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Case Report

Jervell-Lange Nielsen Syndrome: A Case Report

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ABSTRACT

There is a rare genetic disorder called Jervell-Lange Nielsen syndrome that leaves people congenitally deaf and with a long QT interval. This can lead to deadly heart rhythm problems and sudden death. For the treatment of hearing loss, cochlear implants, and for the treatment of heart difficulties, beta-blockers, and in certain circumstances, implantable cardioverter defibrillators, arrhythmias, syncope attacks, and sudden death are recommended. We discuss the case of an 8-year-old child who was referred for cochlear implantation after being diagnosed with Jervell-Lange Nielsen syndrome. In this study, we want to deal with patient management preoperatively and during surgery and describe the side effect of this syndrome.

Introduction

Jervell-Lange Nielsen Syndrome (JLNS) is a rare autosomal recessive disorder in which both parents are heterozygous for the disease. Bilateral sensorineural hearing loss and a QT interval of more than 500 milliseconds are signs of this syndrome. This can lead to tachyarrhythmias, such as ventricular tachyarrhythmias, torsades de Pointes, and ventricular fibrillation, as well as syncope and sudden death. Surgical stress and general anesthesia can also cause fatal arrhythmias [1]. JLNS is a type of inherited prolonged QT syndrome (LQTS). It was first described by Anton Gerroll and Fred Long Nielsen in 1957 in a study of four babies who were born deaf and all had syncope [2].

Increased QT interval and T-wave change in the electrocardiogram, syncope, ventricular tachycardia (VT), torsades de pointes, and an increased risk of sudden death owing to torsades de pointes or VT. JLNS affects approximately 1.1 to 1.2 million people worldwide. Due to stable genetic characteristics, Norway and Sweden have an abnormally high prevalence of 1 in 200,000. Because cardiac mortality is expected to exceed 50% if left untreated, these statistics are likely to underestimate the true prevalence.

Mutations in the two KCNQ1 genes, KCNE1, are one of the causes of the disorder. The KCNQ1 (90%) and KCNE1 genes encode proteins necessary for the function of potassium channels in the heart and cochlea and account for approximately 90% of KCNQ1 gene mutations [1,3]. The KCNE1 gene is found at 21q22.1-22.2 and measures 40 bp in length [4]. According to the Human Gene Mutation Database, more than 550 mutations in the KCNQ1 gene have been identified so far (HGMD). Potassium channel disruption leads to auditory and cardiac problems [1, 3].

There are three exons, two of which are located in the 5'-UTR. The KCNE1 gene codes for the minK protein, which has 129 amino acid residues and is divided into three parts: an extracellular region, a transmembrane area, and a cytoplasmic area. Two-thirds of homozygotes with KCNQ1 have an autosomal recessive pattern, while the remaining one-third have compound heterozygous mutations, which implies they have two mutant alleles on each chromosome. According to some studies, about 4% of patients with prolonged QT syndrome and KCNQ1 mutations did not have sensorineural hearing loss. This is considered to be caused by a milder mutation that causes

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K+ current to remain inside the ear, allowing normal auditory function but compromising cardiac function [5]. Romano Ward Syndrome (RWS) is a form of LQTS without hearing loss that is inherited autosomally. Other patients with hearing loss and autosomal recessive heredity are classified as JLNS patients; however, they have a considerably lower prevalence than RWS patients [6]. The abnormal expression of KCNE1 can result in malignant ventricular arrhythmias, recurrent syncope, or even sudden death. Congenital deafness is a significant phenotype distinction between JLNS and RWS. Gene changes in the KCNQ1 or KCNE1 genes can lead to the growth of abnormal structures in striated cells in the inner ear. This affects the lymphoid system's ability to secrete substances and causes the cochlear middle ventricle to collapse, which leads to deafness [7]. When this voltage-gated potassium channel is blocked, it becomes harder for the K+ duct to carry potassium from the stria vascularis into the endolymphatic space. This is needed to keep the endolymphatic potential stable. It may be possible to tell if a cochlear implant (CI) will work by looking at where the cochlear impairment is and where the normal auditory nerve is [3]. Most of the genes that cause LQTSs are ion channel genes that control the heart's action potential period. These genes include SCN5A, HERG, KCNE2, KCNQ1, and KCNE1. Genetic changes in the KCNQ1 or KCNE1 genes that are recessive and cause loss of function are what cause JLNS [8]. Cardiac symptoms are most prevalent in childhood and include periods of syncope in response to stress, exertion, or fear, as well as a high risk of sudden cardiac death.

