Efficacy of pharmacological treatment and genetic characterization in early diagnosed patients affected by long QT syndrome with impaired AV conduction

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The coexistence of QT prolongation and impaired atrioventricular (AV) conduction with torsade de pointes ventricular tachycardia (TdPVT) is a rare malignant variant of the long QT syndrome (LQTS). This form of LQTS can manifest during infancy and despite treatment the mortality rate is very high (50% at 6 months; 67% at 2 years) [1–7].

The purpose of this study was to examine the clinical presentation and the outcome of a cohort of 7 unrelated patients (4M/3F), all medically treated, affected by LQTS and impaired AV conduction, referred to the Cardiology Division of the Monaldi Hospital (Naples, Italy) within the first three weeks of life for detection of long QTc (>460 ms) and impaired AV conduction alone (1 patient) or combined with TdPVT (5 patients, Fig 1) or non-sustained VT (1 patient). A complete medical history, physical and instrumental examination (standard and 24-hour Holter ECG, echocardiogram) were obtained in all patients. No instance of major congenital heart defect, no electrolyte or haematological abnormalities and no clinical or serological evidence of maternal lupus erythematosus were found in any patient. The results of hearing tests and central nervous system test were normal. AV conduction was impaired in all patients before the administration of antiarrhythmic treatment (Figs 1 and 2). We found no temporal relationship between episodes of AV block and TdPVT. Episodes of T-wave alternans occurred during continuous ECG monitoring only in one patient (Pt5). No “notched T-waves” were observed in patients with TdPVT. Nonetheless, we observed the contemporary presence of 2:1 AV block and TdPVT also in LQTS patients with a QTc between 495 and 580 ms, which places these patients at higher life-threatening risk.

All patients were treated with propranolol (1–6 mg/kg/day per os). Mexiletine (1–6 mg/kg/day per os) was associated to propranolol when the latter alone did not control the arrhythmia or when TdPVT occurred during the night. Propranolol alone (Pt2) or combined with mexiletine resulted in the disappearance of life-threatening VT and AV conduction disturbances. There were no cardiac or systemic side effects of pharmacological treatment in any patient except Pt1, who at age 11 months, had an episode of transitory hypoglycaemia, successfully treated with glucose solution.
Patients were discharged when there had been no life-threatening VT and symptomatic bradycardia for at least two weeks of treatment. They were seen in the Outpatient Clinic 2, 4 and 6 weeks after discharge and at 2-month intervals thereafter, planning standard and 48-hour Holter ECG, echocardiogram, and baseline biochemistry analysis. Follow-up time was changed in case of impaired clinical status or referred cardiac events.

Patient 3, aged 13 months, was lost to follow-up; Pt5, aged 3 months, succumbed to untreatable cardiac arrest while in hospital, despite repeated external cardioversions. At a median follow-up of 62 months (23 to 118 months), five patients are alive, and regularly seen in the Outpatient Clinic; they are still being treated, and do not have any arrhythmias or conduction defects (Table 1).

The resting ECG and QT intervals of the patients’ parents and grandparents were normal for all except one (Pt1’s father). This asymptomatic father was found to have QTc = 480 ms in the resting ECG and a history of recurrent unexplained syncope in infancy and adolescence. A newborn brother of Pt2 had a QTc = 480 ms at birth but no conduction defect.

The guardians of all patients but one gave written informed consent for molecular analysis. Coding regions and 5’ and 3’ untranslated regions of the KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 genes were amplified by polymerase chain reaction (PCR). PCR products were then examined for sequence variations by denaturing high-performance liquid chromatography using the Wave System 3500 (Transgenomic, Omaha, NE, USA) and direct sequencing. When a sequence variation was detected, the patient’s parents and available relatives underwent genetic screening. Mutation screening identified four disease-causing mutations in four unrelated patients: the known mutations c.C1682T in KCNH2 and c.G1573A in KCNQ1; and the novel mutations c.C3989A in SCN5A and c.1450_1467del in KCNH2. These latter occur in highly conserved regions of the corresponding proteins (http://www.ebi.ac.uk/Tools/blastall/) and were excluded in at least 250 healthy individuals, whose DNA was provided by the Biological Sample and Cell Bank of CEINGE (CEINGE scarl–Bioteconomia Avanzate, Naples, Italy). Familial screening revealed mutation c.C3989A in the SCN5A gene as a de novo mutation, after paternity was proved. Screening of the other three families revealed a mutation in 5 of the 11 available
Fig. 2. Conduction abnormalities in LQTS: Two to one AV block in Patient 4 (A); Wenckebach type AV block in Patient 2 (B).

