The Jervell and Lange-Nielsen syndrome; atrial pacing combined with ß-blocker therapy, a favorable approach in young high-risk patients with long QT syndrome?

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BACKGROUND Patients with Jervell and Lange-Nielsen syndrome (JLNS) exhibit severe phenotypes that are characterized by congenital deafness, very long QT intervals, and high risk of life-threatening arrhythmias. Current treatment strategies include high doses of beta-blocker medication, left cardiac sympathetic denervation, and ICD placement, which is challenging in young children.

OBJECTIVE The purpose of this study was to evaluate the safety and effect of pacing in addition to beta-blocker treatment in children with JLNS.

METHODS All genetically confirmed patients with JLNS born since 1999 in Norway were included in the study. Data on history of long QT syndrome–related symptoms, QT interval, and beta-blocker and pacemaker treatment were recorded.

RESULTS A total of 9 patients with QT intervals ranging from 510 to 660 ms were identified. Eight patients developed long QT syndrome–related symptoms, and 1 patient died before diagnosis. The survivors received beta-blocker medication. Seven patients also received a pacemaker; 1 had a ventricular lead and 6 had atrial leads. The patient with the ventricular lead died during follow-up. The 6 patients with atrial leads survived without events at a mean follow-up of 6.9 years after pacemaker implantation. Two patients received prophylactic upgrade to a 2-chamber ICD.

CONCLUSION No arrhythmic events occurred in 6 very young JLNS patients who received atrial pacing in combination with increased doses of beta-blockers during 7-year follow-up. If confirmed in additional patients, this treatment strategy may prevent life-threatening arrhythmias in this high-risk patient group and may act as a bridge to insertion of a 2-chamber ICD when left cardiac sympathetic denervation is not available.

KEYWORDS Arrhythmia; Cardiac pacing; Genetics; Implantable cardioverter–defibrillator; Jervell and Lange-Nielsen syndrome; Long QT syndrome

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Introduction

Jervell and Lange-Nielsen syndrome (JLNS)[1] is an autosomal recessive form of the long QT syndrome (LQTS), which is caused by mutations in the *KCNQ1*[2,3] or *KCNE1*[4] gene. JLNS is characterized by congenital deafness and severe cardiac phenotypes with very long QT intervals, high risk of life-threatening ventricular arrhythmias, and breakthroughs of arrhythmias despite beta-blocker treatment.[5,6] We previously reported a high prevalence of JLNS in Norway[7] due to founder mutations.[8] A small subgroup of patients with mutations on both *KCNQ1* alleles and prolonged QT intervals do not present with deafness but appear to have a similar risk of cardiac events as JLNS patients.[9]

Beta-blocker medication is the mainstay therapy in patients with LQTS, and high doses are often required to suppress ventricular arrhythmias. High doses of beta-blocker medication are associated with several side effects, the most important being bradycardia. Pacemaker implantation in patients with severe bradycardia may help them tolerate the medical treatment. Furthermore, pacemaker therapy with relatively rapid pacing can also prevent torsades de pointes ventricular arrhythmia and suppress electrical storms in acquired[10,11] and congenital LQTS.[12]

ICD placement has been recommended in children with JLNS, particularly after 10 years of age.[5] ICD therapy is

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sometimes necessary even in younger patients, but it is complicated by lead problems due to the patient's small body size, growth, and the prospect of lifelong ICD therapy. Thus, when beta-blocker therapy is not sufficient in very young JLNS patients, the choice of therapy is challenging. Left cardiac sympathetic denervation (LCSD) has been reported as an option.[13,14] However, this surgery is not available in all countries, and the experience with alternative therapies in this patient group is limited.

