

Cardiac Arrest in Kearns–Sayre Syndrome

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Abstract The prognosis of progressive ophthalmoplegia in patients with large-scale mitochondrial DNA deletions is highly variable and almost unpredictable. The risk to develop cardiac involvement and sudden cardiac death is strikingly high, especially in patients with Kearns–Sayre syndrome (KSS). The most typical cardiac complications of the disease are conduction defects, which usually begin with left anterior fascicular block with or without right bundle branch block (RBBB), progressing sometimes rapidly to complete atrioventricular block. Other cardiac manifestations reported are first or second degree of AV block, QT prolongation, torsades de pointes ventricular tachycardia, and rarely dilated cardiomyopathy. Most frequently syncope, sometimes even sudden cardiac death, is the first clinical sign of the cardiac disease in KSS. Due to these life-threatening cardiac conditions, patients should be carefully monitored for cardiac signs and symptoms and

pacemaker implantation should be suggested early to avoid sudden cardiac arrest in KSS.

Here, we present two cases of KSS with life-threatening syncope due to complete atrioventricular block. To emphasize the importance of an early pacemaker implantation, we review the literature on cardiac complications in KSS in the last 20 years. In almost all of the reviewed cases, ophthalmoplegia or ptosis was present before the cardiac manifestations. In most of the cases, syncope was the first symptom of the cardiac involvement. There was no correlation between the age of the onset of the disease and the onset of cardiac manifestations.

With our current report, we increase awareness for life-threatening cardiac complications in patients with KSS.

Introduction

Kearns–Sayre syndrome [KSS; (MIM 530000)] is a mitochondrial syndrome, in most cases caused by large scale mitochondrial DNA deletions or mitochondrial DNA depletion (Maceluch and Niedziela 2007). Multiple organ systems are affected in KSS. The syndrome is defined by the obligatory triad of onset before the age of 20 years, progressive external ophthalmoplegia, and pigmentary retinopathy. In addition, at least one of the following must be present: heart block, cerebellar ataxia, or cerebrospinal fluid protein greater than 100 mg/dL (Rowland et al. 1991). Cardiac manifestations in KSS are as high as 50% and sudden cardiac death reported in up to 20% (Chawla et al. 2008).

Here, we present two cases of KSS with life-threatening syncope due to complete atrioventricular block. Furthermore, we review the literature on KSS with a focus on cardiac complications to increase awareness for this life-threatening complication.

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Case Reports

Patient 1

The male patient was born at term as the first child of healthy parents. For the first few years of life, he was healthy and had no clinical symptoms. From the age of 7, he was evaluated for growth delay and a failure to thrive despite normal caloric intake and age-appropriate nutrition. He developed a mild ptosis at the age of 10 years, and complained of easy fatigue. He had a normal IQ and followed regular mainstream education. Laboratory screening revealed a chronic lactic acidemia, elevated serum alanine levels, and GH deficiency. At the age of 11 years, he developed ophthalmoplegia and was diagnosed with reduced mitochondrial ATP production and a complex I deficiency in a surgical muscle biopsy. Southern blot for mtDNA deletions and sequence analysis of the mtDNA in blood revealed no abnormalities. The first cardiac evaluation at the age of 11 years revealed a structurally normal heart with good left ventricular function on the echocardiography. The electrocardiogram (ECG) showed left anterior fascicular pattern with normal PR and QTc intervals. He developed a severe failure to thrive and used a wheelchair for long distances. He was started on tube feeding to optimize his caloric intake combined with GH therapy. Based on the clinical features of KSS sequence analysis of the mtDNA at the age of 12 years was performed again; this time on mtDNA extracted from muscle, showing the common 5 Mb mtDNA deletion. His cranial MRI at the age of 14 showed cortical atrophy and bilateral signal intensity changes of the posterior cerebellum. An EEG showed diffuse encephalopathy.

During cardiac follow-up at the age of 12 beside the known left anterior fascicular block an incomplete right bundle branch block (RBBB) appeared on the ECG, which remained unchanged up to the age of 15 years. At the age of 16 years, he lost his consciousness three times in a period of 1 month. ECG showed now complete RBBB and a left anterior fascicular block. Echocardiography remained normal. 24 hours Holter ECG showed sinus rhythm, first degree AV block, and the known bifascicular block. An event recorder was given to the patient to register a definitive cardiac cause during syncope, but a week later he was admitted to the intensive care unit and was resuscitated for a complete AV block with a very slow escape rhythm. A DDD pacemaker was implanted successfully.