Table 1
Clinical and genetic characteristics, electrocardiographic features and drug treatment of the patients.

<table>
<thead>
<tr>
<th>Pts</th>
<th>Sex</th>
<th>Age at presentation</th>
<th>QTc/PP/RR at presentation</th>
<th>Conduction abnormalities</th>
<th>Arrhythmias</th>
<th>QTc at discharge</th>
<th>Therapy at discharge</th>
<th>Length of follow-up</th>
<th>QTc at last follow up ECG</th>
<th>Outcome</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1</td>
<td>M</td>
<td>1 day</td>
<td>580/380/760 ms</td>
<td>2:1 AV Block</td>
<td>TdPVT</td>
<td>540 ms</td>
<td>Propranolol 6 mg/kg/day + Mexiletine 5 mg/kg/day</td>
<td>118 months</td>
<td>510 ms</td>
<td>No arrhythmias. No conduction abnormalities.</td>
<td>KCNH2</td>
</tr>
<tr>
<td>Pt2</td>
<td>F</td>
<td>1 day</td>
<td>480/500/700 ms</td>
<td>Wenckebach-type AV Block</td>
<td>TdPVT</td>
<td>465 ms</td>
<td>Propranolol 3 mg/kg/day</td>
<td>115 months</td>
<td>460 ms</td>
<td>No arrhythmias. No conduction abnormalities.</td>
<td>KCNQ1</td>
</tr>
<tr>
<td>Pt3</td>
<td>F</td>
<td>10 days</td>
<td>495/360/720 ms</td>
<td>2:1 AV Block</td>
<td>TdPVT</td>
<td>480 ms</td>
<td>Propranolol 3 mg/kg/day + Mexiletine 3 mg/kg/day</td>
<td>13 months</td>
<td>480 ms</td>
<td>Lost to follow up.</td>
<td>Screening not possible to be performed</td>
</tr>
<tr>
<td>Pt4</td>
<td>M</td>
<td>1 day</td>
<td>625/400/800 ms</td>
<td>2:1 AV Block</td>
<td>TdPVT</td>
<td>485 ms</td>
<td>Propranolol 6 mg/kg/day + Mexiletine 5 mg/kg/day</td>
<td>62 months</td>
<td>480 ms</td>
<td>No arrhythmias. No conduction abnormalities.</td>
<td>SCN5A</td>
</tr>
<tr>
<td>Pt5</td>
<td>M</td>
<td>1 day</td>
<td>500/360/720 ms</td>
<td>2:1 AV Block</td>
<td>TdPVT</td>
<td>480 ms</td>
<td>Propranolol 4 mg/kg/day + Mexiletine 3 mg/kg/day</td>
<td>3 months</td>
<td>500 ms</td>
<td>Death</td>
<td>KNCH2 c.3460_1467del (p.S484_I489del)</td>
</tr>
<tr>
<td>Pt6</td>
<td>M</td>
<td>21 days</td>
<td>490/35/730 ms</td>
<td>nsVT</td>
<td></td>
<td>430 ms</td>
<td>Propranolol 5 mg/kg/day + Mexiletine 5 mg/kg/day</td>
<td>51 months</td>
<td>440 ms</td>
<td>No arrhythmias. No conduction abnormalities.</td>
<td>No mutation found in screened genes</td>
</tr>
<tr>
<td>Pt7</td>
<td>F</td>
<td>1 day</td>
<td>490/360/720 ms</td>
<td>2:1 AV Block</td>
<td>None</td>
<td>440 ms</td>
<td>Propranolol 5 mg/kg/day + Mexiletine 6 mg/kg/day</td>
<td>23 months</td>
<td>445 ms</td>
<td>No arrhythmias. No conduction abnormalities.</td>
<td>No mutation found in screened genes</td>
</tr>
</tbody>
</table>

Arrhythmias were recorded during continuous ECG monitoring through ECG Holter or telemetry.
PP: atrial cycle length, RR: ventricle cycle length; AV: Atrioventricular, nsVT: Non sustained ventricular tachycardia, TdPVT: Torsade de pointes ventricular tachycardia.
relatives (Fig. 3): two relatives positive at genetic analysis showed long QTc, whereas the remaining three were without signs or symptoms suggestive of LQTS and/or impaired AV conduction. Because of their potential risk, these three silent carriers underwent treatment with beta-blockers.

