JERVELL AND LANGE-NIELSEN SYNDROME;
PREVALENCE IN DEAF CHILDREN AND ITS SIGNIFICANCE IN RELATION TO COUSIN MARRIAGES

ORIGINAL
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ABSTRACT…Objective: This study was carried out to find out the prevalence of Jervell and Lange Nielsen Syndrome (JLNS) in deaf school children for impaired hearing and to correlate this with consanguineous marriages. **Setup:** Schools for deaf and dumb children and Sheikh Zayed Medical College, Rahim Yar Khan. **Design:** Cross sectional, case control study. **Period:** 2006 - 2007. **Methods:** Electrocardiographs (ECG's) of 114 congenitally deaf school children (ages 4-20 years) and also of 23 healthy children with normal hearing function of same age group were recorded. The corrected QT (QTc) interval of all 137 ECGs was evaluated by Bazett's formula. Mean QTc of healthy children was taken as reference of normal QTc interval. The deaf children with normal QTc were labeled as control group. Patients with long QTc were further evaluated for JLNS by applying Schwartz's criteria. We also calculated the relationship of the positive cases to consanguineous marriages. **Results:** We found that 28 deaf children out of 114 cases had QTc intervals longer than 0.44 seconds. This interval was significantly longer [P=0.008] than the QT interval in control group. As per Schwartz's criteria, 15 out of 28 LQTs cases scored high points (3.5 to 5.5). The presence of consanguineous marriage was 100% in first pedigree of these 28 children. **Conclusions:** JLNS (an alarming arrhythmic disease associated with congenital deafness) is significantly present (24.6%) in Rahim Yar Khan's deaf school children. The presence of cousin marriage was 100% in first pedigree of these children.

Key words: Syndromic Deafness, Jervell and Lange-nielsen Syndrome, Long Qt Interval, Rahim Yar Khan.

INTRODUCTION

Hearing impairment due to genetic mutations occurs in about 0.1% of new borns[1]. In 30% of these cases, the deafness is syndromic (associated with abnormalities in other systems)[2]. Jervell and Lange – Nielsen Syndrome (JLNS) is one such rare condition seen in children suffering from congenital sensorineural hearing impairment[3].

JLNS is an autosomal recessive disorder characterized by congenital sensorineural deafness and prolonged QT interval in ECG and a propensity to ventricular tachyarrythmias[4,5].

In this syndrome the IKs (K+ channel protein Fig 1) KVQLT1 is mutated[6]. This protein is a part of IKs, the potassium channel mediating K recycling in stria vascularis of cochlea and ventricular repolarization[7]. The individuals having homozygous gene mutation in KVLQT1 are deaf and predisposed to syncope, ventricular tachycardia, cardiac arrest and sudden death on adrenergic stimulation[8]. Such cases are seen in consanguineous families[9]. Previous research work in Pakistan has been done on nonsyndromic deafness[10]. As consanguineous marriages are customary in Rahim yar Khan so we tried to assess the presence and extent of JLNS in deaf school children of this area.

Aims and Objectives

Our aims for the study were:

1. To look for the long QT syndrome in deaf school children of Rahimyar Khan.
2. To determine its relationship to cousin marriages

SUBJECTS AND METHODS

This cross sectional, case control study was conducted in 117 deaf school children, attending Iqra School for deaf and dumb (low income group) & Cholistan Institute for special education (high socioeconomic group) during December 2007. Children with acquired deafness (n=3) were excluded, and our study group included 114 children of ages (4-20 years) with congenital deafness. A preformed questionnaire was employed and information about associated findings, symptoms, and family history

Fig-1. KVQLT

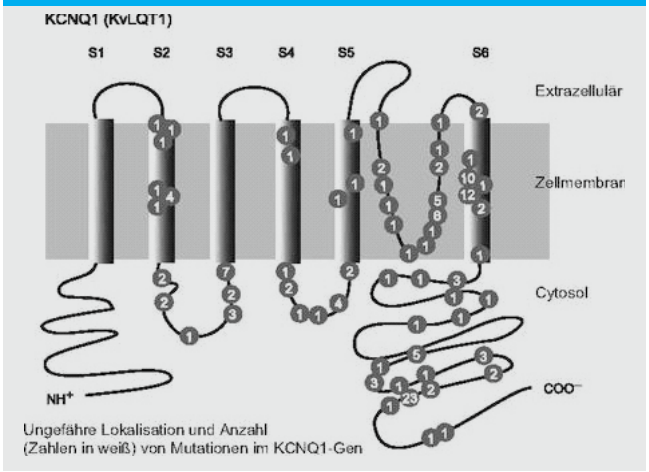
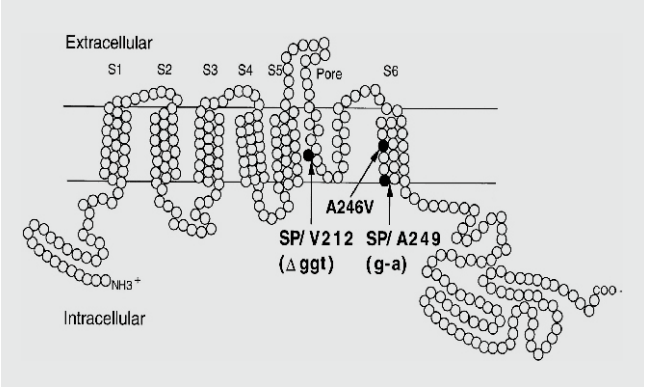


