Jervell And Lange-Nielsen Syndrome In A Deaf Children Population

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Citation

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Abstract

The Jervell and Lange-Nielsen syndrome is an infrequent form of long QT syndromes in which prolonged QT interval and congenital deafness exist together. Affected patients are prone to syncopal attacks and sudden death due to fatal ventricular arrhythmias. In this study, we attempted to identify patients with Jervell and Lange-Nielsen syndrome amongst children with congenital hearing loss. The corrected QT interval was measured from the 12 lead electrocardiogram using Bazett's formula, and was considered prolonged when it exceeded the normal upper limit of 440 ms. Nine out of 116 patients (11,8±2,7 years, range 7 to 18 years) with congenital deafness had a corrected QT interval longer than 440 ms. Although they did not met the definite diagnostic criteria according to Schwartz criteria, all could be defined as having intermediate probability of LQTS according to revised criteria. Family history for deafness was positive in 59 (50.8 %) patients, and consanguinity marriage was present in parents of 50 children (43.1 %). In conclusion, this recessively inherited syndrome should be screened in children with congenital deafness especially in areas where consanguineous marriages are frequent.

INTRODUCTION

Jervell and Lange-Nielsen syndrome is characterized by congenital sensorineural deafness and prolonged QT interval. It forms a small percentage of all long QT syndromes (LQTS) ([1,2]). Moss et al1 described 196 patients with LQTS and only 11 (6 %) of them had congenital deafness. In another report hearing loss was present in 4.5 % of 287 patients with LQTS (2). Several studies investigated the prevalence of Jervell and Lange-Nielsen syndrome in deaf population ([3,4,5]). In 10 studies that screened 6557 deaf children, the prevalence was found to average 0.21 % with a range of 0-0.43 % ([6]). Two studies from Turkey estimated the prevalence to be 0.57 % and 1.3 %, which are higher than that reported in the literature (4,5). It was the aim of this present study to define the prevalence of LQTS among deaf school children.

MATERIAL AND METHODS

A hundred and thirty-seven deaf children attending Denizli deaf mute school were studied. Children with acquired deafness (21 children) were excluded, and our study group consisted of 116 children with congenital deafness. A questionnaire was employed and sought information about associated findings, symptoms, and family history. As a first step of the study all children were examined by an otorhinolaryngologist and pediatric cardiologist. Audiometric records were examined.

Twelve-lead electrocardiogram (ECG) were recorded with an electrocardiographic recorder (Cardiopak) at a paper speed of 25 mm/s. QT interval was manually measured from the first deflection of the QRS complex to the point of T wave offset, defined by return of the terminal T wave to the isoelectric T-P interval baseline. When a U wave was present, the QT interval was measured to the nadir of the curve between the T and U waves. The lead was not included if the end of the T wave could not be determined correctly. QT interval was corrected for heart rate (QTc) according to Bazett's formula. The QTc interval recorded was the longest found on a 12 lead ECG. Because of sinus arrhythmia, the RR intervals were calculated according to the average heart rate. None of the patients had bundle branch block or arrhythmia.

In the second step children who had QTc interval longer than 440 ms were further evaluated. Two more times ECG, echocardiography, exercise testing, and 24 hour Holter monitoring were performed in these children. Echocardiographic evaluation was performed to assess left ventricular function and any structural anomalies. The exercise test was performed as a symptom-limited treadmill

effort test according to the modified Bruce protocol. Heart rate, blood pressure, and QTc interval were determined at rest, at the maximal effort, and at the first and third minutes of recovery period. Twenty-four hour ambulatory Holter monitoring was evaluated for arrhythmias, heart rate, and T wave configuration. Family members of these cases were investigated for history of deafness, syncopal attack, and sudden death. Electrocardiographic examination of family members were also performed for determination of QTc interval. All available data were evaluated according to Schwartz criteria and revised criteria (Table I).

Figure 1

Table I: Long QT Syndrome Diagnostic Criteria*

Original criteria	
Major criteria: Prolonged QT interval (QTc>440 ms)	
Stress induced syncope	
Family members with LQTS	
Minor criteria: Congenital deafness	
Episodes of T wave alternans	
Low heart rate	
Abnormal ventricular repolarization	
The diagnosis of LQTS is made in the presence of either two major criteria or one major and two minor criteria.	
Revised criteria	
ECG findings	
QTc>470 ms	3
460-470 ms	2
450 ms (in males)	1
Torsade de pointes	2
T wave alternans	1
Notched T wave in three leads	1
Low heart rate for age	0,5
Clinical history	
Syncope with stress	2
Syncope without stress	1
Congenital deafness	0,5
Family history	
Family members with definite LQTS	1
Unexplained sudden cardiac death	0,5
Scoring	
<1 Low probability of LQTS	
2-3 Intermediate probability of LQTS	
>4 High probability of LQTS	

*Adapted from references 14.

