

LONG QT SYNDROME IN A PATIENT WITH ALLERGIC RHINOCONJUNCTIVITIS AND AUTO-IMMUNE DIABETES: FOCUS ON THE CHOICE OF ANTI-H1 DRUGS

Moneret-Vautrin D.-A. (1), de Chillou C. (2), Codreanu A. (2)

SUMMARY: The long QT syndrome is a rare disease. The prevalence is estimated at 1/5 000 to 1/20 000. Numerous drugs are contra-indicated because they can lengthen the QT interval. A case of pollen allergy in an adolescent with LQTS is described. The possibility to prescribe anti-H1 drugs is reviewed since cases of torsades de pointe and even deaths have been reported for terfenadine and astemizole. Diphenhydramine, orphenadrine and hydroxyzine are contra-indicated. No accidents and no effects on the QT interval have been published for ebastine, fexofenadine, desloratadine and levocetirizine. These anti-H1 drugs could be used with great care, without any association with drugs resulting in low serum potassium level. Azelastine eye drops have been authorized and a routine protection by inhaled corticosteroids during the pollinic period has been advised in this adolescent treated by betablockers.

Key-words: Long QT syndrome - Anti-H1 drugs.

A 16^{1/2} year old boy suffering from seasonal allergic rhinoconjunctivitis (May to July) since childhood has a history of infantile asthma, but no ongoing asthma. He has also suffered type 1 diabetes since 2001 and receives insulin. He has a long QT syndrome, discovered after the death of a cousin from arrhythmogenic dysplasia. Until now he has not experienced symptoms of this condition but receives beta-blocker treatment. So far, the allergic rhinoconjunctivitis has not been treated but it has become incapacitating over recent months in spring and the young man has sought advice and treatment

Allergy tests have confirmed his sensitivity to grass pollens (prick-test: 3.5 mm with a codeine control at 3 mm). There is a cross sensitization to cereal pollens: oats: 5.5 mm, barley: 4 mm, rye: 3 mm, wheat: 2 mm. He is also sensitized to two molds: *Ulocladium*: 2.5 mm, *Alternaria*: 2 mm, and to ash tree pollen: 2.5 mm. Specific IgE to rye grass are present: 15 kU/l.

The allergologist must ask himself the following questions: What is a long QT syndrome (LQTS)? Which anti-allergic treatments are contra-indicated? What should this patient be offered?

(1) Department of Internal Medicine - Clinical Immunology and Allergology, University Hospital, 29 avenue du Maréchal de Lattre de Tassigny - 54035 Nancy Cedex - France and Research Team 3399 : Allergic diseases : diagnosis and therapeutics. Laboratory of Molecular Medicine and Therapeutics - 15 rue du Bois de la Champelle - Vandoeuvre-lès-Nancy (France).

(2) Department of Cardiology, University Hospital, Brabois, Avenue de Bourgogne, 54511 Vandoeuvre-lès-Nancy (France).

WHAT IS A LONG QT SYNDROME?

Normal values for QTc interval in relation with age have been published (5). Congenital long QT syndrome is characterized by an abnormal lengthening of the QTc interval related with changes in the ionic currents of myocardial cells. It is related to a genetically

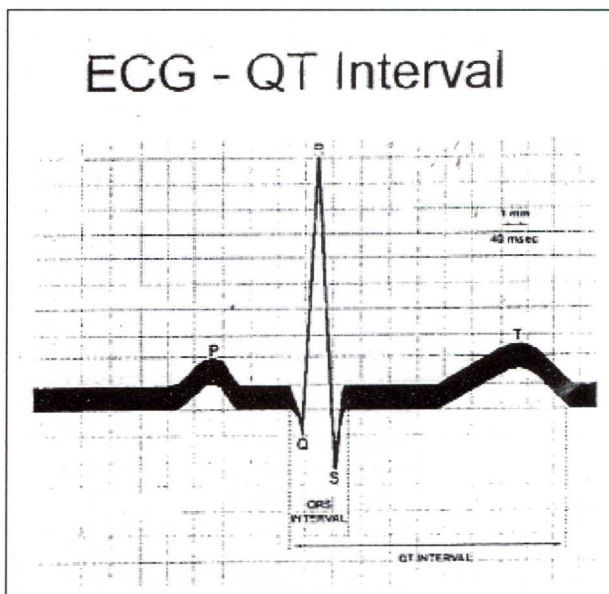


Figure 1. Congenital long QT syndrome is a disorder characterized on the ECG by abnormal lengthening of the QT interval and intermittent episodes of *torsades de pointes*, with or without symptoms. According to the traditional definition, congenital long QT syndrome is characterized by a longer QT interval corrected for heart rate (QTc) of a duration exceeding 440 milliseconds in men and 460 milliseconds in women.

