Case Report

Cochlear Implantation in a Patient with Kearns-Sayre Syndrome: Case Report and Literature Review

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Abstract

Introduction: The Kearns-Sayre syndrome (KSS) belongs to the group of mitochondrial diseases. Cells that require more energy intake, such as muscle, nerve, retinal and cochlear, are most commonly affected.

The established diagnostic criteria are: 1) the age of onset before 20 years old (100%), 2) progressive external ophthalmoplegia (100%), 3) pigmentary retinopathy (100%), and 4) at least one of the following: heart block, cerebellar ataxia (84%) and protein > 100 mg/dL in the cerebrospinal fluid. Additional features are the presence of bilateral sensorineural hearing loss and myopathy.

Genetic testing of mitochondrial DNA can confirm the diagnosis. The aspect of muscle biopsy is typical, showing ragged red fibers (RRF).

Objectives: Present a literature review and report the cochlear implantation in a patient with KSS.

Case Report: ACVF, female, was born in 1989 from a gemelar pregnancy. At the age of ten years, the patient began manifesting hypoacusia associated with a continuous and bilateral tinnitus. In 2000, the patient was evaluated by a medical geneticist because of palpebral ptosis, progressive ophthalmoplegia, reduction in muscle mass, facies myopathica, an alteration in the index-nose test and slight restriction of ocular motricity. A muscular biopsy revealed RRF. The genetic test performed showed deletion of mitochondrial DNA compatible with a diagnosis of KSS. Her twin sister also had the diagnosis of the syndrome based on the same tests.

The patient showed a deterioration of hypoacusia even after the adaptation of the hearing aid. During the tone audiometric exam, it was seen that the patient had evolved towards a bilateral and profound deafness. The results of the complete audiological evaluation enabled the realization of Cochlear Implantation.

INTRODUCTION

The Kearns-Sayre syndrome (KSS) belongs to the group of mitochondrial diseases, which have as their main feature the tendency to affect the tissues that depend substantially on the oxidative phosphorylation process. Cells that require more energy intake, such as muscle, nerve, retinal and cochlear, are most commonly affected [1].

The mitochondrion is a cytoplasmic organelle. It is known that, during the process of fertilization, only the ovum contributes to the cytoplasm of the embryo and, therefore, the mitochondrial DNA (mtDNA) descends exclusively from the maternal lineage. Mutations in mtDNA can be inherited or occur sporadically; affect both sexes and are not transmitted to offspring compulsorily, since the random replication of this material originates from a few copies, known as the effect of “genetic bottleneck”. The variable phenotypic expression is explained by a threshold effect, which heteroplasmy with a proportion of at least 80-90% of mutant mtDNA tissue, as a general rule, determine organ dysfunction and clinical symptoms [2-4].
Congenital hearing loss can be classified in terms of etymology, contemplating environmental and genetic causes, accounting for 50% each. Within the genetic causes, syndromic forms are implicated in about 30% of cases, in contrast to 70% of forms of nonsyndromic deafness. The genetic forms of inheritance are dominant autosomal (77%), recessive autosomal (21%), X-linked (~ 1%) and mitochondrial (~ 1%) [5]. Despite the fact that the mitochondrial form is rare, sensorineural hearing loss (SNHL) is found in 42% to 70% of patients with mitochondrial disorders [6,7] and 97% in KSS [4]. A study of Japanese group with SNHL identified a prevalence of 3% mtDNA mutation [8].

Mitochondrial deafness obeys the symmetry law of hearing loss of Langenbeck, exhibits a sensorineural pattern, and also affects characteristically high frequencies. The progressive deterioration can occur at rates of 1.5 - 7, 9dB a year and usually evolves towards profound SNHL [9,10]. The occurrence in individuals with mutations of an early reduction of oxidative phosphorylation due to aging and tenuous mtDNA repair mechanisms is postulated. The decrease in ATP levels causes dysfunction in endocochlear potential provided by Na + K + ATP pumps of stria vascularis. In addition, the fact that the outer hair cells receive indirect metabolic support of Deiters cells, particularly those that are most metabolically active and located in the basal coil (tonotopy high frequency), would provide enhanced susceptibility to damage [3,11].

The KSS is presented as a multisystemic, degenerative and rare disease with an estimated incidence of 1-3 per 100,000 in the population. De novo mutation is more prevalent than that of maternal inheritance, occurring either in the mother’s oocyte or very early in embryonic development. The mtDNA deletion in large scale from 1.1 to 10 kilobases the mechanism associated in 90% of cases. More than 150 different mtDNA deletions have been associated with KSS. A deletion of 4977 bp known as m.8470_13446 del 4977 is encountered most frequently. Large-scale duplications of mtDNA coexist with deletions in some individuals with KSS [12].