Homozygous or heterozygous mutations cause 90% of JLNS cases in KCNQ1 at 11p15.5. Bilateral KCNE1 mutations at 1q22.1-q22.2 have been identified as an additional component in JLNS, resulting in genetic heterogeneity in the disease. These two genes regulate the α and β subunits of the voltage-gated potassium channel subunit, which delay cardiomyocyte depletion in the heart and the synthesis of potassium-rich endolymph in the ear, respectively [9]. Depolarization, a plateau/refractory period, and lead repolarization are all phases of the cardiac action potential. On the ECG, the QT interval represents the repolarization phase.

The repolarization phase is seen on the ECG as the QT interval. This phase is associated with increased potassium permeability, which removes potassium from the heart cells. Potassium contains a fast-acting component and a slow-acting component. Mutations in the KCNQ1 and KCNE1 genes encode the α and β subunits of the slow-acting components, leading to slower potassium transport out of the cell and a longer QTc interval [10].

Case Report

An 8-year-old female weighing 15 kg and having profound bilateral sensorineural hearing loss was planned for cochlear implantation. The child was born at full term by cesarean section due to fetal distress. The patient is a first-born child with no history of premature labor and low birth weight, neonatal hospitalization history, jaundice and phototherapy in infancy, and no transfusion history. There is a family link between the child's parents (cousin, cousin). The family has no history of deafness, and neither do the other children. The patient has been diagnosed with significant bilateral sensorineural hearing loss since birth.

Since he was six months old, he has been using a two-way hearing aid, and he has no family history of heart problems, syncope, or sudden death. A long QT in the ECG (512 ms) and genetic tests on the KCNE1 gene helped the doctor figure out that the person had Jervell-Lange syndrome before surgery. Propranolol 10 mg tablets were administered every 12 hours during cardiac counseling. The only lab test that wasn't normal was for mild microcytic hypochromic anemia (Hb: 9.2 g/dl, Hct: 29.7%, MCH: 19.5, MCHC: 31%, MCV: 62, anisocytosis). The infant was calm when she arrived. The heart rate was 90/min. After pre-oxygenation and dehydration of the required equipment (defibrillator), the child was ready for induction of anesthesia. The patient was anesthetized with 30 μg of fentanyl, 40 mg of propofol, 15 mg of lidocaine, and 10 mg of atracurium and intubated with a 5.5 spiral endotracheal tube. After listening to the lungs and ensuring the correct location of the endotracheal tube, it was fixed with glue. During surgery, the temperature (to avoid hypo- and hyperthermia), $ETCO_2$ (to avoid hypercarbia), ECG, blood pressure, and heart rate were all monitored. To avoid hypovolemia, 20 cc/kg normal saline was prescribed. It takes approximately 5 hours to complete the surgery. Finally, the patient was reversed with neostigmine (1 mg) and atropine (0.3 mg). After removal of the endotracheal tube, he was monitored for two hours in recovery and then transferred to the ICU with normal vital signs.

Discussion

Long-QT syndrome (LQTS) encompasses a range of conditions that arise from mutations affecting the heart's ion channels. Specifically, homozygous or heterozygous mutations in the KCNQ1 and KCNE1 genes result in the recessive form of LQTS known as Jervell and Lange-Nielsen syndrome (JLNS). These genes are crucial for forming voltage-gated potassium channels, which are vital for both cardiac function and the healthy operation of inner ear cells, playing a significant role in the flow of the IKs potassium current. Mutations in KCNQ1 and KCNE1 disrupt potassium transport in the heart muscle and the inner ear, leading to both auditory impairments and cardiac rhythm irregularities. According to the Human Genome Database (HGMD), 21 unique mutations in the KCNQ1 gene and three mutations in the KCNE1 gene have been identified in patients with JLNS [3,11]. Notably, a homozygous frameshift mutation (c.7337344delGG) found in exon 5 of the KCNQ1 gene was reported in two unrelated families within an Iranian

cohort of LQTS patients in a 2018 study. This particular mutation was not previously documented in either the HGMD or the 1000 Genomes databases. The mutation occurs within the cytoplasmic ring C, which is located between the S4-S5 regions of the KCNQ1 membrane, and is significant because mutations in this area can impact the voltage dependence of potassium channel activation, thereby heightening the risk of fatal cardiac events. Although the functional impact of this mutation has yet to be evaluated in affected patients, frame-shifting mutations are typically expected to be pathogenic, especially those with a predicted effect value (EPV) of 99% [11].

