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Review

Systematic review of cardiac electrical disease in Kearns–Sayre syndrome and mitochondrial cytopathy

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ABSTRACT

Kearns–Sayre syndrome (KSS) is a mitochondrial disorder characterised by onset before the age of 20 years, progressive external ophthalmoplegia, and pigmentary retinopathy, accompanied by either cardiac conduction defects, elevated cerebrospinal fluid protein or cerebellar ataxia. 50% of patients with KSS develop cardiac complications. The most common cardiac manifestation is conduction disease which may progress to complete atrioventricular block or bradycardia-related polymorphic ventricular tachycardia (PMVT).
The management of cardiac electrical disease associated with KSS and mitochondrial cytopathy is systematically reviewed including the case of a 23 year-old female patient with KSS who developed a constellation of cardiac arrhythmias including rapidly progressive conduction system disease and monomorphic ventricular tachycardia with myocardial scarring. The emerging role of cardiac magnetic resonance imaging (CMR) in detecting subclinical cardiac involvement is also highlighted. This review illustrates the need for cardiologists to be informed about this rare but emerging condition.

1. Systematic review

1.1. Methods

We performed a systematic search of articles describing the cardiac manifestations of Kearns–Sayre syndrome and mitochondrial cytopathy using PubMed, Scopus Embase, Database of Abstracts of Reviews of Effects, and Cochrane Database of Systematic Reviews using the search terms "mitochondrial OR Kearns–Sayre AND heart OR cardiac OR arrhythmia OR tachycardia." This search was supplemented by manual searching of bibliographies of published studies.

1.2. Definition

Mitochondrial disease refers to a heterogeneous group of disorders that result from dysfunction in cellular oxidative phosphorylation due to genetic mutations in the mitochondrial DNA (mtDNA) or nuclear DNA [1,2].

1.3. Cardio-genetics

The respiratory chain is located in the mitochondrial membrane and is responsible for oxidative phosphorylation (OXPHOS), the final common pathway for aerobic respiration. Thirteen respiratory chain complex proteins are encoded by mtDNA, with the rest encoded by the nuclear genome. In addition, the mitochondrial genome encodes two ribosomal RNAs (12S and a 16S rRNA), and 22 transfer RNAs involved in protein synthesis. Impaired OXPHOS leads to depletion of ATP primarily due to defects in the electron transport chain enzymes (Complexes I–IV) which

Abbreviations: mtDNA, mitochondrial DNA; KSS, Kearns–Sayre syndrome; PPM, permanent pacemaker; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; PMVT, polymorphic ventricular tachycardia; RBBB, right bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; LHON, Leber hereditary optic neuropathy; LS, mtDNA associated Leigh syndrome; NARP, neurogenic muscle weakness, ataxia and retinitis pigmentosa; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibres; AV, atrioventricular; CMR, cardiac magnetic resonance imaging; RVOT, right ventricular outflow tract; ECG, electrocardiogram; TTE, transthoracic echocardiogram; OXPHOS, oxidative phosphorylation; ESC, European Society of Cardiology; EP, electrophysiology; AH, atrial-His; HV, His-ventricle.

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are responsible for promoting proton transfer across the inner mitochondrial membrane and utilised by complex V (ATP synthase) in order to generate ATP [3].

1.4. Prevalence

Mitochondrial disease was initially thought to be a rare disorder, affecting mainly children. Early epidemiologic studies estimated a minimum population prevalence of mitochondrial disease between 9.2 and 16.5 in 100,000 [4,5]. However, a large community-based study found that the common pathogenic mtDNA mutation, MELAS m.3243A > G, was present in 1 in 500 Australians [5,6]. Further analysis found that the prevalence of another mtDNA mutation, the m.1555A > G mutation was also 1 in 500 [7]. Thus, the number of Australians at-risk of developing mitochondrial disease or that have mild undiagnosed mitochondrial disease from these two mutations alone is 1 in 250 [7]. Other prevalence studies [8,9] have now confirmed that the frequency of mtDNA mutations amongst "healthy" or oligosymptomatic subjects is probably 1 in 200 to 250 people [10].

1.5. Inheritance patterns

MtDNA disease is transmitted by maternal inheritance whilst nuclear DNA disease can be autosomal dominant or recessive [10,11], or X-linked. 2–10 copies of mitochondrial DNA are found in each mitochondrion. Depending on the energy requirements of the cell or tissue, several hundred mitochondria may reside in each cell, and thus there may be thousands of copies of mtDNA per cell [12]. In affected patients, each cell is comprised of varying proportions of normal and mutant DNA (heteroplasmy). Cardiac myocytes, because of their high demand for oxidative metabolism, have the highest volume density of mitochondria in the body [13].

The clinical heterogeneity of mtDNA-based mitochondrial diseases is determined, in part, by the type of mutation (protein-coding gene vs transfer-RNA vs mtDNA rearrangement) and potential differences in heteroplasmy of the mtDNA mutation between individuals of the same family or between tissues within the same affected individual [14–16]." Severity" of a mutation can be inferred genetically or functionally, based on research studies in patient cell lines and/or transmitochondrial cybrids.