Ten years ago, we were confronted with a series of young JLNS patients who had cardiac events despite beta-blocking therapy in addition to young JLNS patients in whom an effective beta-blocker dose could not be achieved because of bradycardia. We were concerned about the high complication rate after ICD insertion in children in addition to the risk of appropriate and inappropriate shocks and the inherent risk of triggering life-threatening electrical storms in these patients.[15]

Consistent with the above-mentioned rationale for pacemaker therapy, we decided to implant pacemakers in these JLNS patients to achieve higher doses of beta-blocker medication. In this study, we report the clinical characteristics, treatment (both medical and with implantable devices), and outcome of young patients with JLNS.

Methods

Recruitment of study population

All genetically confirmed patients with JLNS in Norway born after January 1, 1999, were included in this retrospective study. Recruitment was facilitated by the start of nationwide genetic testing for LQTS at our center. In the same time period, implementation of a national pediatric cochlear implant program was initiated and conducted from our center, which included children with congenital deafness.

Genetic testing was performed as part of the diagnostic workup and executed as previously described.[8] Only subjects with homozygous or compound heterozygous confirmed pathogenic mutations were included.

Data collection

The medical records of all patients included in the study were retrospectively scrutinized for data, including age, height, and weight at diagnosis and during follow-up. LQTS-related cardiac events were classified as syncope when there was a loss of consciousness alone; as seizures with movements reminiscent of convulsions; as life-threatening attacks when the measures to revival were started; and as torsades de pointes when documented with ECG monitoring. From 12-lead ECGs, the QT intervals were measured from the start of Q to the end of the T wave and corrected for heart rate using the Bazett formula.[16] Beta-blocker medication and dosages were recorded at initiation, at pacemaker implantation, and during follow-up. Medication dosages were reported according to body weight. We recorded age at device implantation, heart rate and programming modus, complications due to device implantation, and indications for device replacement. Routine follow-up included echocardiography to exclude pacing-induced cardiomyopathy, Holter recordings to confirm regular pacemaker function and adequate beta-blocker treatment, and treadmill tests in older children.

Ethics

The study was classified as a quality control study and was approved by the review board of Oslo University Hospital.

Statistical analysis

Group data are presented as mean ± SD or median (range). For QT intervals before and after atrial pacing, a paired *T* test was used. Because of the low number of participants, no further statistical analyses were performed.

Results

Clinical characteristics

The study included 9 genotype-positive patients. All patients were homozygous or compound heterozygous for pathogenic mutations in the *KCNQ1* gene. Age at diagnosis was 1.7 ± 1.6 years [median 1.1 (range 0–3.3) years], and 6 of 9 (66%) were females (Table 1). Four of 9 patients (44%) were diagnosed a few days after birth as a result of low heart rates and very long QT intervals. In 1 patient, the genetic status of the parents was known because an elder sibling had JLNS. The remaining 5 patients were diagnosed with LQTS between 2 and 3 years of age. In cases 8 and 9, the diagnosis was not known at the time of cochlear implantation. In case 9, a deaf 3-year-old boy had a diagnosis of JLNS that was genetically confirmed postmortem, despite suffering >100 events from the age of 14 months, including life-threatening events that were misdiagnosed as seizures and breath-holding spells. This led to a change in policy in our otolaryngology department and a screening program with ECG before cochlear implantation was established. Case 2 was diagnosed by routine ECG before cochlear implantation. Eight of 9 patients (89%) received cochlear implants at a median age of 2.1 (range 0.3–3.2) years and have been previously reported in studies evaluating the causes of hearing impairment[7] and aspects regarding cochlear implantation.[17] One patient (case 6), who was compound heterozygous for 2 pathogenic mutations in the *KCNQ1* gene, had only discrete high-frequency hearing loss but a very long QT interval. Overall, these 9 children were followed for an average of 7.5 ± 5.0 years [median 9.3 (range 0.6–14.2) years] from the first contact with our institution and follow-up, which covered a total of 67.9 patient-years.

ECG and QT interval

QTc was 590 ± 50 ms, median was 600 ms (range 510–660 ms), and ECG in 7 of 9 patients (77%) showed T-wave alternans (Table 2). Figure 1 shows the ECG of case 6 before (panel A) and after (panel B) pacing. QTc decreased in the 6 patients with atrial pacing, from 610 ± 60 ms to 490 ± 10 ms ($P < .01$).