determined dysfunction of potassium channels or the sodium channel and is therefore classified as an ion channel disease. In the myocardium there is only one type of sodium channel but many types of potassium channel (particularly I_{Kr} and I_{Ks}). A defect in the inactivation of these channels lengthens the cell activity potential, resulting in a long QT interval. To date, mutations in eight different genes have been identified as being the cause. Genetic transmission is predominantly autosomic, so the child of a LQTS family stands a 50% chance of being impaired (8). The gene prevalence is currently estimated at 1/5000 to 1/20000 (4, 12). Once LQTS has been diagnosed, family genotyping is recommended. In 2002, 80 families in Ile de France region had been genotyped.

A particular type of LQTS corresponds to each abnormal genotype (LQT1, LQT2, etc.). The clinical characteristics of each genotype are different, especially with regard to the morphology of the T wave. The three commonest syndromes (LQT1, LQT2 and LQT3) have specific characteristics and are summarized in the table below (table 1):

The syndrome causes serious ventricular rhythm disorders (*torsades de pointes*, ventricular fibrillation) with symptoms including syncope and sudden death. The risk of sudden death depends on both genotype and phenotype (14). The three main associated factors are: 1) a QTc interval over 500 ms; 2) female sex (LQT2++); 3) certain ECG abnormalities (particularly alternated T wave, sinus bradycardia or paroxysmal AV block). As with right ventricular arrhythmogenic dysplasia and hypertrophic cardiomyopathy, congenital long QT syn-

drome is a classic cause of syncope and sudden death in children and young adults. There are no epidemiological data available to assess its role in these deaths. However, the lifetime risk of sudden death is about 5% for people with congenital long QT syndrome. This is only a mean value. For some patients the risk of sudden death is the same as that of the general population, but for others, the risk 5 years after diagnosis is over 50% (14). Trigger factors for syncope, or sudden cardiac death, vary (see Table), although effort plays a major role, certainly with LQT1++, and to a lesser extent with LQT2 (4).

The condition must be systematically screened for in the event of loss of consciousness in young people, especially during effort or sleep. Once the diagnosis is established, treatment with β -blockers has remarkable effects in those cases related to potassium channel genes. It has been estimated that β -blockers have decreased mortality by a factor of ten since 1980 (4). For patients with certain forms of congenital long QT syndrome, and at high-risk of sudden death, implantable defibrillators may be indicated for primary or secondary prevention.

Besides congenital LQTS, there are acquired forms, usually diagnosed during water-electrolyte disorders or after the administration of drugs known to lengthen the QT interval. It has been demonstrated that these conditions, when complicated by *torsades de pointes*, may be related to minor impairment of myocardial potassium channels (usually the I_{Kr} channel), dependant on the HERG gene (15). Patients in whom the abnormality is detected under these circum-

	LQT1	LQT2	LQT3
Frequency	55%	35%	1-5%
Gene: former nomenclature current nomenclature	KvLQT1 KCNQ1	HERG KCNH2	SCN5A SCN5A
Channel	I _{ks} (potassium)	I _{Kr} (potassium)	INa (sodium)
Risk of syncope/sudden death	Effort (90%)	Emotion, stress, noise (80%)	At rest, night (70%)
Annual incidence of sudden death	0.30%	0.60%	0.56%
ECG: repolarization morphology	Large flat T wave	Bifid T wave	Flat ST segment
Primary prevention of sudden death	β -blockers +++ PM, Σ denervation	β -blockers ++ PM, Σ denervation, K+	Mexiletine/flecainide β -blockers?
Secondary prevention of sudden death	ICD	ICD	ICD

Table 1: PM = pacemaker, Σ denervation = surgical removal of the left sympathetic cervical lymph node chain, K+ = potassium supplement to reach target serum potassium > 4.5 meq/l, ICD = implantable cardioverter defibrillator.

stances should be considered as presenting a sub-clinical form of congenital LQTS. In the last ten years, many medicinal drugs have been withdrawn from the market because of their blockade effect on the HERG potassium channel. In western countries, national institutions in charge of new pharmacological agent approval for human use demand in vitro analysis of the effects of this agent, as well as its metabolites, on HERG-dependent proteins.

