An uncommon cause of atrioventricular block in young patients: Kearns-Sayre syndrome

Una causa infrecuente de bloqueo auriculoventricular en pacientes jóvenes: síndrome de Kearns-Sayre

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Palabras clave: Síndrome de Kearns-Sayre, oftalmoplejía externa crónica progresiva, blefaroptosis, bloqueo cardiaco, miopatía mitocondrial.

ABSTRACT

Kearns-Sayre syndrome (KSS) is a rare cause of complete atrioventricular (AV) block in young patients. This disorder is caused by mitochondrial DNA (mtDNA) deletions, and unlike other mitochondrial diseases, involvement of the cardiac conduction system is frequent. KSS is characterized by the triad of progressive external ophthalmoplegia, pigmentary retinopathy and cardiac conduction system disturbances, with an onset before 20 years of age. We present a case of complete AV block due to this rare condition, which was diagnosed with a muscular biopsy taken at the time of pacemaker implant.

RESUMEN

El síndrome de Kearns-Sayre (SdKS) es una causa infrecuente de bloqueo auriculoventricular (AV) en personas jóvenes. Este desorden es causado por delecciones del ADN mitocondrial (ADNmt), y a diferencia de otras enfermedades mitocondriales, el compromiso del sistema de conducción eléctrica cardíaca es frecuente. El SdKS se caracteriza por la triada de oftalmoplejía progresiva externa, retinopatía pigmentaria y alteraciones en la conducción eléctrica cardíaca, con síntomas que, por lo general, inician antes de los 20 años de edad. Presentamos un caso de bloqueo AV completo debido a esta rara condición, la cual se diagnosticó mediante una biopsia muscular tomada al momento del implante de marcapasos.

INTRODUCTION

Atrioventricular block (AV) in young adults is infrequent, with non-ischemic heart disease (mainly myocarditis) accounting for a significant percentage of patients. Nonetheless, most patients don’t have structural anomalies or underlying diseases readily identifiable, and ultimately undergo pacemaker implant without a clear diagnosis.¹

Kearns-Sayre syndrome (KSS) is a specific mitochondrial myopathy caused by large-scale deletion of mitochondrial DNA (mtDNA) which is thought to occur somatically during early embryogenesis in the majority of cases. It typically presents as external progressive ophthalmoplegia, pigmentary retinopathy and various degrees of AV block, usually before 20 years of age.² Although rare (estimated prevalence of 1.6 per 100,000 adults), cardiac involvement is the most important factor in prognosis and cardiac conduction disturbances have an unpredictable rate of progression to complete AV block.³,⁴ Mortality has been reported in up to 20% of patients, hence an early diagnosis could potentially modify prognosis.⁵

We present a case of a patient with blepharoptosis, paralysis of the extraocular muscles and complete heart block, in which a diagnosis of KSS was made with a muscular biopsy taken at the time of permanent pacemaker implant.

CASE PRESENTATION

A 22-year-old male with a previous history of bilateral blepharoptosis and external progressive ophthalmoplegia presented to the emergency
department for syncope which was preceded by several hours of dizziness and diaphoresis. He reported a reduction in his exercise capacity over the previous 4 months, and presyncope 2 weeks before the present event.

On examination, his heart rate was 38 bpm. There was no respiratory distress and heart and respiratory sounds were normal. Neurologic examination revealed a conscious, alert and oriented patient with complete bilateral ophtalmoplegia and blepharoptosis (Figure 1) without involvement of the lower cranial nerves and preserved extremity movement and sensibility. His initial electrocardiogram (ECG) revealed a complete AV block with a junctional escape rhythm (Figure 2). He had been previously examined by a neurologist as an outpatient, with magnetic resonance imaging (MRI) of the brain revealing brainstem and thalamus atrophy with prominent sulcus. A previously performed spinal tap reported increased protein concentration. No other members of his family had similar symptoms.

Due to his complete heart block, the patient was scheduled for dual-chamber pacemaker implant. Given his clinical presentation, a mitochondrial myopathy was suspected and a muscle biopsy from his pectoralis major muscle was taken during the procedure. Light microscopy reported the presence of atrophic muscle fibers with ragged red muscle fibers. There were no inflammatory infiltrates, increase in endomysial collagen or glycogen deposits. High resolution optical microscopy reported subsarcolemic and intermyofibrillar mitochondrial accumulation, most of which were increased in size while others were swollen, with abnormal rigid crests or in circular arrangement. Paracrystallin inclusions (parking lot type) and electrodense bodies were identified. These findings were all compatible with a mitochondrial myopathy (Figure 3). Based on his clinical presentation (bilateral blepharoptosis, external progressive ophtalmoplegia and complete heart block), his brain MRI findings and the results of his muscle biopsy, a diagnosis of Kearns-Sayre syndrome was made and coenzyme Q10 supplementation was initiated. Six months after pacemaker implant, the patient has had improvement in his exercise capacity and no further syncope.