The established diagnostic criteria are: 1) the age of onset before 20 years old (100%), 2) progressive external ophthalmoplegia (100%), 3) pigmentary retinopathy (100%), and 4) at least one of the following: heart block, cerebellar ataxia (84%) and protein> 100 mg/dL in the cerebrospinal fluid. Additional features are the presence of bilateral SNHL (97%), myopathy (94%), intellectual deficit (86%), diabetes mellitus (13%), dysphagia, hypoparathyroidism and renal tubular acidosis [12,13].

The clinical diagnosis must be confirmed by molecular studies, both long-range PCR as southern blot, in leucocytes or muscle. Both are recommended to perform from muscle biopsy sample because the mutation may be undetectable in blood cells due to the possibility of different level of heteroplasmy. The appearance of muscle biopsy is typical, showing RRF with the modified Gomori trichrome stain. Histochemical analysis demonstrates a hyperreactivity of fibers with the succinate dehydrogenase reaction; there is also the possibility of failure to stain with the histochemical reaction for cytochrome c oxidase (COX) and decreased activity of respiratory chain mtDNA [12].

**OBJECTIVES**

Present a literature review and report the cochlear implantation in a patient with Kearns-Sayre syndrome.

**CASE REPORT**

ACVF, female, was born in 1989 from a term and gemellar pregnancy, with a vaginal birth without complications, and a weight of 2950 grams. After the birth, she remained hospitalized for three days and lost 200 grams during this period. In her gestational history, she reported that her mother received prenatal accompaniment, but did not get an ultrasound during the pregnancy. In her medical history, she states that at the age of 10 months she was admitted to a hospital due to gastroenterocolitis and dehydration, as well as for a urinary tract infection. At the age of two years she was diagnosed with mumps and chickenpox. She presented a few episodes of tonsilitis that were treated with antibiotics. Her neuro-psychomotor development was normal, in accordance with age.

There is no consanguinity between her parents and there are also no cases of deafness in her family history. Her twin sister also was diagnosed with KSS and at present receives otorhinolaryngological accompaniment at a different medical center because of moderate and bilateral SNHL.

In June of 2000, the patient was evaluated by a medical geneticist because of a complaint of palpebral ptosis and progressive ophthalmoplegia that commenced in 1993. According to data from the consultation, she was diagnosed with astigmatism, hypermetropy, and visual fatigue. During the physical exam, she exhibited a reduction in muscle mass with preserved motor force, facies myopathic, intention tremor, dysmetria in the index-nose test and dysdiadochokinesia suggesting cerebellar ataxia, a slight restriction of ocular motricity, and a normal fundus examination. There was no report of other affected members of the family.

With regard to the geneticists’ report, the following exames of both sisters are within normal range: FTA-Abs (IgG and IgM), VDRL, FAN, VHS, reative protein c, glycerina, and complete blood count. In audiological evaluation showed moderate SNHL, predominantly of high frequencies. The patient had no response in the examination of Otoacoustic Emissions (OAE) and the examination of the Auditory Brainstem Response (ABR) bilaterally. During the audiological evaluation, the hypothesis of mitochondriopathy was considered and the patient was referred to a muscular biopsy, genetic tests, ophthalmological and cardiological exam.

A muscular biopsy, which was performed at the Federal University of São Paulo (UNIFESP) in 2000, revealed a distribution of 80% of type I muscular fibers with preserved mosaic, the presence of atrophy of polygonal fibers, and in the internal architecture, a typical finding of KSS: presence of RRF. Hypertrophy was not seen, nor was nuclear centralization, inflammation, necrosis, inclusion or alterations of muscle spindles.

The genetic test performed twelve years later (2012) showed deletion of mitochondrial DNA compatible with a diagnosis of KSS. We not had access to the results of genetic testing, so we...
cannot mention what type of deletion found on examination. Her
twin sister also was diagnosed with KSS based on the clinical
findings, muscle biopsy and genetic test. We cannot prove that
the patients are identical twins because they do not have a DNA
test or an ultrasound done during pregnancy.

The retinal angiogram that was performed in 2010
exhibited, during initial and intermediary phases of contrast,
hyperfluorescence and hypofluorescence on the posterior
side of both eyes, which is highly suggestive of focal atrophy of
the pigmented epithelium of the retina and areas of pigment,
respectively. The leakage of contrast was not visualized.