Table 1 Summary of the cases

Case	Sex	Gene defect[†]	Age (years)			
			At long QT syndrome diagnosis	At cochlear implantation	At pacemaker implantation	At last follow-up
1	F	c.572delTGCGC (p.R192Cfs*91)/c.572delTGCGC (p.R192Cfs*91)	0.0	0.7	6.4	9.7 (a)
2	F	c.572delTGCGC (p.R192Cfs*91)/c.572delTGCGC (p.R192Cfs*91)	3.0	3.2	NI	10.3 (a)
3	F	c.572delTGCGC (p.R192Cfs*91)/c.1552C>T (p.R518X)	0.0	2.3	7.5	15.2 (a)
4	M	c.572delTGCGC (p.R192Cfs*91)/c.1552C>T (p.R518X)	0.0	0.3	0.0	9.4 (a)
5	M	c.572delTGCGC (p.R192Cfs*91)/c.1588C>T (p.Q530X)	2.2	2.3	2.3	2.7 (d)
6	F	c.783G>C (p.E261D)/c.1588C>T (p.Q530X)	3.3	*NI*	3.8	7.0 (a)
7	F	c.1588C>T (p.Q530X)/c.1588C>T (p.Q530X)	0.0	0.5	0.0	9.3 (a)
8	F	c.1588C>T (p.Q530X)/c.1588C>T (p.Q530X)	3.3	1.9	5.3	14.0 (a)
9	M	c.1588C>T (p.Q530X)/c.1760C>T (p.T587M)	Postmortem	2.5	NI	3.2 (d)

a = alive; d = dead; NI = not implanted.

[†]*KCNQ1* reference sequence: NM_000218.2.

Medication

All patients, except case 9, who died before diagnosis of JLNS, were treated with beta-blockers at the highest possible dose considered by the treating physician (Table 2). Propranolol was usually divided into 3 doses, and metoprolol and nadolol into 2 daily doses. In 3 patients (cases 4, 7, and 8), sufficient beta-blocker dosages were not reached before pacemaker implantation. Case 4 had a documented minimum heart rate of 40 bpm before initiation of beta-blocker and several symptomatic bradycardiac episodes between 40 and 50 bpm combined with T-wave alternans on propranolol 0.3 mg/kg. Case 7 had a documented sinus arrest with a long pause when beta-blocker therapy was initiated. Case 8 was symptomatic with fatigue and had a low mean heart rate on Holter (below 2 SD for age) and an insufficient chronotropic response; increase of beta-blocker was refused by the parents. Another 3 patients had syncopal events on beta-blocker before pacemaker implantation. We were able to increase beta-blocker treatment in 7 of 9 patients (78%) after pacemaker implantation. In 1 patient (case 5), the daily metoprolol dose was increased from 3.3 mg/kg to 6.2 mg/kg after pacemaker implantation. In the other patients, median daily propranolol dose was 1.2 mg/kg (range 0.3–3.1 mg/kg) before and 3.6 mg/kg (range 2.2–5.7 mg/kg) after pacemaker implantation. Beta-blocker therapy was subsequently changed to nadolol in these patients. Daily median nadolol dosage at the most recent visits was 2.1 mg/kg (range 1.5–2.4 mg/kg), and dosages were further increased in patients with the lowest doses at the last visit according to weight gain. One patient, who was asymptomatic but was diagnosed by ECG screening (case 2), received only beta-blockers and no pacemaker implantation and remained asymptomatic on propranolol 3 mg/kg/d. Case 5 remained on metoprolol and had cardiac events with documented torsades before and after pacemaker implantation.