Kearns–Sayre syndrome (KSS) is a specific type of mitochondrial myopathy caused by single, large heteroplasmic deletions of mtDNA that can range from 1.3 to 10 kb, with the most common abnormality being a 4.9 kb deletion from nucleotide positions 8469 to 13,447 of the mitochondrial genome. This deletion is thought to almost always occur somatically in the early embryo, since the vast majority of cases are sporadic [17]. For the very rare cases of inherited KSS, this may be due to maternal inheritance of the mtDNA deletion.

Mutations in nuclear DNA can also result in mitochondrial myopathy via a range of mechanisms including multiple mtDNA deletions. These disorders follow Mendelian inheritance. For example, mutations in the TWINKLE gene are a recognised cause of autosomal dominant progressive external ophthalmoplegia, with some patients demonstrating cardiac abnormalities including dilated cardiomyopathy, atrial arrhythmias and mild conduction system disease [18]. Similarly, autosomal dominant progressive external ophthalmoplegia with associated cardiomyopathy may result from mutations in the POLG gene encoding mtDNA polymerase [19,20], as well as the ANT1 gene which facilitates transport of ATP and adenosine diphosphosphate (ADP) across the mitochondrial membrane [21]. ANT1 mutations have also been described in Senger's syndrome, an autosomal recessive disease characterised by mitochondrial myopathy, lactic acidosis, and hypertrophic cardiomyopathy [22]. Mutations in the nuclear genes (SCO2 and COX15) have also been reported in the autosomal-recessive condition characterised by features of Leigh syndrome and presence of hypertrophic cardiomyopathy [23–25]. The nuclear gene (OPA1) is a facilitator of mitochondrial fusion in cardiac myocytes, and mutations may lead to a deficiency in antioxidants, mitochondrial dysfunction and the development of late-onset cardiomyopathy [26].

1.6. Pathology

Cardiac biopsy reveals an absolute increase in the number and size of mitochondria in the presence of decreased mitochondrial enzyme activity [27]. It is not entirely clear why there is a predilection for cardiac conduction tissue or indeed whether the degree of structural abnormalities on biopsy correlates with the clinical presentation. Kearns [28] found evidence of left ventricular hypertrophy and hyperchromatic enlarged myocyte nuclei following an autopsy of a 17 year old boy with KSS who had sudden cardiac death. Clark et al. reported autopsy findings of a 13 year old boy with KSS, progressive atrioventricular and intraventricular conduction system disturbances [29]. This revealed microscopic degeneration and fibrosis in the distal portion of the bundle of His and right and left bundle branches. Schwartzkopff et al. described findings of a right septal endomyocardial biopsy in nine patients with KSS [30]. Five of the study patients had manifest conduction tissue abnormalities on their ECGs (LAFB with or without RBBB, incomplete RBBB). Abnormally large or small mitochondria with an empty or vacuolated matrix often packed with glycogen granules were found. In addition, cardiac cells with abnormal mitochondria had reduced myofibril content. Interestingly, one patient with conduction abnormalities did not have abnormal mitochondria in their myocytes. In the majority of patients there was normal composition of intracellular organelles. Similarly, Gallastegui et al. have demonstrated evidence of fatty infiltration and fibrosis of the bundle branches, sinoatrial and AV nodes in biopsies of patients with KSS [31].

1.7. Clinical syndromes

There are many syndromes based on typical clinical phenotypes that have been described in patients with mtDNA mutations. Of these, Leber hereditary optic neuropathy (LHON), mtDNA-associated Leigh syndrome (LS), Neuropathy, ataxia and retinitis pigmentosa (NARP) Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), Myoclonic epilepsy with ragged-red fibres (MERRF) and KSS are most frequently associated with cardiomyopathy and/or cardiac electrical disease. The genetic background, clinical features and cardiac manifestations in some non-KSS mitochondrial cytopathies are summarised in Table 1. The remainder of the review will focus on KSS because cardiac features predominate in this sub-type. A clinical case of a patient with KSS is presented which highlights some of the clinical issues associated with managing patients with KSS.

1.7.1. Clinical case

A 23 year old female student diagnosed with KSS on the basis of chronic progressive external ophthalmoplegia, bilateral ptosis, retinal pigmentary changes, sensorineural hearing loss, multiple sub-cortical white matter changes on magnetic resonance imaging of the brain, myopathic changes on electromyography, and insulin resistance. Long-range PCR amplification of the entire mitochondrial genome extracted from her urinary epithelial cells demonstrated an additional band that was approximately 5 kb shorter (~11 kb) than full length mtDNA (16.5 kb), indicative of a heteroplasmic single mtDNA deletion. There was no family history of mitochondrial or cardiac disease. Her medications were magnesium and co-enzyme Q10. She had undergone serial cardiac assessment since the age of 18. Serial electrocardiograms (ECGs) during this period had shown left anterior fascicular block (LAFB) and septal Q waves (Fig. 1a). Three years later, she reported dizziness and a transient sensation in her chest reminiscent of palpitations. At this time, her ECG showed new right bundle branch block (RBBB) with pre-existing LAFB (Fig. 1b).

A transthoracic echocardiogram (TTE) revealed a structurally normal heart and Holter monitoring revealed asymptomatic atrial ectopy (500 in 24 h). There was no evidence of atrioventricular (AV) block or tachyarrhythmia. She completed 10 min of a standard Bruce protocol exercise stress test, stopping due to general fatigue. During exercise recovery, she developed a self-limiting episode of sustained