The result of the echocardiogram, which was done in 2012,
revealed mixomatose degeneration of the mitral valve with
prolapse of the anterior leaflet into the interior of the left atrium
with minimal reflux detected by color Doppler.

In relation to hearing, at the age of ten years, the patient
began manifesting hypoacusia associated with a continuous
and bilateral tinnitus. In 2000, she was submitted to an
audiological evaluation that consisted of a tone audiometry,
speech audiometry, immittance audiometry (typanometry
and the study of acoustic reflexes), as well as a differential
audiological evaluation, by means of an electroacoustic and
electrophysiological exam, being OAE and ABR, respectively. The
exams indicated severe and bilateral SNHL and a hearing aid was
adapted within the same year. The patient was maintained under
our care until 2002, when she decided to attain assistance at a
different hearing center that was closer to her place of residence.

During twelve years of accompaniment at another hearing
center, the patient showed a deterioration of hypoacusia even
after the adaptation of the hearing aid, which was maintained
in continuous usage. Consequently, she was referred yet again
to our hospital in August of 2014, which is considered to be
a reference in audiology, as well as for cochlear implantation
evaluation. During the otorhinolaryngological exam, an integral
tympanic membrane was observed and in the audiological
exam, the patient reported to have noticed better hearing in
her right ear. During the tone audiometric exam, it was seen
that the patient had evolved towards a bilateral and profound
defauness (Figure 1B), according to the established WHO criteria
(WHO, 1997). Because of the degree of hearing loss, it was not
possible to execute the speech recognition tests (SRT), such as
Percentage Index of Speech Recognition (PISR). It was then
necessary to evaluate the Voice Detection Threshold (VDT).
During the immittance audiometry exam, a type A curve in the
right ear was seen, and the type Ad curve was seen in the left
ear, according to the Jerger classification scale [14]. There was
an absence of contralateral acoustic reflexes, as well as ipsilateral
reflexes in both ears. The examination of transient OAE and
distortion product OAE was absence of bilateral responses. ABR
by click stimulation demonstrated an absence of neural potential
bilaterally in 95dBA and the presence of cochlear microphonism
in 90 dBA in both ears. The results of the complete audiological
evaluation enabled the realization of Cochlear Implantation.

In February of 2015, the patient was submitted to cochlear
implant surgery in her left ear. During the procedure, the
tympanic membrane was visualized and was integral and shiny.
A retroauricular incision of 3 cm was performed, followed by the
drilling of the mastoid bone, which permitted the visualization
of an integral and articulated bony chain. The facial nerve was
integral in its tympanic and mastoid trajectory. A posterior
tympanotomy was performed, maintaining as a reference the

![Figure 1A](image-url) Tonal audiogram performed in 2002 that exhibited severe SNHL in the left ear and profound in the right ear. B. Tonal audiogram
conducted in February of 2015, pre-operational, that demonstrated profound and bilateral SNHL.

Legend: O: airway of the right ear / <: bone conduction of the right ear (in red) / X: airway of the left ear / >: bone conduction of the left ear (in blue)
/ no response to the given stimulus: ↙ right ear (in red) / ↘left ear (in blue)
short branch of the incus, facial nerve, and the corda tympani nerve. Following that, a cochleostomy was done with a 1 mm drill perpendicularly to the stapes tendon and it was seen that the cochlea was in a normal state. After that, the total insertion of electrodes was conducted (Figure 2) and an intra-operative neurotelemetry was registered. The model used for the cochlear implant in this surgery was HiRes90K™ Advantage cochlear implant, by Advanced Bionics.

One month after the procedure, new exams were conducted, such as telemetry, telemetry of neural responses, the study of the stapedial reflex, electrode mapping, electrode activation, as well as phonoaudiological evaluation. During a consultation after four months of surgery, the patient mentioned great improvement of quality of life with the cochlear implant. She is still using the hearing aid in her right ear. During the tone audiometry exam, she presented a hearing improvement of 55 dB during frequencies of 500 Hz, 75 dB during 1000 Hz, and 95 dB during 2000 Hz and 4000 Hz (Figure 3).

DISCUSSION

Kearns-Sayre syndrome (KSS) was first described by Thomas P. Kearns and George Pomeroy Sayre in 1958 [15]. It is a rare disease and to our knowledge, there are only three reported cases of the disease published in the English language that were submitted to cochlear implantation surgery. Furthermore, there is only one report of twin brothers with the syndrome. There are no reports in medical literature of female twins with the syndrome.