Pacemaker therapy, complications, and follow-up

Indications for pacemaker therapy were cardiac events despite beta-blocker therapy and intolerable bradycardia and pauses at insufficient beta-blocker doses. In all, 7 of 9 children (78%) received a single-chamber pacemaker in addition to beta-blocker treatment at a median age of 3.8 years (range 0–7.5 years). Six patients received atrial leads, and 1 child (case 5) received a ventricular lead (Table 3). Upgrades from a unipolar epicardial to a bipolar transvenous atrial lead were performed in 2 children at the ages of 6.8 and 7.2 years. Upgrades from a transvenous atrial pacemaker to a

Table 2 Symptoms, ECG, and beta-blocker dosage before pacemaker implantation, of case 1 immediately before death, and of case 5 at initial presentation

Case	Symptoms	Heart rate	Range QTc (ms)	T-wave alternans	Mean QTc (ms)	Beta-blocker	Dosage (mg/kg/d)
1	Bradycardia, syncope	60	580–660	Yes	600	Propranolol	2.9
2	No symptoms	80	510–550	No	530	None*	
3	Bradycardia, syncope	53	570–640	Yes	620	Propranolol	3.1
4	Bradycardia	94	520–570	Yes	550	Propranolol	0.3
5	Seizures, life-threatening attacks	65	560–580	Yes	580	Metoprolol	3.3
6	Syncope	70	640–700	Yes	660	Metoprolol	1.7
7	Bradycardia, asystole	97	630–670	Yes	630	Propranolol	1,1
8	Seizures	80	490–540	No	510	Propranolol	1.2
9	Seizures, life-threatening attacks	100	590–670	Yes	630 590 (median 600)	None	

*No beta-blockade at the time of ECG, later propranolol 3 mg/kg/d.

