CASE REPORT

Progressive cardiomyopathy as manifestation of mitochondrial disease

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Cardiomyopathies are a clinically and genetically heterogeneous group of cardiac diseases in which the myocardium is primarily involved. Mitochondrial DNA point mutations have been identified in a broad spectrum of mitochondrial disorders, which are associated with neurological diseases. However, they also have been reported in patients with cardiomyopathy, either alone or as part of a multisystem disorder. A patient who presented with severe heart failure and was diagnosed as having a mitochondrial A3243G mutation is described.

The mitochondrial diseases are a heterogeneous group of disorders that result from the structural, biochemical, or genetic derangement of mitochondria.¹ Although they are usually characterised by encephalomyopathy, these syndromes are multisystemic and virtually every organ system can be involved. We describe a woman who presented with severe heart failure and was diagnosed as having mitochondrial A3243G mutation.

CASE REPORT

A 47 year old woman was admitted to hospital because of congestive heart failure. She had been pregnant six times, always ending in miscarriage. At the fourth pregnancy, when she was 30, diabetes was diagnosed, and insulin treatment started. Blood glucose at previous pregnancies had been normal. At the age of 34, she started to suffer from progressive bilateral hearing loss, and at 45, she was examined because of a slight cognitive deterioration and apathy. Computed tomography of the brain showed bilateral basal ganglia calcification and generalised cerebral and cerebellar atrophy, and an ophthalmological examination revealed optic neuropathy and diffuse chorioretinitis. In the year before admission she had experienced episodic vomiting and exercise intolerance. An echocardiogram was normal. There was no history of hypertension, myocarditis, or exposure to toxic agents. Her diabetes control had always required insulin treatment, without any events worth mentioning. A high degree of consanguinity was present in her family since both her parents and one of the pairs of grandparents were first degree cousins. There was a family history of deafness, but not of dementia, cardiopathy, or diabetes. On admission, physical examination showed short stature, sensorineural hearing loss, raised jugular venous pressure, and rales at both lung bases. Biochemical blood studies including creatine kinase, aspartate aminotransferase, lactic dehydrogenase, and aldolase were normal. There was no evidence of lactic acidosis. An echocardiogram showed a normal sized left ventricle with slight septal hypertrophy (11 mm), lower grade of ejection fraction (10%), and diffuse hypokinesis of the cardiac wall. Coronary angiography found no stenosis of the coronary artery. An electromyogram was carried out which showed a myopathic

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 mt DNA. The patient was treated with diuretics and angiotensin converting enzyme (ACE) inhibitors, which produced a favourable clinical response.

DISCUSSION

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.¹ 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.² The threshold effect depends on the delicate balance between oxidative supply and demand.³ 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.⁴

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).⁵ Besides that, it has been recently associated with other phenotypes, such as familial progressive external ophthalmoparesis, maternally inherited diabetes mellitus, and deafness and maternally inherited cardiomyopathy.^{6–9} 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.¹⁰ 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

organs over an individual's lifetime. The patient progressively developed diabetes mellitus, hearing loss, and adult onset cardiomyopathy. 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.¹¹ 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.

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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.

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