RESULTS

The study group consisted of 116 children (45 female and 71 male) with a mean age of 11.8±2.7 years (range 7 to 18 years). All children had severe and/or profound bilateral sensorineural hearing loss. Fifty-nine (50.8 %) of the enrolled patients had family members with congenital deafness. Consanguinity marriage of parents was present in 50 children (43.1 %). QTc intervals were found to be between 320 ms and 480 ms (405.2±26.4 ms), and heart

rates between 68 and 112 bpm (79.06±7.5 bpm). There was no electrocardiographic finding characteristic of the syndrome, such as T wave configuration changes or any significant arrhythmia.

QTc interval longer than 440 ms were found in nine of the 116 patients (7.7 %). The clinical and electrocardiographic findings of these patients are shown in Table II. Two patients (Case 2 and 6) had one syncopal attack, one of them while eating and the other while laughing. The father of Case 5 died suddenly at the age of 38 years, he had no health problem until that time. Echocardiographic examination of these nine patients showed no cardiac anomaly with normal ventricular function. Twenty-four hour Holter monitoring failed to disclose any important cardiac arrhythmia or T wave abnormality. All nine patients achieved the maximal heart rate in exercise testing. Two patients had prolongation of QTc interval at the 1st minute of recovery (Case 8 and 9), and an additional three patients showed QTc prolongation at the 3rd minute of recovery period (Cases 2,4,and 7). Electrocardiographic screening of the family members of these nine patients documented lengthening of the QT interval in the eight years old sister of Case 3 (QTc 462 ms) and in the ten years old brother of Case 9 (QTc 452 ms). None of them had congenital deafness, and they didn't met the diagnostic criteria for LQTS.

Although none of the patients had definite diagnostic criteria for LQTS according to Schwartz criteria, when we used the revised criteria, all nine patients could be defined as having intermediate probability of LQTS (Table II).

A hundred and seven out of 116 patients with congenital deafness had QTc intervals shorter than 440 ms. Different syndromes were defined in these patients; 6 patients with Wardenburg syndrome, one with Pendred syndrome, and one patient with albinism. Structural heart disease was found in four of these 107 patients (two mitral valve prolapse, one mild pulmonary stenosis, and one mitral insufficiency). None of the patients in this group had family history of sudden death.

Figure 2

Table II: Clinical and Electrocardiographic Findings of The Nine Patients With Long QT Interval

Case no	QTc interval*	Age (years) /sex	(ms)	Syncope	LQTS** score	Sudden death in family members	Family members with deafness
1		9, Female		-		-	+
	470	472	451	3,5			
2		14, Male		+		-	+
	459	423	451	2,5			
3		14, Male		-		-	-
	471	448	453	3,5			
4		8, Male		-		-	+
	452	470	448	2,5			
5		8, Male		-		+	+
	451	440	470	3			
6		13, Male		+		-	-
	453	449	431	2,5			
7		13, Female		-		-	-
	472	450	451	3,5			
8		13, Female		-		-	+
	480	472	441	3,5			
9		14, Female		-		-	+
	470	440	437	2,5			

QTc: Corrected QT interval for heart rate (ms), *QTc measurements at first, second and third electrocardiographic examinations, **According to revised criteria, probability of LQTS is low: <1, intermediate: 2-3, high: >4

DISCUSSION

The Jervell and Lange-Nielsen syndrome is a heritable disorder of the heart and hearing system. The congenital deafness is usually severe, bilateral and more marked for high frequencies. Symptoms are due to malignant ventricular arrhythmias and are associated with a propensity to syncope and sudden death. It is known that, repolarization disorder of the heart and hearing loss are caused by a recessively inherited gene. In autosomal recessive diseases, both the alleles of a particular chromosomal locus are abnormal. In Jervell and Lange-Nielsen syndrome, the deafness and the cardiac lesions may be pleiotropic effects of an abnormal gene in homozygous form, but the relationship between the genotype and phenotype is not clearly defined yet ([7,8]). First of all in 1980, Schwartz proposed that the spectrum of LQTS might be larger than that previously thought and it is possible to be a LQTS gene carrier without a prolonged QT interval ([9]). It is also described that the hearing defect could be the only expression of Jervell and Lange-Nielsen syndrome ([10]). It is widely accepted that the disease has a penetrance of more than 90 %. Contrary to current

assumptions, Priori et al [11] demonstrated that LQTS may appear in some families with an extremely low penetrance.

