Low incidence of cardiac events with β-blocking therapy in children with long QT syndrome

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Aims To evaluate the effect of beta-blockers in children with long QT syndrome (LQTS) we reviewed the outcome of 122 patients (pts).

Methods LQTS was diagnosed in 24 neonates and in 98 pts aged 0.5–15 years. Diagnosis was made because of syncope in 51 pts, bradycardia in 10 neonates and family history in 61 pts. The longest QTc ranged from 400 to 700 ms. Thirteen pts had 2:1 atrioventricular block and/or ventricular arrhythmias. Screening for mutations was performed in 118 pts. All children were treated with beta-blockers, annually checked by exercise testing and/or 24 h ECG monitoring.

Results Four pts died. Survivors were followed-up for 1–18 years (7.5±5.3 years). Five neonates and 3 older pts received a prophylactic pacemaker (1 death) so that only 111/122 pts survived and were followed-up with beta-blockers alone. None of them died and five experienced a non-fatal cardiac event. There was no cardiac event among pts who were diagnosed because of familial history and among symptomatic KCNQ1 pts who were effectively treated with beta-blockers.

Conclusion The outcome of children with LQTS under effective beta-blockers is favourable. Persisting arrhythmia or symptoms despite beta-blockers should aim at identifying other genotypes than KCNQ1.

Introduction

The long QT syndrome (LQTS) is a familial disease characterised by prolonged and abnormal repolarisation, associated with a high risk of ventricular arrhythmias, syncope and sudden death. Recent molecular genetic studies have shown that LQTS is due to mutations in genes encoding cardiac ion channels. As cardiac events are most often triggered by stress, emotion and acute arousal, beta-blockers are considered the treatment of choice in LQTS patients. Although beta-blockers have been shown to significantly reduce cardiac events, various studies have raised controversies on the adequate therapeutic strategies to be applied to patients with LQTS to prevent
potentially fatal cardiac events. However, data from the International Long QT Registry may be inaccurate, due to information gathered and transmitted from many centres in which management of patients is in essence heterogeneous. In this study, we sought to determine if beta-blockers are sufficient for secondary, as well as primary, prevention of cardiac events in children with LQTS. We therefore retrospectively evaluated our experience of LQTS in a series of 122 children treated with beta-blockers with a standardised follow-up.

**Methods**

**Patients**

The study population included 122 children, who were diagnosed with LQTS between 1984 and 2002. Diagnosis was made in the first month of life in 26 patients and episodes of bradycardia had been documented during routine in utero screening in seven of them. In the other children, age at diagnosis ranged from 5 months to 15 years, mean (SD) 6.4 (3.7) years, median: 6 years.

Sixty-one patients including 35 males and 26 females were symptomatic (Table 1, group 1): 51 had experienced non-fatal cardiac events, syncope in 44 cases and cardiac arrest requiring resuscitation in seven cases; the other 10 had been referred for neonatal slow heart rate due to sinus bradycardia in six cases and 2:1 atrioventricular (AV) block in four cases. Age at diagnosis was less than one month in 18/61 and ranged from 0.5 to 15 years, mean (SD) 7.2 (3.8) years, median: 7 years (n=43) in the rest of this group. Another group of 61 patients, including 25 males and 36 females, had no symptoms and were diagnosed after systematic familial screening (Table 1, group 2). Eight were neonates and age at diagnosis ranged from 0.3 to 14 years, mean (SD) 6 (3.7) years, median 5 years for the others.

The QT interval was measured prior to therapy in lead II (lead I or III if it could not be measured in lead II) from the 12-lead ECG during stable sinus rhythm and corrected by using Bazett’s formula. At the time of diagnosis, the longest corrected QT (QTc) interval ranged from 400 to 700 ms, mean (SD) 495 (59) ms, median: 480 ms. QTc was longer in symptomatic compared to asymptomatic patients (510 (62) ms versus 469 (31) ms, respectively; p=0.009). Fifteen children had a QTc<450 ms of which four were symptomatic and 11 asymptomatic. Diagnosis of LQTS was confirmed by molecular biology in all 15 cases.