**DISCUSSION**

Kearns-Sayre syndrome (KSS) is a specific mitochondrial myopathy characterized by progressive external ophtalmoplegia, pigmentary retinopathy and cardiac conduction system...
disturbances. Although it is a mitochondrial disease, it is rarely due to maternal inheritance and most cases are caused by de-novo large-scale deletions (1.3 to 10 kb) of mitochondrial DNA (mtDNA), which occur somatically in the early embryogenesis period resulting in impaired cellular oxidative phosphorylation. Symptom onset occurs before 20 years of age, and patients usually exhibit cerebellar ataxia, heart block, increased cerebrospinal fluid protein concentration, short stature and multiple endocrine conditions including diabetes mellitus, hypoparathyroidism or Addison disease. As in our case, ophthalmic manifestations in KSS precede cardiac complications and the presence of these may be sufficient to suspect the syndrome and actively search for cardiac involvement and confirmation of the diagnosis. Clinical course is progressive, with mortality occurring between the third and fourth decade of life, usually due to cardiovascular events (sudden death).

In addition to KSS, several other syndromes have been described in patients with mtDNA mutations, including Leber hereditary optic neuropathy (LHON); mtDNA-associated Leigh syndrome (LS); neuropathy, ataxia and retinitis pigmentosa (NARP); mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged-red fibres (MERRF). In fact, mitochondrial diseases have an estimated prevalence of 9.2 to 16.5 in 100,000 adults, with asymptomatic mtDNA mutations occurring 1 in 200 to 250 persons. While cardiac conduction system anomalies are uncommon in other mitochondrial diseases, cardiac manifestations (including syncope, heart failure and cardiac arrest) occur in as many as 50% of patients with KSS. Magnetic resonance imaging has demonstrated frequent subclinical cardiac involvement, even in patients with normal echocardiograms. In fact, cardiac involvement is the most important factor in prognosis, with conduction disturbances frequently involving the distal His bundle and bundle branches. KSS patients undergoing electrophysiological studies typically show normal sinus node...
recovery times and AH intervals but prolonged
HV intervals. These conduction disorders
can rapidly and unpredictably progress to
complete AV block which is associated with
a high mortality (up to 20%) due to fatal
arrhythmias associated with severe bradycardia
(that is, bradycardia induced torsade des
pointes). Other electric alterations such as
QT prolongation or ventricular polymorphic
tachycardia in the absence of QT prolongation
and or bradycardia have been reported,
suggesting that not only bradycardia may be
the only mechanism responsible for cardiac
mortality. Whether or not patients with
KSS may benefit from a cardiac implantable
defibrillator rather than a pacemaker, or the
possible use of an electrophysiological study
to document inducible arrhythmias is yet to
be determined. No specific criteria have
been developed to clearly identify this subset
of patients and there is uncertainty on how
frequently patients should be evaluated for
cardiac conduction disease. However, early
adoption of a strategy to search for cardiac
conduction alterations, including ECG, Holter
and eventually electrophysiological study could
have a role in modifying the prognosis of the
disease. In our patient, we believe syncope
was caused exclusively by his complete AV block,
since there were clear previous symptoms of
reduced cardiac output (exertional dyspnea)
and no other electrocardiographic relevant
findings suggestive of an alternative arrhythmic
condition. After pacemaker implantation, his
cardiovascular symptoms improved.

Although genetic testing was not available in
this case, his clinical presentation along with the
results of his muscle biopsy (such as myofibrillar
separation due to proliferation of swollen
and abnormal mitochondria) make KSS highly
possible. As in our case, high clinical suspicion
is needed, and muscle biopsy can be undertaken
during pacemaker implantation, thus allowing
for a prompt diagnosis. Interestingly, in our
case ophthalmologic evaluation did not reveal
pigmentary retinopathy. Since classic criteria
for the diagnosis of pigmentary retinopathy
are not present in all patients, and varying
retinal compromise can occur particularly
in early stages of the disease regardless of
the degree of extraocular compromise, it
is possible that they were not seen during
ophthalmologic evaluation. The use of full-
field electroretinography is considered the
traditional standard in diagnosis of pigmentary
retinopathy, since it can detect changes in the
retinal electrical response in response to light
stimulus even when the retina appears to be
normal. Unfortunately, it was not performed
in our patient.

CONCLUSIONS

AV block is a relatively uncommon condition
in young patients, and as such less frequent
causes must be kept in mind. We present a case
of KSS with typical extracardiac phenotypic
findings that are highly suggestive of this
specific mitochondrial disorder. Pacemaker
implantation provides a unique opportunity
to perform muscle biopsy, allowing for correct
diagnosis of this condition.

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