

Jervell and Lange-Nielsen syndrome with homozygous missense mutation of the *KCNQ1* gene

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Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive cardioauditory ion channel disorder characterized by congenital bilateral sensorineural deafness and long QT interval. JLNS is a ventricular repolarization abnormality and is caused by mutations in the *KCNQ1* or *KCNE1* gene. It has a high mortality rate in childhood due to ventricular tachyarrhythmias, episodes of *torsade de pointes* which may cause syncope or sudden cardiac death. Here, we present a 4.5-year-old female patient who had a history of syncope and congenital sensorineural deafness. She had a cochlear implant operation at 15 months of age and received an implantable cardioverter defibrillator (ICD) at 3 years of age because of recurrent syncope attacks. Five months after cochlear implant placement, she could say her first words and is now able to speak. With β -blocker therapy and ICD, she has remained syncope-free for a year. On the current admission, the family visited the genetics department to learn about the possibility of prenatal diagnosis of sensorineural deafness, as the mother was 9 weeks pregnant. A diagnosis of JLNS was established for the first time, and a homozygous missense mutation in the *KCNQ1* gene (c.128 G>A, p.R243H) was detected. Heterozygous mutations of *KCNQ1* were identified in both parents, thereby allowing future prenatal diagnoses. The family obtained prenatal diagnosis for the current pregnancy, and fetal *KCNQ1* analysis revealed the same homozygous mutation. The pregnancy was terminated at the 12th week of gestation. The case presented here is the third molecularly confirmed Turkish JLNS case; it emphasizes the importance of timely genetic diagnosis, which allows appropriate genetic counseling and prenatal diagnosis, as well as proper management of the condition.

Key words: Jervell and Lange-Nielsen syndrome, *KCNQ1* gene, deafness, prenatal diagnosis.

Jervell and Lange-Nielsen Syndrome (JLNS) is a genetic syndrome characterized by congenital sensorineural deafness and long QT interval, and is associated with a high risk of sudden cardiac death due to episodes of polymorphic ventricular tachycardia^{1,2}. Because of high infantile mortality, misdiagnosis and a lack of comprehensive neonatal screening programs, the real incidence of JLNS is unknown. The prevalence has been estimated to be about 1/200,000³. JLNS is caused by homozygous or compound heterozygous loss of function

mutations in the *KCNQ1* and *KCNE1* genes, encoding subunits of the voltage-gated potassium ion channel (K⁺)⁴. The K⁺ ion channel function is essential in the slow rectifier current of the myocyte action potential for proper cardiac repolarization and in endolymph production of the inner ear hair cells, so loss of function causes prolonged cardiac repolarization, prolonged QT interval and sensorineural deafness. As with other forms of long QT syndrome, JLNS causes fatal ventricular arrhythmias, especially *torsade de*

pointes-type polymorphic ventricular tachycardia and ventricular fibrillation, syncope and sudden cardiac death. Treatment options in JLNS are limited to implantation of implantable cardioverter defibrillators (ICD) and cochlear implants.

Proper management and appropriate genetic counseling depends on accurate clinical and molecular diagnosis. In this report, a female patient with JLNS is described, in whom the diagnosis was established clinically and then molecularly with sequence analysis; subsequently prenatal diagnosis was provided to the family.

Case Report

The index patient is a 4.5-year-old girl, whose family visited the genetics department in search of prenatal diagnosis regarding the possibility of sensorineural deafness in the ongoing pregnancy of the mother. The index patient was the first child of healthy consanguineous parents. There was no family history of sudden death, deafness, syncope, epilepsy or any other genetic disease. She was born at 36 weeks of gestation by caesarean section. Prenatal follow-up was normal. Birth weight was 2850 g (50th-75th percentile), and no dysmorphic signs were recorded. She was first referred to the audiology department in our hospital by the neonatal hearing screening program. The transiently evoked otoacoustic emission test and automated auditory brainstem response test revealed that she had severe congenital bilateral sensorineural deafness. Cranial, temporal and ear magnetic resonance imaging was normal. At 15 months of age, she received a cochlear implant in the right ear. Five months after the implant operation, she spoke her first words. Her first syncope episode had occurred at 30 months of age. In the emergency department, physical and neurological examinations were normal except for hearing impairment, and the electroencephalogram was also normal. She did not have an electrolyte imbalance; the cardiac rate was 98 beats/min and blood pressure was 80/50 mmHg. A 12-lead electrocardiogram (ECG) revealed a markedly prolonged QTc interval of 530ms (corrected by Bazett's formula) and T-wave alternans on V1-V4 (Fig.1). Echocardiography showed a structurally normal heart. 2 mg/kg β -blocker treatment was started upon the diagnosis of long QT