Thirteen symptomatic patients had documented ventricular arrhythmias at the time of diagnosis. Nine neonates had episodes of partial AV-block, mostly 2:1, and intermittent bundle branch block, with torsades de pointes and/or ventricular tachycardia in 5 (Fig. 1) and with premature ventricular beats in one. Two older children had 2:1 AV-block on the ECG recorded after an initial syncope. Finally, two patients had episodes of torsades de pointes during permanent ECG-monitoring while they were in hospital for non-cardiological reasons (orthopaedic operation and ventilatory support in a premature baby).

Screening for mutations in KCNQ1, HERG and SCN5A was performed in 118/122 children.

Children were characterised as high risk, intermediate and low, taking in account QTc value, sex, and genotype when available, according to the stratification proposed in the reference.

<table>
<thead>
<tr>
<th>Table 1 Clinical data of LQTS patients</th>
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<tbody>
<tr>
<td><strong>Group 1: symptomatic</strong></td>
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<tr>
<td>N</td>
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<tr>
<td>Sex 35 M, 26 F</td>
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<tr>
<td>Symptoms 44 syncope, 7 cardiac arrest</td>
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<tr>
<td>Age 18 neonates 43 pts: 0.5–15 years</td>
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<tr>
<td>m: 6±3.7, M: 5 yrs</td>
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<td>QTc 420–700 ms</td>
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<tr>
<td>&lt;450 ms</td>
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<tr>
<td>&gt;500 ms</td>
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<tr>
<td>Gene KCNQ1 30</td>
</tr>
<tr>
<td>HERG 13</td>
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<tr>
<td>SCN5A 1</td>
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<tr>
<td>4 homozygous: JLN, HERG+KCNQ1, KCNQ1x2, SCN5Ax2</td>
</tr>
<tr>
<td>Risk Low 18</td>
</tr>
<tr>
<td>Intermediate 2</td>
</tr>
<tr>
<td>High 35</td>
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<tr>
<td>β-Alone 51/61</td>
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<td>Cardiac events 5</td>
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Beta-blocking treatment

All children were treated with beta-blockers, with standardised doses and follow-up. The choice of the drug was made according to age, weight and body surface area and treatment was started during hospitalisation with continuous monitoring in all neonates and in the symptomatic group. Nadolol (50 mg/m² body surface area/day, in two doses) was given to 74 patients, propranolol to 30 (3–5 mg/kg/day in three to four doses), acebutolol to 10 (10 mg/kg/day in three doses). In patients diagnosed because of family history, atenolol was given in three cases (50 mg/day) and bisoprolol in five others (10 mg/day). Temporary pacing was performed in 6/9 neonates who had partial AV-block with a ventricular rate of 120 beats per minute (bpm) combined with beta-blocking treatment, because of poor clinical tolerance at admission. Patients were only discharged when they had a stable cardiac rhythm, with no arrhythmia, and a limited maximum heart rate indicating effective beta-blockade. Beta-blocker treatment was considered effective if the maximum heart rate did not exceed 150 bpm in patients less than 2 years and 130 bpm in children and teenagers.

Close follow-up was performed every 6–12 months in three institutions in Paris: Necker Enfants-Malades, Robert Debré and Lariboisière. Controls relied on clinical events and 12-lead ECG. Twenty-four hour ECG monitoring and/or exercise testing were performed at least once a year. Exercise testing was performed by treadmill or by bicycle; when sufficient activity for age was not obtained, due to poor compliance or insufficient graded test, effective beta-blockade was assessed on 24-h Holter monitoring, showing a flattened heart rate curve with limited maximal heart rate. When the maximum heart rate was found to be higher than the maximum accepted value for age, patients were hospitalised; the treatment was given under medical control, 24-h Holter monitoring was checked again and beta-blocker dosage was increased if necessary.

Statistics

All statistical analyses were done using StatView SE software. Data were expressed as means±SD or medians (ranges). Univariate comparison of parameters between groups was performed by ANOVA for quantitative parameters with an unpaired t test and by the χ² test for qualitative parameters. The cumulative probability of a first cardiac event during follow-up were determined in the population of patients receiving beta-blockers only and in each genetic subgroup by means of the life-table method of Kaplan–Meier, and results were compared with the use of the log-rank test. Values of p<0.05 were considered statistically significant.

