinados alimentos simplemente (productos lácteos, buey, cordero y algunos mariscos. etc). . Ojala por la paciente esto se sea suficiente en el estadio de la enfermedad actual. A medida que progresa la enfermedad es pobre la respuesta a esto.

Le envío un abrazo

Saludos querido Dr Edgardo.

Martin Ibarrola

PD: los dejo con el repaso del tema y articulos de referencia. Obviamente son extractos de diferentes resúmenes y les adjunto bibliografia.

**ENFERMEDADES NEUROMUSCULARES Y AFECTACION CARDIACA**

Muchas de las enfermedades neuromusculares afectan al corazón y en ocasiones con gran relevancia clínica. Las distrofias musculares (distrofinopatías, distrofia muscular de cinturas, distrofia de Emery-Dreifuss o distrofia miotónica de Steinert), las miopatías congénitas, las miopatías inflamatorias y las enfermedades metabólicas (glucogenosis, parálisis periódicas o enfermedades mitocondriales) pueden producir miocardiopatía dilatada o hipertrófica, así como trastornos del ritmo y de la conducción. También algunas enfermedades heredodegenerativas (ataxia de Friedreich y enfermedad de Kugelberg-Welander) y las neuropatías periféricas adquiridas (síndrome de Guillain-Barré) o hereditarias (enfermedad de Refsum y de CharcotMarie-Tooth) pueden tener repercusión cardiológica

La aparición de fallo cardiaco en una cardiopatía (hipertrófica o dilatada) o más frecuentementeuna cardiopatía asociada a hipotonía,debilidad muscular y fallo de medro sugiere una enfermedad de la cadena respiratoria, enfermedad de Pompe o trastorno de la oxidación de los ácidos grasos. Muchos defectosde la oxidación de los ácidos grasos de cadena larga pueden descubrirse por una cardiomiopatía y/o alteraciones del ritmo cardiaco

(bloqueo auriculoventricular, bloqueo de rama, taquicardia ventricular). El reciente síndrome multisistémico de la glicoproteína deficiente en carbohidrato puede presentarse en el lactante como fallo cardiaco debido a derrame

pericárdico o taponamiento cardiaco.

Tipos de leucodistrofias

Las leucodistrofias pueden clasificarse en diferentes categorías: las leucodistrofias del grupo de lasenfermedades peroxisomales, del grupo de lasenfermedades lisosomales, de tipocavitarias,hipomielinizantes,no clasificadasoindeterminadas

Entre lasenfermedades peroxisomales, encontramos:

- la adrenoleucodistrofia / adrenomieloneuropatía
- **la enfermedad de Refsum adulta**
- Las enfermedades del espectro Zellweger, también conocidas como enfermedades con defecto de formación de los peroxisomas, a saber:
    - el síndrome de Zellweger
    - la adrenoleucodistrofia neonatal
    - la enfermedad de Refsum infantil

Enfermedad de Refsum Es una polineuropatía sensitivomotora hereditaria autosómica recesiva con retinitis pigmentosa y ataxia que se acompaña frecuentemente también de malformaciones esqueléticas, ceguera nocturna, sordera y miocardiopatía que puede ser dilatada o hipertrófica. La edad de aparición varía desde la infancia a la segunda década. Se produce por un defecto en la metabolización del ácido fitánico de la dieta y puede tratarse excluyéndolo de ésta.

La miocardiopatía puede ser relevante clínicamente sólo en los estadios finales de la enfermedad, incluso fallecer los pacientes por fracaso ventricular izquierdo o arritmias. No obstante, el electrocardiograma es generalmente anormal con taquicardia, alteraciones de la conducción, anormalidades de la onda P y complejos QRS anchos. En algunos casos la enfermedad se ha puesto de manifiesto con la miocardiopatía.

La enfermedad de Refsum es genéticamente heterogénea, tiene dos genes, PHYH (conoc ido como PAHX) y PEX7, identificados como causales de la enfermedad. Las condiciones de la enfermedad de Refsum muestran heterogeneidad genética en el locus del cromoso ma 10 y en el cromosoma 6. El ácido fitánico se acumula en el pigmento del epitelio retina l y en otros tejidos, que causa muerte celular por la desregulación del calcio, la formación de radicales libres y la apoptosis.

El ácido fitánico se eleva en otras enfermedades peroxisomales, sin embargo, puede ser distinguido por análisis moleculares y por el fenotipo clínico.

Tratamiento El tratamiento de la enfermedad de Refsum consiste en limitar los alimentos que contienen ácido phytanique (fitánico). El plasmaferesis (retirada y reinyección de plasma sanguínea) puede también ser necesarias.

Pronóstico

El pronóstico para los pacientes afectados por enfermedad de Refsum es variable. Con tratamiento, los síntomas de neuropatía periférica e ictiosis desaparecen generalmente. No obstante, el tratamiento no puede reabsorber las lesiones de la vista y la audiencia.

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Yo al menos no tenia idea que existiera y leeré el tema el fin de semana, una pregunta por ignorancia nada más, además del tratamiento específico de la enfermedad, e independientemente de esto, tiene indicacion de marcapasos, verdad?, saludos y felicitaciones Martin,

Francisco Femenia

¡Felicitaciones, Martincito!

¡Excelente actualización de una enfermedad de la que no tenía ni idea!

Le dejo al Sensei filosofar por qué, pero la sensación que produce aprender algo nuevo es inconmensurable

Querido Franciscoo:

Te respondo desde la ignorancia.

La enfermedad se acompaña o mejor, puede acompañarse de variados trastornos de conducción. Por ejemplo esta paciente tenía un ECG previo con BCRI y en aquella oportunidad, no tenía indicación de MP. Ahora, la indicación de MP es la clásica. A esta chica se le implantó por el BAVC que presentaba a su ingreso

Un abrazo

Edgardo Schapachnik

Gracias querido Dr Edgardo, no creo merecer las felicitaciones pero no las voy a despreciar. Las tomo con el mayor de los orgullos.

Estimado Dr Femenia por lo que he leído el daño al sistema de conducción es permanente, no retrograda con la restricción dietética. Con la dieta se trata de evitar la progresión del daño miocárdico, ya que sin esta pueden evolucionar a miocardioaptía dilatada o hipertrófica. Además del aumento de riesgo de enfermedad coronaria.

Lejos estoy de ser un experto en esta materia.

Un abrazo y saludos

Martin Ibarrola