syndrome. During Holter monitoring no attacks of ventricular tachycardia were recorded; the mean heart rate was 91 (66-114) beats/min and the QTc interval was 480 msn. Due to the known poor prognosis of long QT syndrome with sensorineural deafness, two days after the first syncope episode an ICD was implanted on an urgent basis. After ICD placement the patient had two more syncope episodes; in one of them the ICD was activated and delivered one electric shock. Currently, she has remained syncope-free for a year, is able to speak properly with support from speech therapy and has no physical or intellectual disabilities.

The presentation of congenital bilateral sensorineural deafness together with long QT syndrome in this patient led us to the diagnosis of JLNS. For confirmation of the clinical diagnosis, we performed Sanger sequencing of all coding exons and exon/intron junctions of the *KCNQ1* gene. Sequence analysis revealed a homozygous missense mutation of the *KCNQ1* gene (c.728G>A, p.R243H) in exon 5 (Fig. 2). The same mutation, in heterozygous form, was also identified in both parents. For the mother's current pregnancy, chorionic villus sampling was performed at the 11th week. Fetal DNA was isolated from the chorionic villus sample and Sanger sequencing was performed for *KCNQ1* gene exon 5. The same homozygous mutation (c.728G>A, p.R243H) was detected in the fetal DNA, and the pregnancy was terminated upon the parents' choice.

Discussion

Jervell and Lange-Nielsen syndrome is characterized by congenital bilateral hearing loss and prolonged corrected QT (QTc) interval¹. The classical presentation of this disease is a child with hearing impairment who also has episodes of syncope during stress or exercise.

Inherited heart rhythm disorders, namely long QT syndrome, Brugada syndrome and polymorphic ventricular tachycardia are uncommon but emergent life-threatening disorders encountered in pediatric practice. Congenital long QT syndrome is due to mutations of several genes that result in prolongation of corrected QT interval. All genes identified in the etiology of long QT syndrome encode cardiac ion channels and function in regulating cardiac action potential. If not recognized and treated, prolonged QT interval

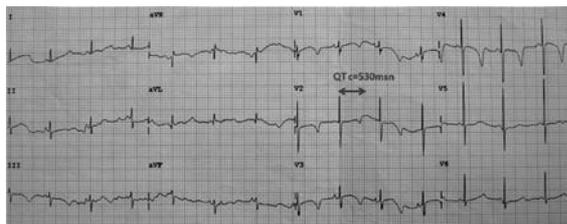


Fig. 1. Twelve-lead ECG of the patient, demonstrating prolonged QTc interval (530ms) and T-wave alternans on V1-V4.

may precipitate fatal ventricular dysrhythmias. JLNS patients are at high risk, especially during sympathetic activation.

Two inherited forms of congenital long QT syndrome are present. JLNS is less common than Romano-Ward syndrome. Unlike JLNS, Romano-Ward syndrome is an autosomal dominant form of long QT syndrome and is not associated with deafness or other phenotypic abnormalities⁴. The diagnosis of JLNS is established by the presence of clinical findings and confirmed by the detection of homozygous mutations in one of the two disease-causing genes known today, *KCNQ1* and *KCNE1*. Molecular genetic analysis is not only useful in confirming the clinical diagnosis, but also provides the opportunity for prenatal diagnosis in the case of pregnancy⁴. Most JLNS mutations are described in the *KCNQ1* gene (90%); in only 10% of patients have they been shown in the *KCNE1* gene³.