Results

Genotype

A heterozygous mutation was identified in KCNQ1 in 61 (51.2%) patients, in HERG in 36 (30.5%) patients and in SCN5A in two (1.7%). Interestingly, five (4.2%) patients had two mutations, each one being inherited from one parent (Table 1). No mutation was identified in the 14 remaining patients so far. Mutations were found in 48/61 symptomatic patients and in 56/61 asymptomatic patients diagnosed because of family history, without any difference of distribution of mutations in KCNQ1 (Table 1).

Risk stratification
Risk stratification could be performed in 112/122 children (Table 1). In the symptomatic group, 35 children were classified as high risk patients and 18 as low risk patients. In the pre-symptomatic group, 39 children were classified as low risk and eight at high risk.

**Control of beta-blocker treatment**

In three cases, the maximum heart rate reached by the patient was higher than the authorized threshold and this ineffective beta-blockade was due to non-compliance. There were 6 side effects of the therapy: two patients had asthma that disappeared when nadolol was changed for bisoprolol and celiprolol, two patients had postural hypotension, one patient had transient hypoglycaemia, and the last had Raynaud phenomenon that disappeared with bisoprolol.

During follow-up, acebutolol and propranolol were systematically changed to nadolol in 10 patients, for drug administration convenience. A total of 86 patients were on nadolol at the end of the follow-up.

**Overall deaths (Table 2)**

Two neonates died before hospital discharge. One patient died at 9 days of sudden AV-block, three days after the femoral pacing lead had been removed because of apparent recovery of a stable 1:1 sinus rhythm under propranolol (pt 3). Another one (pt 4) died of infection after implantation of a permanent pacemaker (PM). One fatal cardiac event occurred after hospital discharge in a patient in whom the family had stopped the beta-blocking treatment (pt 1). Finally, one death was unrelated to LQTS (car accident). Survivors (n=118) were followed-up for 1–18 years, mean (SD) 7.5 (5.3) years, median: 7.5 years (see Table 2).

**Additional therapy (Table 2)**

Before being discharged from the hospital, five neonates (pts 4–8) required implantation of a single chamber ventricular PM because they had episodes of 2:1 AV-block despite a slower sinus rate with beta-blocking therapy (1/5 death).

Although they had remained asymptomatic with beta-blockers, three patients received a prophylactic PM during follow-up, because they had abnormal 24-h ECG monitoring (pts 9–11). One patient had T-wave alternans at night. Another one had dissociation between a slow sinus rhythm and a faster junctional escape rhythm, as his older brother (pt 13) prior to syncope. The third patient had paroxysmal 2:1 AV-block, with block below the His. These three patients belonged to the high risk group.
Outcome of patients treated with beta-blockers alone (Table 2)

Thus, among the whole population, 111/122 patients survived and had a complete follow-up with beta-blockers alone (Fig. 2). None of these patients died, but 5/111 experienced non-fatal cardiac events during follow-up, with documented ventricular arrhythmias in three of them. Three patients are doing well since PM implantation (pt 12–13) or sympathectomy (pt 14). Two other patients had recurrent syncope and event counters of the PM memory displayed ventricular arrhythmia contemporary to syncope: patient 15 received an implantable cardioverter defibrillator (ICD) and patient 16’s parents have always refused ICD implantation. These five patients all belonged to the high risk group.

The other 106 patients, including 46/51 symptomatic cases and 60/61 diagnosed after familial screening (Table 1) remained free of symptoms with beta-blockers alone over a maximal follow-up of 18 years. Exercise testing and 24-h ECG monitoring showed 1:1 properly beta-blocked sinus rhythm without significant bradycardia or ventricular arrhythmia, including ventricular premature beats.

Genetic screening and correlation genotype-cardiac event

Among the 111 survivors who were treated with beta-blockers alone, 0/59 KCNQ1, 2/32 HERG and 2/5 patients with two mutations had a non-fatal cardiac event. All together, 4/5 patients with two mutations required additional therapy.