WHICH ANTI-ALLERGIC TREATMENTS ARE CONTRA-INDICATED?

Many medicinal products of different pharmacological classes are contra-indicated, or not recommended. There is an exhaustive list in the article published by Le Heuzey (8).

As for H1-antihistamines, it must be emphasized that the risk of QT interval lengthening depends on the particular compound since it is not a class effect (17). Cases of *torsades de pointe* and even sudden death have been reported for **terfenadine** and **astemizole** (2, 3, 7, 10, 17), usually in association with agents inhibiting drug metabolism through the P450 3A4 cytochrome (imidazoles, macrolide antibiotics, psychotropes), or with hepatic insufficiency (cirrhosis) or with doses greatly exceeding those recommended. The H1-antihistamines noted above block certain types of potassium channel and may perturb electrolyte transport (cell potassium exit), causing repolarization disorders and arrhythmia. Major effects are related to blockade of I_{Kr} channels (14).

One study model uses *Xenopus* oocytes, expressing I_{Kr} potassium channels: **astemizole**, **terfenadine**, **ebastine**, **loratadine** at high concentrations, block these channels, whereas **cetirizine** and **fexofenadine** do not. In the ovarian cells of the Chinese hamster, mizolastine also blocks I_{Kr} channels (17).

It has been known since 1975, that hydroxyzine, a piperazine derivative, lengthens the QT interval in older people taking 300 mg/day (13). Other physico-chemical characteristics of certain compounds may be considered potentially cardiotoxic: for example **diphenhydramine** (17). There is a recent publication on **orphenadrine**, a compound close to diphenhydramine (9). **Azelastine** may induce lengthening of the QT interval (one study). In the exhaustive review of papers between 1986 and 1996 by Yee Guan Yap, rhythm disorders and cardiac death involved loratadine (13 cases), cetirizine (2 cases), acrivastine (one case) (for further details, see Passalacqua).

As for ebastine: the multicenter study on 1,076 patients showed no significant abnormality (6). Study of the loratadine metabolite (desloratadine), and of levocetirizine (only 14% is metabolized by the P 450 3A4 cytochrome) showed no effects on the QT interval, either in animals or in man. No accidents have been reported for those two anti-H1 drugs, or for ketotifen.

So there is no absolute contra-indication for H1-antihistamines in cases of LQTS, but they should be used with great care. Fexofenadine could be used. As for ebastine, a group of expert cardiologists concluded that when administered alone, ebastine did not affect the QT interval and is not therefore contra-indicated in LQTS. However, care should be taken (11).

There are many precautions to take when prescribing H1-antihistamines. These include associations with other medicinal products resulting in low serum potassium and magnesium levels, and the association with grapefruit juice, which is why the laboratories marketing desloratadine (Aérior®) and levocetirizine (Xyzall®) provide no information at all.

WHAT SHOULD THIS PATIENT BE OFFERED?

Immuno-therapy was ruled out for the following reasons: first, beta-blockers, that cannot be discontinued, might result in an increased risk of severity of a reaction induced by IT. Besides, in the case of an allergic reaction elicited by an IT injection, the release of histamine or leukotrienes could interact with the cardiac rhythm. Third, the fact that the young man has not only atopy (Th2 activation), but also insulin-dependent diabetes (involving Th1-related auto-immunity), makes it impossible to predict the immunological modifications induced by immuno-therapy.

Allergic rhinitis may be treated by topical corticosteroids, prescribed before the pollen season begins. Cromones are not recommended as they are not effective.

The allergic conjunctivitis could be treated by disodium cromoglycate (DSCG) (Opticron®). If DSCG is not effective, azelastine (Allergodil®) eye drops will be used (with the approval of the expert pharmacologist at the French Agency for the Safety of Health Products (AFSSAPS)).

Oral H1-antihistamines could be prescribed, should this treatment prove ineffective. It would be necessary to choose between fexofenadine, levocetizine and

ebastine. It would be necessary to discuss this prescription with a cardiologist to specify whether special cardiac monitoring (24 to 48 hours) were required at the start of treatment.

Finally we have to tackle the issue of asthma that could be elicited by pollen allergy, since asthma in childhood indicates a probable bronchial hyperreactivity. Since sensitization is likely to increase gradually, it seems justifiable to recommend routine protection by inhaled corticosteroids during the pollinic period, to prevent the gradual appearance of the allergic inflammation, at risk of triggering asthma which could not be treated by beta-agonists (because of beta-blocking treatment).

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