The patient in our study presented the stipulated diagnostic criteria established for KSS, because the initial symptoms due to progressive ophthalmoplegia occurred before the age of twenty and was associated with pigmentary retinopathy, as well as a cerebellar ataxia. Also present were the bilaterally symmetric SNHL, a genetic test showing a deletion in the mitochondrial DNA, a muscular biopsy that exhibited a myopathic pattern, and the presence of RRF, which is a typical finding of the disease.

Deletions of mtDNA, ranging in size from 1.1 to 10 kb are associated with KSS, Pearson syndrome, progressive external ophthalmoplegia (PEO), and rarely Leigh syndrome. In Pearson syndrome, deletions are usually more abundant in blood than in other tissues and PEO deletions are confined to skeletal muscle [12].

Most mitochondrial diseases arise from a disruption in oxidative phosphorylation, often due to a defect in one or more respiratory complexes of the mitochondrial respiratory chain. A decreased activity leading to a reduced cellular energy production in the form of adenosine triphosphate (ATP), resulting in functional cell impairment, oxidative cellular injury or even apoptosis. This multienzyme system, located in the inner mitochondrial membrane, is made up of five polypeptide complexes (I, II, III, IV, and V) and two mobile electron carriers: coenzyme Q (quinone derivative with ten isoprene units) and cytochrome c (a small, extrinsic protein). Each complex consists of various subunits encoded by nuclear DNA, which is imported into the mitochondria. The gene products, in a process that is poorly understood, then combine to comprise the inner mitochondrial respiratory chain [16,17].

Cytochrome c donates electrons from complex III to complex IV (COX). Coenzyme Q10 (also known as ubiquinone) behaves as a homogeneously pooled redox carrier between flavin dehydrogenases and the cytochrome system, transferring reducing equivalents from complexes I and II to complex III. It may also translocate protons from the mitochondrial matrix to the intermembrane space, contributing to the energy conservation occurring at coupling site 2 of the respiratory chain. Reduced coenzyme Q10 also acts as an antioxidant, protecting...
mitochondrial inner membrane lipids and proteins, and mitochondrial DNA against oxidative damage. This coenzyme is slightly decreased in KSS [16,17].

Lactic acidosis is caused by pyruvate accumulation when the inner mitochondrial respiratory chain is dysfunctional. The morphology of this occurrence is seen as RRF in muscle pathologic specimens. As mentioned earlier, the mitochondria use genetic products from mitochondrial DNA as well as from nuclear DNA. Complex II, also labeled succinate dehydrogenase, is composed exclusively of nuclear components. The ragged red appearance is a classic morphologic feature of mitochondrial disease caused by high levels of succinate dehydrogenase generated to compensate for low levels of oxygen [16].

Abnormalities are observed with aging process: a loss of COX activity and concomitant increase in succinate dehydrogenase activity (succinate dehydrogenase hyperreactive regions, also known as a ragged red phenotype) [18]. Consequently, the percentage of RRF is variable in the syndrome.

Hearing impairment is a common feature of the KSS, however, can be found less often in other mitochondriopathies as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), PEO, mitochondrial myopathy (MM), maternally inherited diabetes and deafness (MIDD), myoclonic epilepsy with ragged red fibers (MERRF) [19]. There are other diseases that can cause similar findings to those of KSS as ophthalmoplegia, weakness and pigmentation retinopathy. The main differential diagnosis of KSS are the Pearson Syndrome, MELAS, PEO and MERRF [20,21].

MELAS syndrome onset may occur early in infancy with a history of developmental delay and learning disabilities. Patients may have visual complaints due to ophthalmoplegia, blindness because of optic atrophy and difficulties with night vision due to pigmentary retinopathy. The absence of stroke-like episodes (hallmark feature of this disorder), episodes of seizures (tonic-clonic or myoclonic) and visual abnormalities followed by hemiplegia decrease the probability of this diagnosis for the patient of this report. Some patients may experience hearing loss and diabetes [22].

In comparison with patients who have MELAS, patients with KSS also present with RRF that are COX-negative because their mitochondrial DNA genome is not synthesizing COX 2, an important subunit of the mitochondrial genome. MELAS patients typically have muscle biopsies revealing classic COX-positive ragged red fibers [16]. Unfortunately, there was no information about the COX activity in the muscle biopsy of our patient.

