LQT3 VARIANT CHARACTERISTICS

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Name: LQT3
Affected gene: SCN5A
Chromosome: 3. Mapped for the first time in 1994 by Jiang et al(1). Later a p21-24 mutation was detected in the SCN5A gene, in chromosome 3 by Wang et al(2).
Mutation: 3p21-24
OMIM number: 600163
Affected channel: Na^+ channel
Affected AP phase: Plateau, dome or phase 2.
Transmission: Autosomal dominant. In 1998, Dr. Silvia Priori et al, showed the first evidence that the Romano-Ward syndrome (RWS) could be recessive(3). Note: all LQT3 correspond to RWS; however, it is not so in reverse, because RWS could be of the LQT4 type, LQT2 7(HERG) and LQT5 21q22.1 (Mink)(4).
Triggers: Sleep, night vagotonia. Most of the events occur during sleep or in rest (61%)(5). Unlike in LQT1, they occur almost exclusively during strain or stress.
Phenotype

a) Clinical: there are reports that LQT3 could be associated to syndactyly(6);

b) Electrocardiographic:

1) Heart rate: tendency to bradycardia related to age and in some cases, decrease during rising efforts has been observed. When HR increases, the QT interval shortens more in LQT3 than in LQT1 and LQT2;
2) PR interval: usually normal. However, we found a family with short PR.
3) ST segment: significant prolongation. Consequence: late appearance of T wave. The deltaKPQ mutation causes a small and persistent inflow of Na^+ in phase 2 with late reopening, which explains QT interval prolongation.
4) QT interval dependence of heart rate: significant.

5) QT interval: In the LQT3 variant it is usually longer than in LQT1 and LQT2.
6) U wave: it could be prominent in many cases as a consequence of longer repolarization of the M cell. It increases in bradycardias and in pauses and it may present alternating polarity.
7) Accentuated QT interval dispersion(7). In turn, this fact is a risk marker for the appearance of arrhythmias(8).

Response to exercise stress test

Normalization of ventricular repolarization alterations may be occasionally observed. In the LQT1 and LQT2 variants, it may trigger tachyarrhythmic events.

Relative incidence: When compared to LQT1 and LQT2, the least frequent 1%.

Number of events: Less than in LQT1 and LQT2.

Lethality of events: Greater than in LQT1 and LQT2.

Accumulative lethality: Similar in the three variants.

Alleles:

1) Brugada disease.
2) Mixed forms with Brugada disease.
3) True idiopathic ventricular fibrillation.
4) Lenègre disease.

Brugada disease:

This variant is considered allelic to Brugada disease. For this reason it is said that it is the “mirror image” of LQT3, because both affect the alpha subunit of the Na^+ channel and are autosomal dominant. Approximately 2/3 of Brugada cases are sporadic (Brugada syndrome) and only 1/3 present autosomal dominant inheritance with positive family history. The genetic proof is possible in only 15% to 20% of the cases (Brugada disease).

Mixed forms with Brugada disease:

The Na^+ channel in the SCN5A gene is involved both in Brugada disease and in LQT3. These syndromes lead to opposite effects on the channel. Thus, in Brugada syndrome the mutation causes Na^+ inflow reduction, while in LQT3 it is associated to a gain in function with low inflow of the cation in phase 2.

Investigations indicate the existence of mixed forms characterized by overlapping phenotypical manifestations with prolonged QTc interval and ST segment elevation from V1 to V2 or V3.

Flecainide is a drug used to unmask Brugada disease, and it may cause ST segment elevation in some patients with LQT3(9).

True idiopathic ventricular fibrillation (IVF):

True IVF, the LQT3 variant and Brugada disease affect the same SCN5A gene, hold the same OMIM number (600163) and the same locus (3p21-p34).