JLNS is a rare genetic disorder characterized by its impact on the heart's electrical system and hearing ability. It is inherited in an autosomal recessive manner. Those affected often experience syncope triggered by intense emotions or physical activity, alongside considerable QT interval prolongation and congenital deafness. This syndrome comprises one of the more severe types of LQTS; by the age of three, about 50% of JLNS patients exhibit symptoms, and this figure rises to 90% by age eighteen. Consequently, the actual prevalence of JLNS may be underreported, particularly in populations with high rates of consanguinity, such as in Morocco. Even with proper medical treatment, the syndrome carries a sudden cardiac death rate exceeding 25% [9].

Clinicians should consider the likelihood of JLNS in any child with a family history of both hearing impairment and syncope. Typically, an electrocardiogram (ECG) is included in the preoperative evaluations for children undergoing cochlear implantation at certain hospitals, and it is proposed that this practice be established across all centers. Due to the potential for surgical stress and anesthesia to induce lethal arrhythmias, parents need to be informed about the increased likelihood of postoperative complications, including mortality, when weighing the risks and benefits of surgery [3]. The primary treatment objectives involve addressing hearing loss and preventing syncope and sudden death, with cochlear implants being recommended for hearing restoration [12].

For managing cardiac symptoms, beta-blockers are advised, as these medications diminish electrical impulses in the heart and help avert irregular heart rhythms that could lead to fainting episodes [13]. If beta-blockers are ineffective, implantable cardioverter defibrillators (ICDs) may need to be considered for patients at significant risk. These devices monitor for abnormal heart rhythms, delivering shocks to the heart when necessary to prevent syncope. Additional recommendations include minimizing sympathetic stimulation, avoiding anesthetics known to prolong the QT interval, administering magnesium sulfate, and ensuring immediate access to defibrillation equipment during surgeries. Although numerous cardiac complications and preoperative mortality cases have been documented, determining the exact risks remains challenging due to the limited number of reported cases. Genetic evaluation for patients and their families is also advised. The first-line strategy aims to prevent syncope, cardiac arrest, and sudden death through beta-blockade. Among the beta-blockers, propranolol and nadolol are favored over metoprolol for cardiac event prevention, with nadolol currently being the standard choice. For patients with prior cardiac arrest, ICD placement is indicated, particularly for those presenting a QTc interval greater than 550 ms, those with syncope before age five, or males older than 20 with pathogenic mutations in KCNQ1[6,13]. Additionally, expert consensus suggests utilizing a combination of beta-blockers and atrial pacemaker therapy when appropriate [14].

Surgical anesthesia poses unique risks for JLNS patients, necessitating measures to avoid factors that might trigger arrhythmias, such as sympathetic stress, extreme temperatures, fluid imbalances, and elevated airway pressures. A robust readiness with beta-blockers, pacing options, and immediate defibrillation protocols is essential [13,15].

Statistics indicate that more than half of untreated JLNS patients do not survive past 15 years of age. Prognosis largely depends on the specific mutation involved, patient sex, and the QT interval. Mutations in the KCNE1 gene generally correlate with a milder disease progression. Women presenting with a QTc of less than 550 milliseconds are considered at lower risk. In research by Goldenberg et al., the use of implanted defibrillators was shown to mitigate mortality linked to JLNS [16]. Prompt initiation of beta-blocker therapy is associated with a reduction in cardiac events and improved survival rates [15].

Conclusion

Cochlear implantation in children with JLNS requires a thorough understanding of diagnosis and precautions. Cardiac and ECG counseling should be performed for all children with congenital deafness who are candidates for surgery. It is suggested that people get heart counseling before surgery, take beta-blockers, use an ICD (if needed), have an intraoperative defibrillator on hand, stay away from medicines that lengthen the QT interval (like antihistamines), and avoid sympathetic stimulation during surgery.

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