Kaplan–Meier analysis showed that the cumulative rate of survival without cardiac event in the 111 patients receiving beta-blockers was 94.4±0.025%. The cumulative rate of survival without cardiac event or death at 12 years after diagnosis differed among the subgroups according to the genotype (p<0.001 by the log-rank test). It is of note that we did not exclude from this analysis the two patients with KCNQ1 mutations who died during follow-up. If these two patients were excluded, no cardiac event was observed in the subgroup of patients with KCNQ1 mutation. Specifically, the cumulative survival rate without cardiac event or need for additional treatment on top of beta-blockers was lower among patients with a mutation in KCNH2 or SCN5A or with two mutations than among those with a single mutation in KCNQ1 (Fig. 3). The same pattern was observed when the analysis was performed with a risk stratification analysis according to the risks groups defined by QTc length, sex and genotype7 (p=0.001 by the log-rank test).

Discussion

There was no sudden death in our group of children with LQTS under beta-blocking therapy, provided the choice and dosage of beta-blocker was appropriate and the compliance carefully checked. None of the LQT1 patients and pre-symptomatic children treated with beta-blockers alone had syncope, cardiac arrest or sudden death during follow-up.

The use of beta-blockers is now widespread in patients with LQTS and with such treatment, reports based on large populations showed a radical improvement in outcome with a 15 year-mortality below 10%.2 However, recent studies have suggested that beta-blockers are not fully effective in preventing cardiac events and sudden death. Moss et al.4 have reported their analysis of beta-blocker therapy in LQTS patients, including adults and children. Therapy significantly reduced the rate of cardiac events but 32% of symptomatic patients experienced recurrent symptoms or death within 5 years while on beta-blockers. The risk of cardiac event was higher in patients with beta-blocking therapy initiated before ten years of age and in those who had a history of aborted cardiac death. In Garson’s series about 287 LQTS patients less than 21 years, 5% of patients who were thought to be
"effectively" treated had sudden death; however, the authors noticed that, among the children who died suddenly, fewer patients had had 24-h ECG monitoring and treadmill tests performed than those who did not die, which raises the question about the control of beta-blocking therapy. They also found that age at presentation was related to sudden death, as 16% of those who presented at less than 1 month of age died, compared with 7% of those presenting at older age. Our population is similar to those described in the literature regarding age at diagnosis and severity of prognosis in neonates, as 9/26 patients who were diagnosed at birth required additional treatment during follow-up or died before being discharged from the hospital.

The main limitation of these studies is that the authors did not know how compliant the patients were in taking the prescribed therapy. Assessment of the response to beta-blockers is difficult, due to the difficulties in standardising therapeutic protocols, obtaining regular and updated information about the patients and collecting the data. This is the reason why we selected an homogeneous group of children, who received uniform dosages of beta-blockers, had a standardised follow-up including yearly exercise tests and 24 h ECG monitoring, and were checked by only three physicians. Among beta-blockers, we recommend nadolol as first choice because of its long half-life, demonstrated powerful beta-blocking effect and low brain penetration, improving the efficacy/tolerance ratio. It is noticeable that 86 of our patients were treated with this drug, at a dose of 50 mg/m² body surface area/day, in two doses. Beta-blockers had very few side effects in the group of children we have treated.

In our population, there was no death among the 111 children who survived the neonatal period, received beta-blockers alone and were compliant to treatment. Furthermore, 106/111 (95.5%) had no cardiac event during the follow-up. All LQT1 patients belong to this uneventful group of children we have treated. In Schwartz’s recent series 81% of LQT1 patients remained free from recurrence, with a total mortality rate of 4%. In our group of patients, all heterozygous KCNQ1 patients are doing well with beta-blockers alone. Neonatal conduction disorders are especially frequent in HERG mutations, which were found in all six genotyped neonates who presented with 2:1 AV-block. The incidence of cardiac event was also very rare in the group of 61 pre-symptomatic patients, including 18 intermediate or high risk patients, who received beta-blockers alone; only one of these patients, a Jervell and Lange-Nielsen syndrome, received a prophylactic PM. We believe that all the LQTS children should be treated and carefully checked. In the whole population, the only patient who died had a mutation in KCNQ1 with a normal QTc interval and an estimated low risk of cardiac event; the family had stopped treatment because the child was doing well. This confirms that a normal phenotype in the presence of an abnormal genotype may be associated with a risk of syncope or death.