Patient 2

The female patient was born at term as the first child of healthy parents. After a normal delivery and normal psychomotor development, she remained healthy and besides

frequent infections she had no clinical symptoms. From the age of 10 years, she developed growth delay and a failure to thrive despite appropriate nutrition. She was evaluated for muscle weakness, night blindness, and progressive visual loss. She had a normal IQ and followed special education for children with visual loss. MRI showed changes consistent with Leigh syndrome. Ophthalmologic evaluation showed retinitis pigmentosa. She was further evaluated for a chronic lactic acidemia. EMG showed symptoms of myopathy. She was diagnosed with a reduced mitochondrial ATP production and a complex I deficiency in a surgical muscle biopsy. The complex I deficiency was also detected in cultured skin fibroblasts. Southern blot for mtDNA deletions, sequence analysis of the mtDNA in blood, and sequence analysis of the structural nuclear genes of complex I revealed no abnormalities. At that time, KSS was not suspected. At the age of 11, the first cardiac evaluation showed a normal ECG with normal conduction intervals. Echocardiography showed a borderline left ventricular hypertrophy. She developed diabetes at the age of 12 and ptosis at the age of 14 years. In the same year, she presented two episodes of syncope and the ECG showed complete AV block. A pacemaker was implanted with success. She developed bilateral ophthalmoplegia at the age of 15 years. Based on the clinical features of KSS, sequence analysis of the mtDNA was performed in muscle showing the common 5 Mb mtDNA deletion.

Review of the Reported Cases

To summarize the experience in the last two decades, we reviewed the literature on KSS and cardiac complications. A summary of 16 clinical reports on the age of onset, the presentation of cardiac manifestation and the outcome in KSS is given in Table 1. The reported median age of presentation of cardiac manifestations was at the age of 28 years, ranging between 9 and 47 years (Table 1). There was no correlation between the age of the onset of the disease and the onset of cardiac manifestations (not shown in the table). The median time reported between newly diagnosed cardiac conduction defect and first symptoms of cardiac complications (Table 1) was 5.5 years (2–9 years). In one case, the first symptom was syncope with RBBB on the ECG, and 10 days later the patient died of sudden cardiac death at the age of 18 years. In most cases (87%), ophthalmoplegia or ptosis was present before the cardiac manifestations (not shown in the table). In 69% of the cases, syncope was the first cardiac symptom of the disease. Conduction defects are the most typical cardiac manifestations; but also ventricular tachycardia, long QT, and cardiac failure were observed in some cases. In published cases, more female patients were found with KSS involving cardiac complications.

Table 1 Cardiac complications in KSS. Summary of the literature between 1989 and 2009

Reference	Age at cardiac symptoms (in years)	Cardiac symptoms	Cardiac manifestation	Intervention	Gender (M/F)
Remes et al. (1992)	29	–	Intraventricular conduction delay;	DDD PM	Unknown
	38	Syncope	Complete AV block (infra-His block)		
Anan et al. (1995)	15	Syncope	Complete AV block (infra-His block)	PM (type is unknown)	M
Kakura et al. (1998)	17	Cardiac failure	Complete heart block	DDD PM	M
Katsanos et al. (2002)	18	Syncope 10 days later SCD	RBBB, Mitral valve prolapse	Died before PM impl.	F
Oginosawa et al. (2003)	29	Syncope	1st degree AV block, LAFB, Polymorphic ventricular tachycardia (normal QT interval)	Dual chamber ICD	F
Hara et al. (2004)	29	Syncope	Mobitz type II 2nd degree AV block, RBBB, LAFB, Ventricular tachycardia	Dual chamber ICD	F
Young et al. (2005)	39	Syncope	1st degree AV block RBBB, LAFB	DDD PM	M
Karanikis et al. (2005)	47	Syncope	Sinus bradycardia 1st degree AV block RBBB, LAFB, Torsades de pointes ventricular tachycardia (long QT)	DDD PM	F
Letsas et al. (2006)	17	–	RBBB, LAFB; Complete AV block		
	20	Syncope		DDD PM	F
Subbiah et al. (2007)	33	Cardiac failure	Complete AV block Torsades de pointes ventricular tachycardia DCM	DDD PM ICD	F
Skinner et al. (2007)	12	–	RBBB; Complete heart block Torsades de pointes ventricular tachycardia	DDD PM	F
	14	Syncope			
Chawla et al. (2008)	10	Cardiac failure	Complete heart block	VVI PM	F
Riera et al. (2008)	9	–	IRBBB		
	23	–	RBBB, LAFB, LSFB	PM (type is unknown)	M
Yeşil et al. (2009)	22	Syncope	Mobitz type II 2nd degree AV block with RBBB, LAFB	VVI PM (after 12 years total PM dependency)	F
Welzing et al. (2009)	9	Cardiac failure	Complete heart block	VVI PM	F

