CASE REPORT

Progressive cardiomyopathy as manifestation of mitochondrial disease

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Mitochondrial diseases consist of various polymorphic pathological entities which usually involve many organs and systems.1 An important part of this spectrum is caused by mutations of mitochondrial DNA (mtDNA). Mitochondria have a pivotal role in cell metabolism, being the major site of ATP production via oxidative phosphorylation, and contribute to human genetics since they have a functional genome separate from that of nuclear DNA.2 Mitochondria and mitochondrial genome (mtDNA) are exclusively maternally inherited. Each mitochondrion contains two to 10 DNA molecules, and each cell contains multiple mitochondria. Thus, normal and mutant mitochondrial DNA can coexist within the same cell or in the same tissue. The proportion of mutant mitochondrial DNA required for the occurrence of a deleterious phenotype, known as the threshold effect, varies from person to person, among organ systems, and within a given tissue.3 The threshold effect depends on the delicate balance between oxidative supply and demand.4 Because the heart, as well as the central nervous system and the skeletal muscles, is highly dependent on the energy produced by mitochondrial oxidation, these tissues are more vulnerable to mitochondrial defects. It has been demonstrated that the same point mutations of mtDNA are associated with distinct phenotypes, and the same phenotype is caused by different mutations.5 The A-G transition mutation at position 3243 of mtDNA is known to be the main cause of MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes).6 Besides that, it has been recently associated with other phenotypes, such as familial progressive external ophthalmoplegia, maternally inherited diabetes mellitus, and deafness and maternally inherited cardiomyopathy.7-9 The most common of these phenotypes is diabetes mellitus associated with maternally transmitted sensorineural hearing loss, which occurs in an estimated 1.5% of the diabetic population.4 Phenotypic abnormalities in individuals bearing these genetic defects may be evident at birth or may not be apparent until years later. In the case of our patient, the coincidence of diabetes, hearing loss and cardiomyopathy, together with a personal history of repeated miscarriages and family history of deafness, as well as a high degree of consanguinity, caused us to suspect a mitochondrial condition, which was confirmed by muscular biopsy and DNA analysis. Hearing loss in the family was suffered by the mother and two maternal aunts. No family history of diabetes or cardiomyopathy was present.

A major clinical feature of mitochondrial disease is a progressive increase in the number of affected tissues or pattern and muscle biopsy revealed abundant ragged red fibres in the muscle. The gene study, sequencing the tRNA Leu(UUR) gene from lymphocyte mitochondrial DNA, found the A-G mutation at position 3243 of mtDNA. The patient was treated with diuretics and angiotensin converting enzyme (ACE) inhibitors, which produced a favourable clinical response.

DISCUSSION

Mitochondrial cardiomyopathy (MCM) is a subtype of cardiomyopathy with characteristic features. It is a genetically heterogeneous disease and is caused by point mutations in mtDNA.10-13 Although it usually presents in late middle age, it can present in childhood, and a wide spectrum of age at presentation has been reported.9,13

The aetiology of MCM is poorly understood, and there is no single genetic defect that has been identified.14-16 The clinical presentation of MCM is variable, and the disease can present as a sudden death or as a chronic, progressive course.17,18

The diagnosis of MCM is usually made by clinical and echocardiographic findings, and the genetic diagnosis is confirmed by muscle biopsy and DNA analysis.10,16,19-21

In this case, the patient presented with progressive heart failure and was diagnosed as having a mitochondrial A3243G mutation.
organs over an individual's lifetime. The patient progressively developed diabetes mellitus, hearing loss, and adult onset cardiomypathy. Particularly remarkable was the rapid progression of the cardiomyopathy, with severe systolic dysfunction developing over the last year. Common causes for this were ruled out, since there was no history of hypertension, myocarditis or exposure to toxic agents, and coronary angiography was normal. The lack of any other known cause of cardiac failure makes mitochondrial disease the most probable reason for the progressive cardiac change of this patient.

Since mitochondrial dysfunction can affect virtually all organ systems, physicians in many specialties may be faced with patients suffering from these diseases. The prevalence of mitochondrial disease among patients with myocardial dysfunction is not known. However, cardiomyopathy can be the presenting and predominant clinical expression of the A3243G mutation, and one of the causes of death from the disease. Therefore, cardiologists and general internists should be aware of mitochondrial DNA disorders and consider them in the differential diagnosis of cardiomyopathy of unknown origin. This suspicion should be increased in patients with other manifestations of mitochondrial disease, such as sensory hearing loss and diabetes, particularly in families with multisystemic disease.

Learning points

• Mitochondrial (mt) gene abnormalities cause disease due to defects in oxidative production of energy.
• Mitochondrial DNA disorders are clinically very heterogeneous, ranging from single organ involvement to severe multisystem disease. One of the most frequently observed mtDNA mutations is the A-to-G transition at position 3243 of the tRNA(Leu(UUR)). This mutation is often related to MELAS syndrome, maternally inherited diabetes and deafness and maternally inherited cardiomyopathy.
• Because the heart, as well as the brain and nervous system, is highly dependent on the energy produced by the mitochondrial oxidation, these tissues are more vulnerable to mitochondrial defects.
• Rapid progression of cardiomyopathy can occur in mitochondrial diabetes.

REFERENCES