Fig-2. KVQLT with areas of mutations affecting transport of potassium ions.



were recorded[11]. These children had been previously examined and a diagnosis of sensorineural deafness was made with the audiometer[12]. Rhythm strip of ECG (electrocardiogram) was recorded with an electrocardiography recorder (Dong Jeang ECG 11 B) 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. QT interval was corrected for heart rate (QTc) according to Bazett's formula[13,14]. Because of sinus arrhythmia, the RR intervals were calculated according to the average heart rate[15]. The children who had QTc interval longer than 0.44 seconds were further evaluated. Twelve lead ECG, echocardiography and exercise testing were performed in these children. The exercise test was performed as a symptom-limited treadmill effort test. 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[15]. Family members of these cases were investigated for history of deafness, syncopal attacks, and sudden death. Electrocardiography examination of family members was also performed for determination of QTc interval. All available data was evaluated according to Schwartz criteria[16] (Table I). Statistical analysis was done by using SPSS and the data was computed on IBM ThinkPad X30. Chi square test was applied to evaluate the family history and history of cousin marriages.

RESULTS

The study group consisted of 114 subjects (48 females and 66 males) between the ages 4-20 years (mean; 12.43 ± 4.14years). They could be divided into the control and long QTc group on basis of QTc interval of ECG. The mean ± SD of QTc interval was 0.40 ± 0.05 seconds in control group (n=86). This matches with the QTc of normal children of same age group with no deafness (mean ± SD 0.40 ± 0.02). We found a QTc longer than 0.44 seconds in 28 (24.6%) subjects (mean ± SD 0.46 ± 0.05 sec). In two cases of long QTc, arrhythmia was also seen.

Among the long QTc group three patients had previous history of syncopal attacks. Father of one subject suffered from sudden death at the age of 36. No echocardiographic abnormality was detected in these 28 subjects.

The family history of deafness was positive in 11 patients (40%) of LQTS group and 38 subjects (44%) in the control group (Graph 1). The history of cousin marriages was positive in 100% of cases in LQTS group and 80% of positive in control group (Graph 2).

During exercise test in patients of LQTc, the heart rate increased with prolongation of QTc interval after first minute of recovery in five patients and in third minute of recovery in one patient. The ECGs of the immediate relatives of these patients showed that brothers of 2 subjects had LQT with no deafness and 3 years old sister of one subject had LQT with congenital deafness. The

Table-I.	
Schwartz criteria16	
ECG findings	
Qtc > 470 ms	3
460-470 ms	2
450 ms	1
Torsade de points	2
T wave a l ternans	1
Notched T wave in 3 leads	1
Low heart rate for age	0.5
Clinical history	
Syncope with stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS	1
Un explained sudden cardiac death	0.5
Scoring	
<1=low probability of LQTS	
2-3=Intermediate probability of LQTS	
>4=Definite probability of LQTS	

control group had a positive history in (n=38) 44% of cases where as the LQTS group had eleven cases (40%, graph 1) of positive family history of deafness.

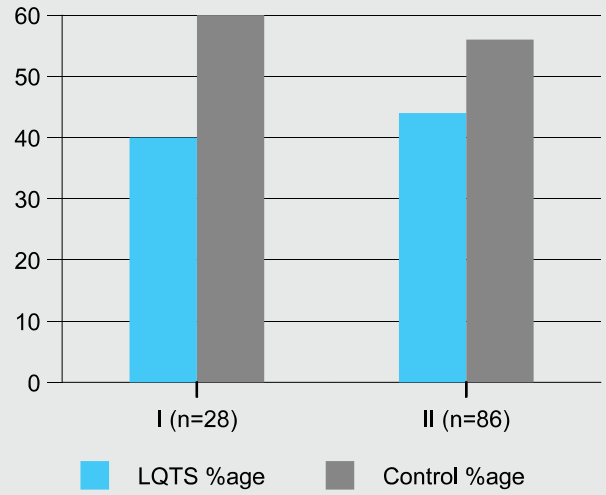
Schwartz criteria was applied to the test group. It showed that 2 patients scored 0.5 points 11 had scored between 2-3 points and 15 patients had a score of more than 4 indicating high probability of LQTS.