Symptoms are due to ventricular repolarization disorder in LQTS. Keating et al [12] detected a DNA marker at the Harvey ras-1 locus on the short arm of chromosome 11 linked to a cohort of families with LQTS. Further investigation of other families led to the discovery of additional linkage to chromosome 3 and 7 ([13]). Not all families with LQTS show linkage to any known locus, supporting the existence of additional heterogeneity. Proteins encoded by these genes appear to modulate ion channels involved in the cardiac action potential. Mutations appear to alter normal cardiac repolarization and, increase the risk of ventricular arrhythmias in patients with LQTS ([14]).

Consanguinity marriage is not unexpected in autosomal recessive inherited diseases such as Jervell and Lange-Nielsen Syndrome. Cusimano et al10 reviewed 46 patients reported between the years 1957 and 1991. In this review 17 of these 46 patients (37 %) had consanguineous parents. It is known that Turkey has a high rate of consanguineous marriage about 21 % ([15]), it is reported that the prevalence is higher than general population in the parents of deaf children ([16,17,18,19]). Two studies performed on Turkish deaf children population has showed the incidence to be 40 % (16) and 46.6 % (17). It was 43.1 % in our patient population with congenital deafness.

The presentation of clinical symptoms varies. Some patients only experience a brief sensation of light-headedness, while others experience a severe syncopal attack leading to sudden death. It is generally accepted that symptoms are precipitated by stress or physical activity. Two of our patients had non-stress induced syncopal attacks. If patients with LQTS remain untreated, the syncopal episodes usually recur and eventually my cause sudden cardiac death. Sudden cardiac arrest may be the first symptom in an otherwise healthy individual with a prolonged QT interval (2). The family history was positive for sudden death in only one patient in our study group. The father of Case 5 died suddenly at the age of 38 years while walking. He had not any complaint or known disease until that time. It was also learned that during the last three years sudden death occurred in two asymptomatic children while exercise attending the same deaf mute school. Unfortunately they never had performed electrocardiographic examination.

The prevalence of LQTS among deaf children is lower than 1 per 100 individuals. In this present study we could not find any case who definitely is LQTS according to Schwartz criteria. However, we found prolonged QT interval in 7,7 % of 116 congenitally deaf children. In fact, we know that not all children with a prolonged QT interval have the syndrome and therefore are not at risk for sudden death, but the difficulty is how to predict which of them have really this syndrome and will experience symptom. The QT interval is only an electrocardiographic marker and just having a prolonged QT interval does not indicate the syndrome. Because of the broad range of presentation, Schwartz proposed certain major and minor criteria for the diagnosis of the syndrome, and recently, these criteria have been revised for all ages to better reflect newly reported information regarding electrocardiographic and clinical findings of LQTS patients (14). According to the revised criteria, all nine patients in this present study could be defined as having intermediate probability of LQTS. Although it was not possible to establish definite diagnostic criteria, because of the large clinical spectrum of LQTS, it appears that these children may have the risk for the disease. For a precise diagnosis it is advised to perform a molecular screening. Molecular diagnosis is slowly entering clinical practice. Its widespread use is delayed by the high cost of the screening process, still performed only by research centers. Its implementation as clinical routine requires clear definition of the criteria for genetic screening. Clinically affected individuals should be genotyped, because this may have implications for therapy and management. It is easy to decide the management or to perform mutational analysis if a patient is definitely LQTS, but what about the patients who have intermediate probability of the disease. It is still unclear whether borderline cases should be genetically tested, if there is no identified gene in a proband in his or her family. Without molecular corroboration or refutation of mutations, it is very difficult to know how to characterize these patients. At this present situation we could not perform mutational analysis and we decided to follow up these children closely without starting therapy. The families are only informed about this possibility and alerted to avoid all drugs that prolongs QT interval.

The spectrum of the disease is very large and the prevalence of Jervell and Lange-Nielsen syndrome in a deaf children population may be as high as 1.3 % (5). On the basis of these data, we would make the following recommendation. It is advisable to perform an ECG at least once in deaf children, especially in countries where consanguineous marriage is widely practice. It is known that neonates exhibit prolongation of the QT interval, which may be transient,

that's why screening of these children may be delayed after neonatal period.

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