Pearson marrow-pancreas syndrome was first described in 1979 as an often fatal disorder of infants with transfusion-dependent sideroblastic anemia, vacuolization of hematopoietic precursors, and exocrine pancreatic insufficiency [23]. It is now known to be a rare, multisystemic, mitochondrial cytopathy with anemia, neutropenia, and thrombocytopenia, as well as variable hepatic, renal, and endocrine failure. Death usually occurs early in life, often during metabolic crises marked by refractory severe lactic acidosis during intercurrent, usually infectious illnesses [24]. Our patient had a complete blood count with normal values and no history of pancreatic, hepatic, renal and endocrine impairment.

PEO is a mitochondrial myopathy with drooping of the eyelids (ptosis), paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness. A few individuals with PEO have other manifestations of KSS but do not fulfill all the clinical criteria for the diagnosis. This situation is called "KSS minus" or "PEO plus". In PEO, mtDNA deletions are confined to skeletal muscle. The disorder is relatively benign and compatible with a normal life span. The multisystemic form is KSS; in the past, KSS was also referred to as "ophthalmoplegia-plus," a term now used to describe individuals who have more than isolated myopathy but do not fulfill the clinical criteria for KSS [12].

Our patient had a mitral valve prolapse displayed on the Echocardiography exam. This finding is not common in mitochondrial diseases. We found only one case report of a patient diagnosed with mitochondrial disease and the presence of mitral valve prolapsed [25]. The electrocardiogram did not show the presence of cardiac blockage, a common finding in KSS.

There are a few studies that show the possible alterations in the auditory system of patients with mitochondrial diseases. Liu [19] et al. (2014) evaluated the hearing of 73 patients with mitochondrial diseases, and amongst them only two had KSS and both patients had complaints of hearing loss. Of the 73 evaluated individuals, 52 (71%) presented alterations of tone audiometry, and in 51 of them the hearing deficit was symmetric. The only patient that did not present symmetrical hearing loss had unilateral otitis media at the moment of the evaluation, which generated an air-bone gap. The patients mentioned in our case report presented symmetric SNHL, corroborating with the Liu [19] et al. study in 2014.

With regard to the two patients with KSS that were mentioned in the Liu [19] et al. study, one of them only had hearing loss in high frequencies and the other presented moderate SNHL, with symptoms worsening in high frequencies. The latter situation is similar to the patient described in this report. One of the patients with KSS mentioned in the study by Liu [19] et al. presented a discrepancy between the findings in the pure tone audiometry and ABR. During the audiometry, the average tone within the range of 0.5, 1, 2 and 4 kHz (WHO standard) of 20 in the left ear and 18 in the right ear was found, with a reduction during acute frequencies. ABR demonstrated a disappearance in neural response in the right ear and the presence of waves in the left ear of 80 dB, with the value of increased absolute latency for I wave.

These abnormalities suggested temporal nonsynchronicity in central auditory pathway or auditory cortex dysfunction, and they should be diagnosed as auditory neuropathy spectrum disorder. Recently, several case reports have shown that auditory neuropathy can occasionally occur in some patients with mtDNA disease [26,27].

Mitochondrial segregation during germline development follows a bottleneck sampling effect, in which only a small fraction of the mother’s mtDNA is shared with progeny. This limits the probability that a mutation will be transferred to the next generation [16]. This can explain why risk of maternal
transmission of mitochondrial DNA deletion disorder has been estimated to be approximately 1 in 24 [28].

Interesting data reported by Khambatta et al. (2014) is that none of the 35 patients with KSS in their study presented a familial history of the disease, which is a situation identical to that of the twin sisters mentioned in our study. Mt DNA deletions generally occur de novo in the mother’s oocyte or during embryogenesis [12] and thus, usually cause disease in only one family member. In addition to the first bottleneck sampling effect, there is also a somatic bottleneck event. As the zygote progresses to the multicellular stage (up to 128 cells) only approximately 3 of those cells will contribute to the formation of the fetus. The other cells will be allocated to support, as extra-embryonic tissue. This sampling effect can partially explain why different patients have varying severities of disease [16].

The diversity of clinical presentations in KSS can be explained by the fact that a single mtDNA mutation can result in the expression of multiple phenotypes [29]. In compliance, Zeviani et al. (1988) concluded that multiple phenotypes (ranging from mild to severe disease) were present with the same mtDNA mutation. The mutated mtDNA coexists with normal molecules (heteroplasmia) and the proportion of mutated to normal mtDNA correlates with the severity of clinical symptoms [31]. Studies identified that mtDNA heteroplasm level, mtDNA deletion size and location are all important in understanding the expression and progression of clinical disease [32]. This data also explains the fact that twins with de same disease can have diverse variations in audiological findings.

REFERENCES

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