PM pacemaker, SCD sudden cardiac death, RBBB right bundle branch block, LAFB left anterior fascicular block, ICD implantable cardioverter-defibrillator, DCM dilatative cardiomyopathy, IRBBB incomplete right bundle branch block, LSFB left septal fascicular block, DDD pacemaker dual chamber pacing and sensing pacemaker, VVI pacemaker ventricular pacing and sensing pacemaker

Discussion

Cardiac involvement has been shown to be the most important prognostic factor for life expectancy, and complete heart block is known to be the major cause of death in patients with KSS (Chawla et al. 2008). KSS typically causes cardiac conduction defects. Intracardiac electrophysiologic studies showed that the primary abnormalities are in the AV node-His-Purkinje system (Polak et al. 1989). In cardiac histopathological studies, fatty infiltration and fibrosis of the bundle branches and of the sinoatrial and atrioventricular nodes have been observed (Gallastegui et al. 1987).

The typical conduction defects are fascicular blocks and bundle branch blocks, progressing to complete heart block. In the reviewed literature, the first cardiac complication of

the disease was at 9 years, but cardiac manifestation even complete AV block might occur earlier. Unfortunately, there is no effective treatment to prevent the manifestation or slow down the progression of cardiac complications (Welzing et al. 2009).

KSS syndrome is not an easy diagnosis to make in the early phase of the disease. Some of the patients demonstrate Pearson's syndrome initially (Rahman and Leonard 2000), others, like our second patient might have associated Leigh disease. Recent diagnostic guidelines suggest mtDNA deletion analysis in muscle already early in the diagnostic process if KSS is suspected (Finsterer et al. 2009). However, even if the correct diagnosis is made, the adequate therapy could be challenging.

In the case of our own first patient in the differential diagnosis of the episodes of losing consciousness, based on

the severe neurological involvement and history of low blood sugar levels, we initially included the possibility of absence epilepsy, hypoglycemia, and AV block as well. The investigations, however, were inconclusive; the glucose day curve was normal, EEG showed diffuse encephalopathy, and the 24 hours Holter ECG monitoring revealed no definitive cause. At this point of the investigations, cardiac cause of the syncope was not obvious. Due to the severe neurological status, a seizure disorder was also suspected in the patient.

In the case of our second patient, avoiding the life-threatening episode was almost impossible, since the correct diagnosis was not even established by the sudden appearance of the cardiac symptoms. The manifestation of the cardiac involvement played an important role in finding the diagnosis.

The European Society of Cardiology guidelines for cardiac pacing, 2007 recommend pacemaker implantation with any degree of fascicular block in patients with neuromuscular diseases with class IIa indication, level of evidence C, or with second- or third-degree AV block with class I indication, level of evidence B (Vardas et al. 2007).

Our two cases further emphasize the need to consider early pacemaker implantation in patients with known KSS with any sign of conduction impairment and the importance of early diagnosis.

We suggest that all patients with KSS should have ECG screening at least once a year to detect conduction defects, ventricular arrhythmias, and QT prolongation. Because of the progressive character of the disease, prophylactic pacemaker implantation should be considered in patients with KSS earlier than it is now accepted in the cases of fascicular blocks. Furthermore, patients who suffered a syncopal episode should be carefully monitored – especially in those cases when an underlying seizure disorder is unlikely – realizing that complete AV block and cardiac arrest can be the first manifestations of cardiac involvement.

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