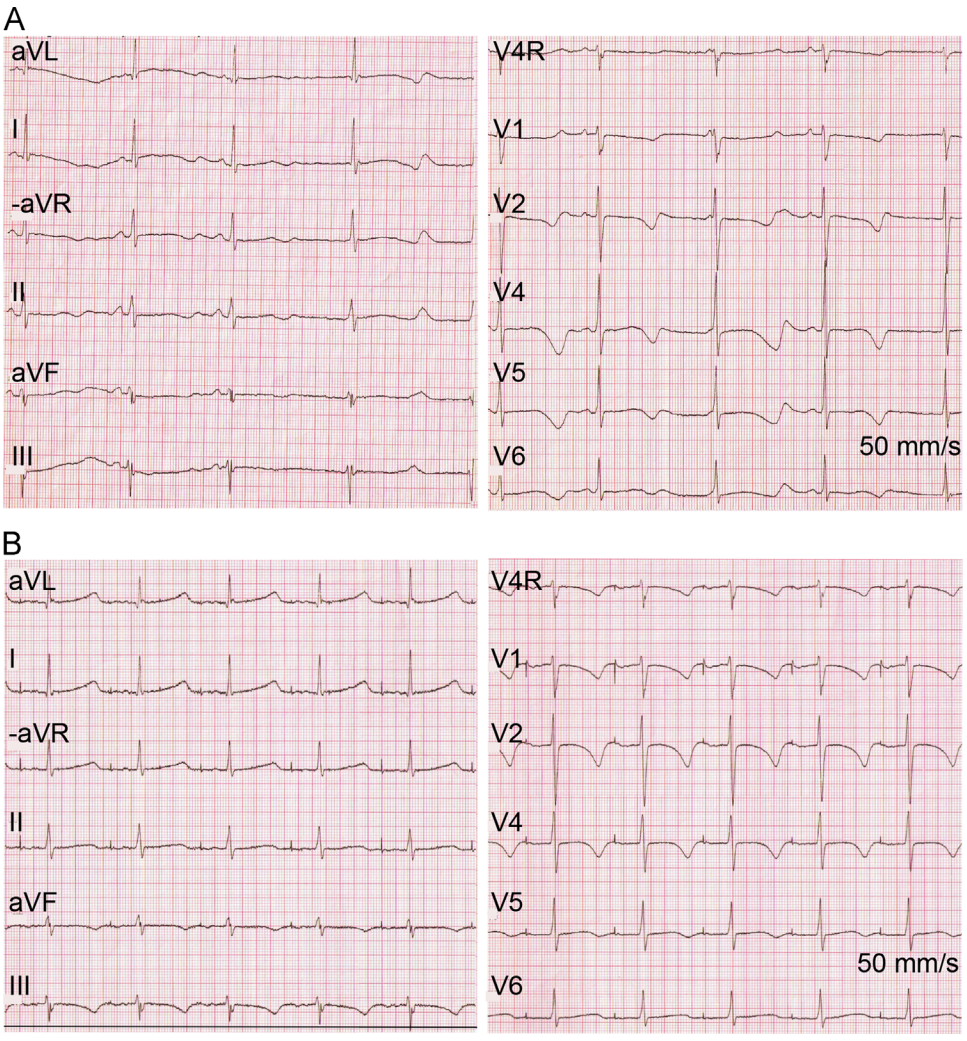

Figure 1 Twelve-lead ECG of case 6 before **(A)** and after **(B)** pacemaker implantation. **A:** Note the loss of sinus rhythm and T-wave alternans with variable extremely long QT intervals. Mean QTc = 660 ms. **B:** With atrial pacing, the rhythm is regular, and QTc = 520 ms.

dual-chamber ICD were performed in 2 children at the ages of 11.8 and 14.7 years. Complications due to lead displacements were observed in 2 patients (Table 3). The patient with the ventricular lead (case 5) had another life-threatening event with torsades de pointes arrhythmia during intermittent pacing due to lead dislocation 8 weeks after pacemaker implantation. Although the lead was revised, the child died 3 months later during a fatal event. None of the patients with atrial leads had any cardiac event during mean follow-up of 6.9 ± 2.9 years after pacemaker implantation. One girl (case 1) also had diabetes type I and was using an insulin pump. During an episode with gastroenteritis, she had a hypoglycemic fainting episode, which was confirmed by blood glucose samples.

The pacemaker of case 5 was first programmed in the VVI mode with a rate of 80 bpm and later in VVIR mode 100 to 130 bpm. The pacemakers of the 2 infants who received epicardial atrial leads were programmed in the AAI mode with rates from 115 to 125 bpm. After 1 year of age, the pacemakers of all children with atrial leads were programmed in the AAIR mode

Table 3 Initial pacemaker implantation and reinterventions

Case	Leads	Pacing mode	Complications and further interventions
1	Bipolar transvenous	AAIR	Electrode dislocation at 3 days revised
3	Bipolar transvenous	AAIR	Upgrade to 2-chamber ICD at age 14.7 years
4	Unipolar epicardial	AAIR	Upgrade to bipolar transvenous lead at age 7.2 years
5	Unipolar transvenous	VVI	Electrode dislocation at 8 weeks revised, death at age 2.7 years
6	Bipolar transvenous	AAIR	None
7	Unipolar epicardial	AAIR	Upgrade to bipolar transvenous lead at age 6.8 years
8	Bipolar transvenous	AAIR	Upgrade to 2-chamber ICD at age 11.8 years

ICD = implantable cardioverter–defibrillator.

with a sleeping rate of 80 bpm, base rate of 80 to 90 bpm, and maximum rate below the rate of AV conduction block. The mean heart rate of the 6 atrial paced patients on the latest Holter recording was 88 ± 4 bpm. Holter recordings revealed occasional premature beats, occasional blocked beats during deep sleep at night, occasional far-field sensing of the ventricular signal with delayed atrial pacing, occasional undersensing of sinus rhythm with competitive atrial pacing, and in 1 case with a unipolar epicardial atrial lead, a pause that could only be explained by far-field sensing of the T wave. The latter was resolved by an upgrade to a bipolar transvenous lead.