DISCUSSION

The Jervell and Lange-Nielsen syndrome is a heritable

Group	Positive cases	%age	Negative cases	%age
LQTS (n=28)	11	40	17	60
Control (n=86)	38	44	48	56

Graph-I. Family history of deafness in LQTS and control group



Group	Positive cases	%age	Negative cases	%age
LQTS (n=28)	28	100	-	-
Control (n=86)	70	80	16	20

autosomal recessive disorder of the heart and hearing system[5]. The congenital deafness is usually severe, bilateral and more marked for high frequencies[7]. The cardiac problems include tachy arrhythmias, torsade de pointes, syncopal attacks and even sudden death[17]. In this syndrome a potassium channel protein, (KVLQT) is mutated and due to this, a potassium channel named IKs is affected[18]. This leads to defected potassium recycling in striavascularis and absent generation of auditary impulses, and also defective repolarization of cardiac conducting tissues (prolonged QT interval)[1].

The recessively inherited disorders are more prevalent in endogamous populations like Pakistan where 60% of marriages are consanguine[10]. The extent of such

Graph-II. Cousin marriages in LQTS and control group

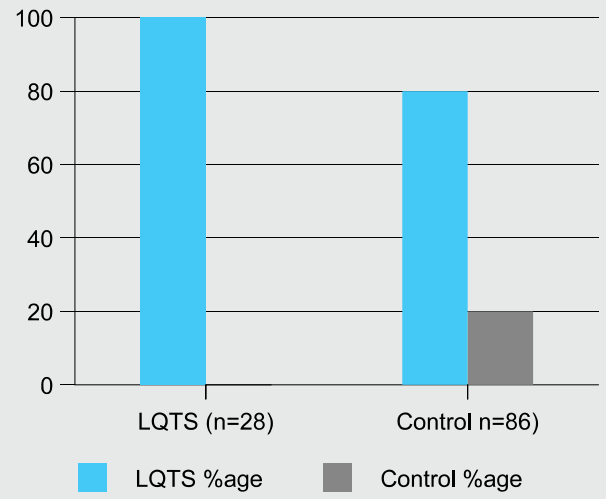


Table-II. Comparison of QTc interval between JLNS group and control group

JLNS Group (n=28)	Control Group (n=86)	p-value
0.46±0.05	0.40±0.05	0.014

**significant*

Table-III. Significance of association between family history of deafness and cousin marriages with JLNS

Association factor	X^2	df	Significance value
Family history of deafness with JLNS (LQTS)	3.071	3	0.381*
Cousin marriages with JLNS	6.06	1	0.014**

**Non significant* ***Significant*

marriages in our study was 86%. We found that there was a high prevalence of JLNS (24.6%) among our study group with a 100% positive relationship to consanguineous marriages (P=0.014). Different studies from Turkey indicate that the rate of consanguineous marriages among parents of deaf children ranges from 40 to 46.6%. The incident of LQTS was 7.7% in one these studies[11].

It has been described that hearing defect could be the only expression of JLNS when transmitted in consanguineous population[9]. It might become a silently spreading lethal disease. We found out that 61% of cousin marriages in our study group lacked a family history of deafness indicating fresh mutation culminating in JLNS due to consanguineous marriages. It is regrettable that many stories of sudden deaths of asymptomatic deaf and mute children during exercise were present prior to this study. This highlights the importance of ECG at least once in deaf children after the neonatal period has passed as neonates may exhibit a transient prolongation of QT interval normally[19]. In cases of sudden infant death syndrome some were identified as suffering from LQTS[20,21].

The prevention of spread of disease can be brought about by genetic counseling against consanguineous marriages among the deaf. Therefore this study has involved extensive field work to identify and enroll large consanguineous families, segregating deafness in multiple individuals in the district of Rahim Yar Khan. We further intend to get DNA extraction from blood samples of affected individuals and their normal family members, linkage analysis to exclude segregation of deafness in theses families to reported loci[9,10].

CONCLUSIONS

The JLN syndrome is a rare disease in the world. In the social settings of Rahimyar Khan, where cousin marriages are a common practice, the prevalence of this hereditary disease has increased drastically (24.6%) among congenitally deaf population. The presence of cousin marriages was 100% in first pedigree of these children. We also propose that the families of the deaf children in this area should be visited and screened for LQTS because it responds to treatments like administration of β blockers, implanted pacemakers, cardioverters and cochlear implants.

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