Additional treatments, other than beta-blockers, may be necessary in some patients with LQTS particularly with other genotypes. Incomplete AV-block mainly occurs in neonates, because they have faster atrial rates and the P-waves occur before the end of a prolonged ventricular repolarisation, leading to functional AV-block. Implantation of a PM, in combination with beta-blocking therapy, is mandatory in neonates who have AV-block, as they have a high risk of sudden death. In our population, five neonates required PM implantation (one death) and another died early in the series, shortly after temporary pacing was stopped. Beyond neonatal period, cardiac pacing may effectively prevent recurrence of torsade de points, and PM implantation is indicated when pause or bradycardia-dependent ventricular arrhythmias are documented. In our population, three patients had a prophylactic implantation after the neonatal period, on the basis of 24-h ECG monitoring.

Despite adequate beta-blocking therapy, five patients had unexpected non-fatal events during follow-up. Four patients received a PM because of recurrent syncope, with two successes and two failures. As long-term studies suggest that sympathectomy can reduce arrhythmias when beta-blockers fail two patients had left cardiac sympathetic denervation performed by the same surgeon, with one success and one failure. Finally, ICDs are increasingly being used to prevent sudden death in patients with LQTS. When beta-blockers fail two patients had left cardiac sympathetic denervation performed by the same surgeon, with one success and one failure. Finally, ICDs are increasingly being used to prevent sudden death in patients with LQTS. Due to a higher rate of complications in young children, it is not our policy to implant ICD in children as a first line therapy, even in patients who experienced aborted sudden death. We have recommended ICD implantation in two patients who had syncope with documented ventricular arrhythmias despite additional therapy with permanent pacing in one case, permanent pacing and sympathectomy in the other.

Cardiac events occur under specific circumstances, which vary in a gene-specific manner. In Schwartz’s recent series 81% of LQT1 patients remained free from recurrence, with a total mortality rate of 4%. In our group of patients, all heterozygous KCNQ1 patients are doing well with beta-blockers alone. Neonatal conduction disorders are especially frequent in HERG mutations, which were found in all six genotyped neonates who presented with 2:1 AV-block. Beyond the neonatal period, 2/32 HERG patients treated with beta-blockers alone experienced a non-fatal cardiac event. Patients with SCN5A mutations mainly have cardiac event and sudden death at rest, so that prophylactic pacing will have more indications in those patients. Additional treatment with a Na+ channel blocker could be discussed. Although QT shortening under mexiletine has been documented, no prospective study has established a beneficial effect on cardiac events and mortality. Finally, 4/5 patients of our series with two mutations required additional therapy, prophylactically or after a cardiac event. Thus, in the future, identification of mutation(s) may help in adjusting the therapy.

Limitations of the study

The high potential of the long QT syndrome to cause lethal events is demonstrated by the incidence of cardiac arrest/sudden death among untreated patients. Beta-blocking treatment has become the standard prophylactic therapy of LQTS, and it appears now ethically unjustifiable to perform double blind placebo controlled trials to evaluate its efficacy. We lack any effective marker of drug efficacy other than continued absence of syncope or sudden death in the group of children that...
we have studied, and patients can only serve as their own control. So far, risk stratification has not allowed identifying patients who have absolutely no risk of sudden death, even in pre-symptomatic patients and it is noticeable that in our series, the only patient who died despite an estimated low risk was not taking his beta-blocking treatment.

In conclusion, the outcome of children with LQTS who were effectively treated with beta-blockers was satisfactory: there was no death among children taking their medications and 95.5% of them had no symptoms. No cardiac events were reported in patients with KCNQ1 mutations and in patients diagnosed because of family history. Among patients who experienced an unexpected clinical cardiac event, despite adequate beta-blocking treatment, none have died nor have sequelae. Additional therapy such as PM and ICD implantation may be indicated in certain forms of LQTS such as LQT2 neonates with conduction disorders, in LQT3 patients or when molecular biology reveals two mutations in the same patient.

References

17. Silka MJ, Kron J, Dunnigan A et al. Sudden cardiac death and the use