Congenital LQTS associated with impaired AV conduction has previously been reported to be an almost untreatable condition. Infants usually die suddenly with most monitored deaths being caused by polymorphic VT [2,4–6]. The treatment of patients with LQTS and conduction abnormalities, especially in the presence of TdPVT, is hotly debated. Implantation of a defibrillator, suggested for children with particularly long QTc [1,8], would be technically difficult to implement in the youngest and is not without complications [9]. These patients had usually shown no abnormalities in the conduction system, its vascular supply and/or the surrounding nerve fascicles [6]. In fact, nearly all AV blocks associated with long QT were considered “pseudo” AV blocks, resulting from the interrelations between ventricular rate, action potential duration and His-Purkinje system refractoriness [5,10].

Our study, despite the small number of patients, shows that propranolol and mexiletine are effective in the treatment of infants with LQTS and conduction defects. If conduction abnormalities associated with LQTS are considered a “pseudo” impairment of AV conduction, beta-blockers could exert a favourable effect by prolonging the sinus intervals so that it exceeds the refractoriness of the conduction system, and mexiletine could act by shortening the ventricular repolarization time, besides reducing transmural dispersion of repolarization, so leading to a 1:1 AV conduction. Furthermore, we continued mexiletine treatment in addition to propanolol, as described in other cases [8], due to the success rate in terms of prevention of TdP and of disappearance of AV block, even in patients who subsequently at genetic analysis proved to be non-LQT3. In only one patient (Pt2), with

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**Fig. 3.** Pedigrees of the families of Patient 1 (panel A), Patient 2 (panel B), Patient 5 (panel C), Patient 4 (panel D) and relative sequence electropherograms showing the mutations identified. Solid and open squares (males) and circles (females) indicate clinically affected LQTS patients and healthy subjects, respectively. Dotted squares and circles indicate asymptomatic carriers (without clinical LQTS but genotype-positive). Arrowhead denotes the proband. Slash line indicates deceased individuals. *: impaired atrioventricular conduction. For details of the molecular analytic procedures see Frisso et al. [20].
Wencheback-type AV block, did beta-blockers alone result in a successful effect, probably due to the patient’s lower impairment of AV conduction.

The prolonged absence of life-threatening arrhythmias and conduction abnormalities, even with a very long QTc (up to 540 ms at last standard ECG at first discharge, or up to 510 ms at long follow-up), cannot invariably be considered, in our series, a marker of successful treatment, because sudden death or untreatable arrhythmias can still occur [11]. However, our study is encouraging being the first report of a single-centre series of patients affected by LQTS and impaired AV conduction in whom propanolol and mexiletine resulted in an event-free survival for a median of 62 months, without recourse to a PMK or an ICD unlike previous studies [2,8,11]. Regarding the patient who died (Pt3) consequent to an electrical storm despite repeated external cardioversion, it is possible that a PMK implantation could have improved the prognosis given the efficacy of pacing therapy together with mexiletine in patients with SCN5A mutations [12]: unfortunately, however, the result of the genetic analysis became available a few days after the patient died.

With regard to genetic background, LQTS with 2:1 AV block seems to be associated preferentially to KCNH2 mutations [13], occasionally to SCN5A or KCNH2 mutations or, more rarely, to SCN4B or CACNA1C mutations [14–18]. Our cohort of 6 genotyped infants shows that coexistence of LQTS and impaired AV conduction is linked to KCNH2 and SCN5A mutations; furthermore in Pt2 we found a KCNQ1 mutation associated with LQTS and impaired AV conduction. Thus far, a KCNQ1 mutation was found to cause AVB only in transgenic mice [19]. Genotype–phenotype analysis of the 4 mutation-positive families showed low penetrance of conduction defects; indeed only the probands of each studied family had impaired AV conduction. Therefore, screening for SCN5A, KCNQ1, KCNH2, KCNE1 and KCNE2 genes does not identify the subset of high-risk patients described in this paper. Conceivably, factors other than the mutations found so far may affect the probability of LQTS being associated to impaired AV conduction.

In conclusion, the possibility of treating this very severe form of LQTS pharmacologically overcomes the significant disadvantages of ICD implantation in young infants, namely, implantation difficulties, prolonged ICD protection with a consequent greater incidence of inappropriate shocks, and potentially more severe psychological problems [11]. Furthermore, genetic familial analysis may indicate treatment in high-risk but yet asymptomatic children.

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