Drugs that improve repolarization

1) Mexiletine
2) Flecainamide

1) Mexiletine: class 1B antiarrhythmic agent, of the lidocaine-like type, which is very efficient to shorten QT only in LQT3. This variant presents a T wave of late appearance by ST segment prolongation as a consequence of the permanent inflow of Na^+. In these patients, mexiletine significantly shortens QTc, preventing the appearance of TdP. Remarkably, the drug does not shorten long QT in congenital long QT syndrome affecting the K^+ channel (HERG defect of the K^+ channel), called LQT2(10,11). The drug does not shorten long QT of the congenital long QT syndrome affecting the K^+ channel (HERG defect of the K^+ channel) or LQT2(12).

2) Flecainide: This drug has been proposed and it seems promising for the oral treatment in LQT3 in patients with the DeltaKPQ mutation in the SCN5A gene. It causes block in the Na^+ late inflow(13).

Drugs that worsen repolarization:

Beta blockers have a protective effect in LQT1 and LQT2, but may trigger TdP in LQT3(14).

Drug that resembles the LQT3 variant

The drug known as ATX-II causes the increase in late Na^+ inflow, I_{Na}, and may resemble the LQT3 situation prolonging ST segment duration and causing late T wave and long QT. This ST prolongation by increase in Na^+ late inflow seems more intense in M cells than in endocardial and epicardial cells, thus increasing repolarization dispersion. This greater increase in M cells is caused by them having a greater late Na^+ channel(15).

Treatment

LQT1 and LQT2 benefit more with beta blockers. In LQT3 these drugs could be harmful. This is the variant that best responds to pacemakers. Some patients may present sudden pauses in sinus rhythm that exceed 1.2 seconds, not preceded by alterations in heart rate. They may be important at the onset of arrhythmias in patients with LQTS and frequently precede the onset of TdP, pointing the indication of pacemakers as the therapeutic choice. Holter may possibly record the characteristics of the onset of TdP runs, i.e. if they are bradycardia-dependent or if it helps in the choice of the therapeutic method to be used. Thus, VT triggered by pauses or bradyarrhythmias have the indication of permanent pacemaker. Several publications advocate pacemaker implantation at rates between 70 and 90 bpm, as treatment of choice in the cases in which inappropriate bradycardia is the main factor generating tachyarrhythmia episodes. Permanent pacemaker is clearly

indicated in those patients with inappropriate bradycardia and evidence of pause-dependent or bradycardia-dependent malignant arrhythmia. The resource should not be made as a single therapy and without supplementing antiadrenergic therapy. In brief, pacemakers are indicated when there is proof that TdP are bradycardia- or pause-dependent. Rates above 110 beats per minute may lead to dilated cardiomyopathy.

The implant of permanent pacemaker at greater rates could be more beneficial in patients carriers of LQT3, because the latter presents a higher risk of arrhythmias at low rates when compared to HERG LQT2. With the increase in HR there is a greater QT shortening in LQT3 than in LQT2(16).

Cardioverter defibrillator should be considered in those patients with recurrent arrhythmias in spite of a proper antiadrenergic therapy. Some genetic subtypes as LQT3 may not respond to antiadrenergic therapy or even respond negatively, requiring an ICD(17).

Up to 10% of asymptomatic patients of any LQTS variety present SCD or cardiorespiratory arrest in the first episode of arrhythmia, particularly the carriers of variant 3 that have a lower number of events, in spite of a greater mortality in every episode. Because of this high risk, the treatment is advised in all asymptomatic patients with LQTS, except for the family members carriers of genetic anomalies, asymptomatic, older than 20 years and with normal QTc interval(18).

A very useful tool for decision making in the therapeutic choice is Holter recording because it allows:

1) To record occasionally the characteristics of the onset of TdP runs; i.e. if they are bradycardia-dependent, a particularly frequent fact in variant 3, which helps in the choice of the therapeutic method to be used. *Thus, VT triggered by pauses or bradyarrhythmias have an indication of permanent pacemaker at a lower rate*.

2) T wave alternans: this parameter is an electric instability and regional heterogeneity of repolarization marker and identifies the patients with LQTS of high risk. These patients have an increased risk of cardiac events; however, T wave alternans does not constitute an independent risk marker(19).