Discussion

This study showed that 6 JLNS patients treated with a combination of an atrial pacemaker and beta-blocker remained free from arrhythmic events during mean follow-up of 6.9 years after pacemaker implantation. One male patient with ventricular pacing died during the follow-up period. These results may indicate that the combination of atrial pacing and beta-blocker therapy may be a potential alternative strategy in very young JLNS patients as a bridge to ICD placement.

Beta-blocker therapy in LQTS

All patients in our study, except the 1 male patient who died before diagnosis was made, were treated with beta-blocking medication during the follow-up period. Beta-blocker treatment is efficient as antiarrhythmic therapy in patients with LQTS, particularly LQTS type 1.[18] The effect appears to vary between different beta-blockers in the treatment of LQTS,[19] and metoprolol is considered less efficient than propranolol or nadolol.[19,20] The limited number of patients in our study did not allow for conclusions regarding the effectiveness of different beta-blockers. Regardless of the type of beta-blocker, a recurrence rate with beta-blocker of 51% to 85% in patients with JLNS has been reported in large surveys.[5,6,20] We also observed several recurrent events in patients on beta-blocker before pacemaker implantation, although 3 of these patients were on insufficient beta-blocker dosages. We were able to increase the doses of beta-blockers after pacemaker implantation, and we preferred nadolol twice daily in older children instead of propranolol three times per day because compliance is an important factor in beta-blocker effectiveness.[18]

Rationale for pacemaker therapy in LQTS

Pacing at higher rates was reported to prevent torsades de pointes ventricular tachycardia in drug-induced LQTS 5 decades ago.[10] Additional case reports have indicated that pacing prevented ventricular arrhythmias in congenital LQTS.[12,21] Four additional studies published from 1987 to 1999,[22–25] which included 8 to 37 patients, showed the potential benefit of pacing when given in addition to beta-blocker therapy in high-risk patients with LQTS.[24,25] However, these studies had partly overlapping patients and consisted of heterogeneous patient populations, including children and adults, LQTS patients with an unknown genotype of LQTS, and those with varying frequencies of AV block.

Importantly, previous studies provided no clear indication of optimal pacing mode, although breakthroughs of arrhythmias on beta-blocker therapy were abolished by switching from ventricular to atrial pacing in an LQTS case report from 1997.[21] Our study indicated that AAI pacing may be preferable when possible, and ventricular pacing should be avoided. Right ventricular pacing may potentially induce significant cardiomyopathy, particularly at high pacing rates. Furthermore, ventricular pacing without AV synchronicity may result in the next AV conducted sinus beat occurring in the vulnerable interval and triggering arrhythmias. Finally, the abnormal T waves in LQTS commonly result in T-wave oversensing, which may result in incorrect pacing inhibition.[26] Thus, VVI pacing in LQTS is not a neutral intervention, and some of the features useful in a normal pacing population might be harmful in LQTS patients.[27] Sporadic undersensing or oversensing of ventricular activity can be deleterious in a LQTS patient, but it is often of minor concern in a normal pacemaker patient. Malfunction of pacing leads has been associated with major problems, as also observed in our case 4.[24,25] We monitored our JLNS population by performing regular Holter recordings to ensure that every beat was correctly paced and conducted. AAI pacing is preferred as long as 1:1 conduction is ensured.[23] Thus, we tested AV conduction in each case at higher rates, and maximum pacing rate was established clearly below the rate of AV conduction block. Furthermore, the sensing threshold and blanking and refractory intervals were carefully programmed to avoid undersensing and oversensing.

Pacing rate

A minimal heart rate between 60 and 80 bpm is considered to prevent torsades de pointes arrhythmias.[23,27,28] In this study, we used pacing rates at 90 bpm during the day and 80 bpm during the night in children >1 year of age, and rates from 115 to 125 bpm in children ≤ 1 year of age. Pacing at higher rates during exercise might reduce stress in LQTS type 1 patients,[27] particularly when the intrinsic heart rate of the patient is not increasing, either due to the lower heart rate in these patients or the effects of beta-blockade. QTc decreased in our 6 patients who were AAI paced. However, the patients were older and received higher doses of beta-blocker at ECG follow-up compared to baseline, limiting the interpretation.