KCNQ1 encodes the α -subunit and *KCNE1* the β -subunit of the voltage-dependent slowly activated delayed rectifier potassium channel, and these two proteins encoded by the *KCNQ1* and *KCNE1* genes assemble to form the K^+ channel. The main mechanism responsible for QT prolongation is blockage of the delayed rectifier potassium current and prolonging of the myocardial action potential. The delaying of the action potential provokes ventricular extrasystoles and fatal ventricular tachycardias. The *KCNQ1* gene, responsible for 90% of all cases, was initially sequenced in the present patient, and the pathogenic mutation was revealed. The mutation we detected in *KCNQ1* gene exon 5 (c.728G>A, p.R243H) was previously reported in the literature in two other Turkish families and a French family, making our family the third Turkish JLNS family with the same mutation⁵⁻⁷. No comprehensive

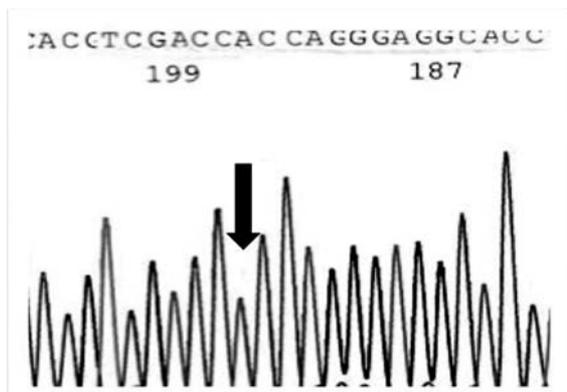


Fig. 2. *KCNQ1* gene exon 5 c.728G>A (p.R243H) homozygous mutation.

study exists concerning Turkish JLNS patients, but this may be a mutational hot-spot in Turkish patients, or suggestive of a founder effect in the Turkish population.

JLNS is the most severe variant of long QT syndrome. Almost 90% of patients become symptomatic, and sudden death exceeds 25% despite medical therapy. During the first year of life, 15% of patients have a cardiac event. By age 3, 50% of patients are symptomatic, and by age 18, 90% of patients have symptoms². Among children with JLNS who are not treated, more than half die prior to age 15^{2,3}. An ICD was placed in our patient shortly after diagnosis, given the poor prognosis of long QT syndrome when it presents in combination with sensorineural deafness. In addition, she was in the high risk group of JLNS patients due to a history of early childhood (from birth to the fourth year of life) syncope, a longer QT interval (>500 msn) and a detected mutation in *KCNQ1*⁸.

About 40% of long QT syndrome patients are misdiagnosed during their first episodes and are incorrectly treated with antiepileptic drugs⁹. All patients with a history of syncope should be evaluated for a cardiac channelopathy. The present patient had her long QT syndrome diagnosed after the first cardiac episode, and β -blocker treatment was started and an ICD placed immediately. Emergency ICD implantation was scheduled after the diagnosis, as most JLNS patient have recurrent syncope attacks despite initiation of β -blocker treatment.

Generally, heterozygous carriers of a JLNS mutation are asymptomatic, but they may have

mild QT prolongation in the absence of hearing loss. The parents of the patient presented here have neither symptoms nor long QT; the plan is to observe them closely. Additionally, parental education and training of all family members in cardiopulmonary resuscitation is recommended in such a case.

Specific clinical and molecular diagnosis is required for appropriate management and precise prenatal diagnosis. Careful clinical evaluation of patients with long QT and/or sensorineural deafness may lead to correct diagnosis of JLNS. As the most severe form of congenital long QT syndrome, JLNS must be kept in mind in the case of patients with syncope episodes and congenital sensorineural deafness, since only timely and correct clinical diagnosis leads to precise molecular diagnosis, appropriate management to prevent sudden death and molecular analysis to prevent recurrence of the disease in the same family. The case presented here is the third molecularly confirmed Turkish JLNS case and homozygous missense mutation of the *KCNQ1* gene (c.728G>A, p.R243H). Given the fact that it has previously been reported only three times in total⁵⁻⁷, this may be a common mutation among Turkish patients.

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