The initial therapy of choice is overdrive atrial pacing. Several publications advocate pacemaker implantation at rates between 70 and 90 bpm, as treatment of choice in the cases in which it is verified that inappropriate bradycardia generates pause- or bradycardia-dependent malignant tachyarrhythmic events. There has been reports about the use for pause prevention, of a pacemaker algorithm (rate smoothing), which increases temporarily the pacemaker rate when the following occur:

1) Spontaneous extrasystoles;
2) Decrease of HR below 18% of base rate;

3) Pauses related to change in T-U and;
4) Recurrent pauses that induce TdP.

The rate smoothing algorithm seems to be a good tool to prevent TdP in LQTS(20).

Pacemaker rates above 110 beats per minute may lead to dilated cardiomyopathy.

Permanent pacemaker implantation at higher rates may be of greater benefit in patients carriers of the LQT3 variant, because this has a greater risk of arrhythmias at low rates (VAGOTONIA) when compared to the HERG LQT2 variant. With the increase of HR, there is a greater QT shortening in the LQT3 variant than in LQT2(16).

Khan suggests that any diagnosed and asymptomatic patient who is younger than 40 years should be treated(21). In the pharmacological therapeutic arsenal in LQT3 we have 2 drugs: mexiletine and flecainide.

Mexiletine Mexitil^{R} (Boeringer Ingenheim) orally with capsules: 100 and 200 mg. Posology: 3 times per day, maximal 1200 mg x day with (antiarrhythmic agent, blocker of Na^{+} channels of the IB class), decreases the QT interval and normalizes T wave morphology only in the LQT3 variant. It is not the same in patients with LQT2 and LQT1. This LQTS variant is secondary to a genetic alteration that affects the Na^{+} channel located in chromosome 3p21, specifically in the alpha subunit of the SCN5A channel, the same one affected in Brugada syndrome. In these patients, mexiletine significantly shortens QTc, preventing the appearance of TdP. The drug does not shorten the long QT interval in congenital long QT syndrome affecting the K^{+} channel (HERG defect of the K^{+} channel) or LQT2(6). Class IB drugs have a rapid kinetics of union and release and thus, they only reduce Vmax slightly, not affecting the QRS complex and the JT interval. They do not modify or shorten AP duration.

The Na^{+} channel block with oral flecainide has been proposed for the treatment of the LQT3 variant. In some LQT3 patients, the drug causes Brugada-like ST segment elevation (intermediary phenotype)(12).

Thirteen patients carriers of the LQT3 variant, were tested with IV flecainamide in the advised dose for the pharmacological test for Brugada syndrome. In 12, QTc interval shortening was observed and in 6 from the 13, ST segment elevation from V1 to V3 ≥ than 2 mm(9).

In the SCN5A gene, the Na^{+} channel mutation DeltaKPQ causes LQT3 and the 1795insD mutation causes both Brugada syndrome and LQT3. The latter mutation, with the administration of flecainide, in a use-dependent mode, delays 4 times the recovery from the inactive state to emphasize the intermediary inactivation. Both mutation with the use of flecainide cause changes in the inactivation behavior from the closed state, with rapid and intermediary inactivation(22).

A low dose of oral flecainide shortens the QTc interval, and normalizes the T wave repolarization pattern in patients with the LQT3 variant, with DeltaKPQ mutation of SCN5A. The DeltaKPQ mutation presents repetitive reopenings of the Na^+ channel and a slow and prolonged inflow current of the cation in phase 2(23). This current manifests in ECG by QT interval prolongation at the expense of the ST segment and late appearance of T wave. Flecainide acting on the Na^+ with the DeltaKPQ mutation, causes preferential block in the late Na^+ inflow with slow recovery, which explains QT interval shortening in the LQT3 variant(24).

Thus, oral flecainide is a promising therapeutic agent for LQTS patients with the DeltaKPQ mutation of SCN5A in the Na^+ channel. It was verified that only flecainide (and not lidocaine) corrects the LQT3 variant phenotype in carriers of the DG mutation.

These results show that this mutation provides a unique pharmacological response in the expression of channels, and it is known that the block of DG channels by flecainide acts on the C-terminal of the alpha subunit of the Na+ channel by flecainide/channel interaction. There are intermediary phenotypes.

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