We believe that there probably is a dual mechanism of beneficial action in our patients: increased heart rate by atrial pacing preventing ventricular arrhythmias and the possibility of increasing antiarrhythmic beta-blocker medication. However, pacing at faster heart rates increases the risk of tachycardia-induced cardiomyopathy. Unfortunately, the maximal heart rate that can be used safely over longer periods is unknown.[27] We monitored heart rate by Holter recordings and exercise tests with the aim of 100% atrial

pacing and increased the beta-blocker dose when the intrinsic rhythm exceeded the pacing rate. Furthermore, echocardiography was performed regularly in all patients to exclude pacing-induced cardiomyopathy.

Recurrent events and ICD therapy in very young LQTS patients

During the follow-up period, we upgraded 2 of the patients with atrial pacing to a dual-chamber ICD on primary indication, after unchanged strategy with continuous AAIR pacing and beta-blockade. They have been arrhythmia-free during the follow-up period. Pacing in LQTS has been less reported less frequently after 2002, most likely because of the greater number of patients receiving an ICD. In 2010, 2 larger studies on ICD treatment in LQTS patients, including children, were published.[29,30] They reported high rates of appropriate and inappropriate shocks and complications. Data from JLNS patients,[6] without providing any information on age at ICD insertion, reported at least 1 appropriate shock in 75% of the patients and multiple shocks in 63% of the patients during follow-up of 4.9 years after ICD placement. In 2006, Schwartz et al[5] reported arrhythmia recurrences in 9 of 11 patients with a pacemaker and in 4 of 13 patients with an ICD, but also in 9 of 16 patients with LCSD. Some of the patients had more than 1 additional therapy, thus limiting comparisons to our study. Apart from these summary data, no data on arrhythmia recurrences and atrial pacing in JLNS are available in some of the largest centers worldwide. The very high risk of shocks highlights the fact that ICD placement alone is not sufficient to treat high-risk LQTS patients, and all possible measures are necessary to ensure event-free survival.[31,32]

Insertion of the ICD device is technically complicated in very young children. The ICD is larger and heavier than a pacemaker, and if an ICD is placed, a dual-chamber ICD should be chosen to avoid ventricular pacing. In our study, 2 patients experienced complications with lead dislocations. Further potential risks include infections, vascular complications, and device erosion, in addition to lead replacement necessary because of growth. Implantation of an atrial pacemaker involves simpler instrumentation and might, in combination with increased doses of beta-blocker medication, serve as a bridge to dual-chamber ICD placement in very young patients with JLNS or high-risk LQTS.

Further intervention to prevent events in high-risk LQTS patients is LCSD.[13,14] LCSD has been proposed as an additional treatment and might also serve as a bridge to ICD in young patients, particularly in case of bradycardia and beta-blocker intolerance because LCSD does not lower the heart rate.[33,34] None of our patients underwent this surgery.

Study limitations

All the JLNS patients in our study had mutations in the *KCNQ1* gene, which includes a higher risk compared to patients with *KCNE1* gene mutations.[5] However, 6 of 9 patients (67%) were female, and 5 of 6 patients (83%) were female in the group with atrial pacing. Females are reported to have a lower risk for life-threatening events,[5,6] and gender differences might have influenced the outcome.

Although this was a comparatively large single-center study of JLNS patients, the study included a very limited number of patients, and the study had a retrospective design. Therefore, our conclusions are limited and preliminary, and future studies are needed to confirm our results.

No arrhythmic events occurred in 6 very young JLNS patients with atrial pacing in combination with increased doses of beta-blocker during 6.9 years of follow-up. The concept of combining atrial pacing with adequate beta-blocker therapy may act as a bridge for subsequent ICD therapy in very young patients with high risk LQTS when LCSD is not available.

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