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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 deleciones del ADN mitocondrial (ADNmt), y a diferencia de otras enfermedades mitocondriales, el compromiso del sistema de conducción eléctrica cardiaca es frecuente. El SdKS se caracteriza por la triada de oftalmoplejía progresiva externa, retinopatía pigmentaria y alteraciones en la conducción eléctrica cardiaca, 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.

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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 ophtalmoplegia, pigmentary rethinopathy 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 ophtalmoplegia presented to the emergency

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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.

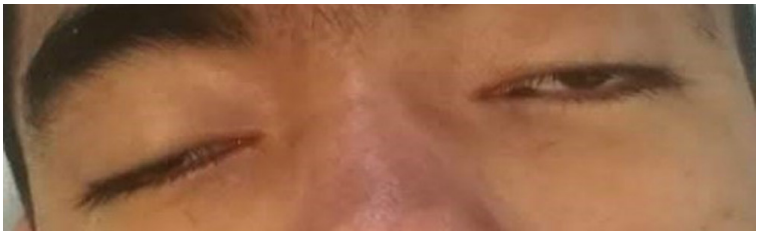

Figure 1: Bilateral blepharoptosis. Although the patient is fully awake, significant ptosis of the upper eyelids is observed. The patient had difficulty with his everyday activities due to loss of vision caused by his bilateral ptosis.

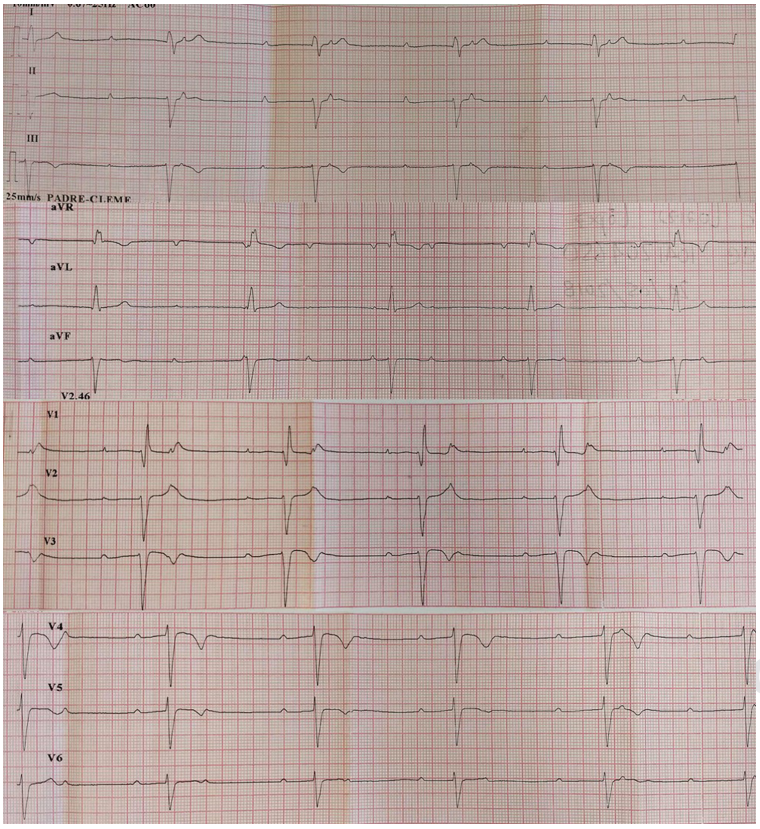

Figure 2: Initial ECG demonstrating complete heart block with a junctional escape rhythm.

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

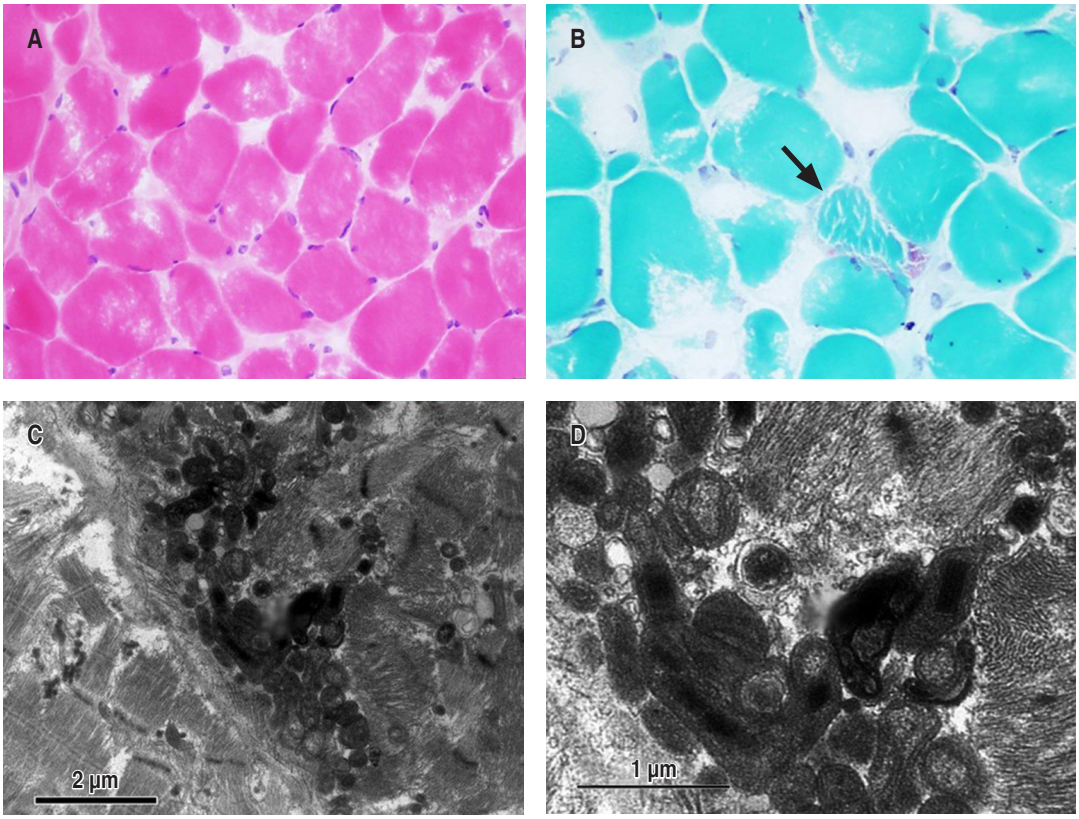

Figure 3:

Muscle biopsy: **A)** Hematoxilin-eosin muscular study without remarkable findings. **B)** Trichrome staining (arrow points subsarcolemmal sarcomere). **C and D)** High resolution microscopy (note swollen mitochondria with paracrystalline inclusions).

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.[2,5] 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.[6] Clinical course is progressive, with mortality occurring between the third and fourth decade of life, usually due to cardiovascular events (sudden death).[2,7]

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.[8] 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.[2,7] In fact, cardiac involvement is the most important factor in prognosis, with conduction disturbances frequently involving the distal His bundle and bundle branches.[9] KSS patients undergoing electrophysiological studies typically show normal sinus node

recovery times and AH intervals but prolonged HV intervals.[10] 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).[8,11] 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.[12,13] 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.[14,15] 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 rethinopathy. Since classic criteria for the diagnosis of pigmentary retinopathy are not present in all patients,[16] 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.[17] 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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