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Reminder of important clinical lesson

A family with diabetes and heart failure

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Summary

The case of a middle-aged woman with early-onset diabetes mellitus, hypertrophic cardiomyopathy, premature sensorineural hearing loss and neuropsychiatric symptoms is described. The patient's family history revealed the classical pattern of maternally inherited diabetes and deafness (MIDD) and isolation of mitochondrial DNA from peripheral blood leucocytes showed an A3243G transition in the gene encoding for the $tRNA^{Leu(UUR)}$. Thus, the suspected diagnosis of a mitochondrial disorder was confirmed. Cardiac involvement turned out to be the dominating clinical feature in the patient. She died of cardiogenic shock and multiple organ failure within 1 year of diagnosis. Three out of nine affected family members had hypertrophic cardiomyopathy.

BACKGROUND

Even though mitochondrial cytopathies are rare disorders, the disease-specific symptoms and the maternal inheritance pattern usually make the diagnosis straightforward. Hence, the diagnostic value of a complete family history in patients who are diabetic cannot be overemphasised. Early diagnosis of a mitochondrial disease is important, as this may lead to a more accurate treatment for the individual patient person and for several family members as well. The high proportion of individuals with cardiac involvement in our patient's family highlights the need for genetic counselling and optimal medical attendance of these patients.

CASE PRESENTATION

A 52-year-old woman was admitted to our hospital after a few days of nausea, vomiting and medication non-adherence. Her general practitioner reported that she had hearing loss, behavioural disorder and insulin-dependent diabetes mellitus diagnosed at the age of 26 years. When the patient arrived at the emergency unit she was alert but did not follow commands. She was of short stature, lean, tachypnoeic (respiratory rate 28 breaths/min), hypotensive (blood pressure 90/55 mm Hg) and tachycardic (heart rate 115 beats/min). Initial serum glucose levels were 39 mmol/litre and blood gas analysis showed severe combined lactic acidosis and ketoacidosis (pH 6.85, serum bicarbonate 4.7 mmol/litre, pCO_2 2.9 kPa, pO_2 16.5 kPa, lactate 15 mmol/litre). Therefore, insulin treatment and aggressive fluid replacement were immediately given. However, the course was complicated by prolonged lactic acidosis, congestive heart failure and hepatocellular injury. Transthoracic echocardiography revealed marked hypertrophic cardiopathy with severely impaired left ventricular function (ejection fraction 25%), high-grade diastolic dysfunction and pulmonary hypertension with an estimated pulmonary artery systolic pressure of 75 mm Hg (figure 1). The clinical constellation led us to the hypothesis of an underlying mitochondrial disorder that was then confirmed by the family history revealing a pattern of maternally inherited diabetes mellitus (figure 2). Analysis of mitochondrial (mt) DNA showed an A to G transition at position 3243 of the $tRNA^{Leu(UUR)}$ gene. The patient was discharged with an optimised heart failure treatment, diabetes treatment and healthcare support. She died 1 year later of cardiogenic shock and multiorgan failure.

DISCUSSION

Mitochondrial disease occurs with an estimated incidence of 1:5000 to 1:10 000 in the general population and a prevalence of 1% in patients who are diabetic.[1] The family history in these disorders is of particular interest as mitochondria are present in oocytes but are not transmitted by spermatozoa, and the inheritance pattern is therefore almost exclusively maternal. The phenotypic variability of the affected individuals is a consequence of the coexistence of variable amounts of mutant and wild-type mtDNA in the cells and tissues (heteroplasmy). It is believed that mitochondrial disease becomes clinically apparent as soon as the proportion of mutated mtDNA exceeds a tissue-specific threshold level, with organs that are highly dependent on oxidative metabolism being the most susceptible.

Since the mtDNA was mapped in 1981, more than 150 pathogenic mtDNA point mutations have been reported. Among them, the A3243G transition is the most frequently detected.[2] With few exceptions, there is no strong correlation between genotype and phenotype in mitochondrial disease. Hence, an A3243G transition can result in many different syndromes, such as maternally inherited diabetes and deafness (MIDD), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, hypertrophic cardiopathy, or chronic progressive external ophthalmoplegia.[3] However, our patient's clinical presentation with early-onset diabetes mellitus, lactic acidosis, neurosensory deafness, cardiomyopathy, as well as neuropsychiatric disorders was found to be typical for the A3243G mutation in MIDD.[4] Penetrance of diabetes in a family with a proven

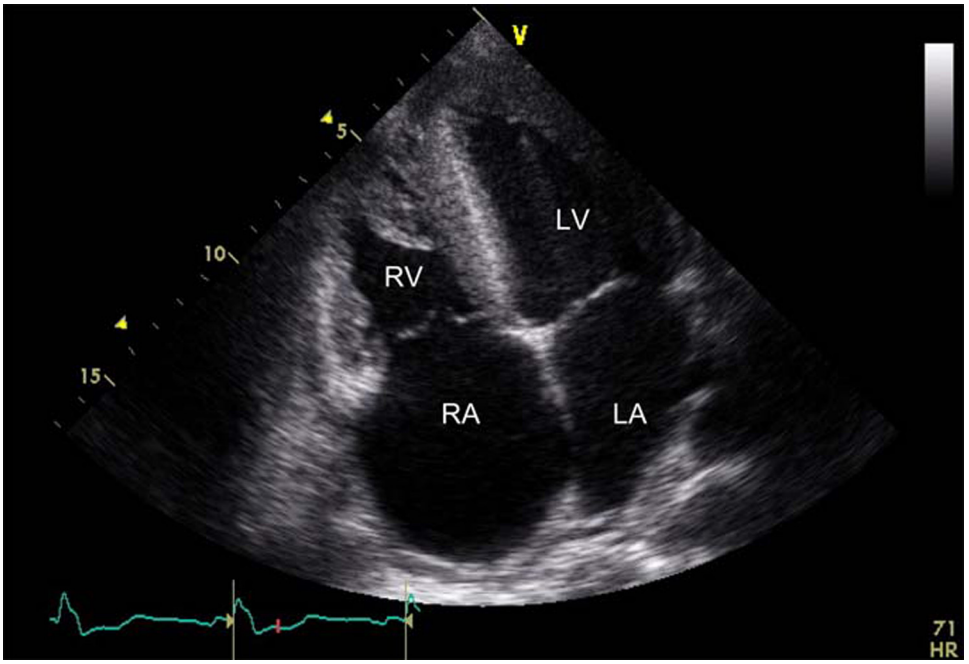

Figure 1 Transthoracic echocardiography. Image from the apical four-chamber view illustrating marked hypertrophy of the left ventricle (LV) and the right ventricle (RV), hyperechogenic myocardium, RV dilatation as well as dilatation of the right atrium (RA) and, to a lesser extent, the left atrium (LA).

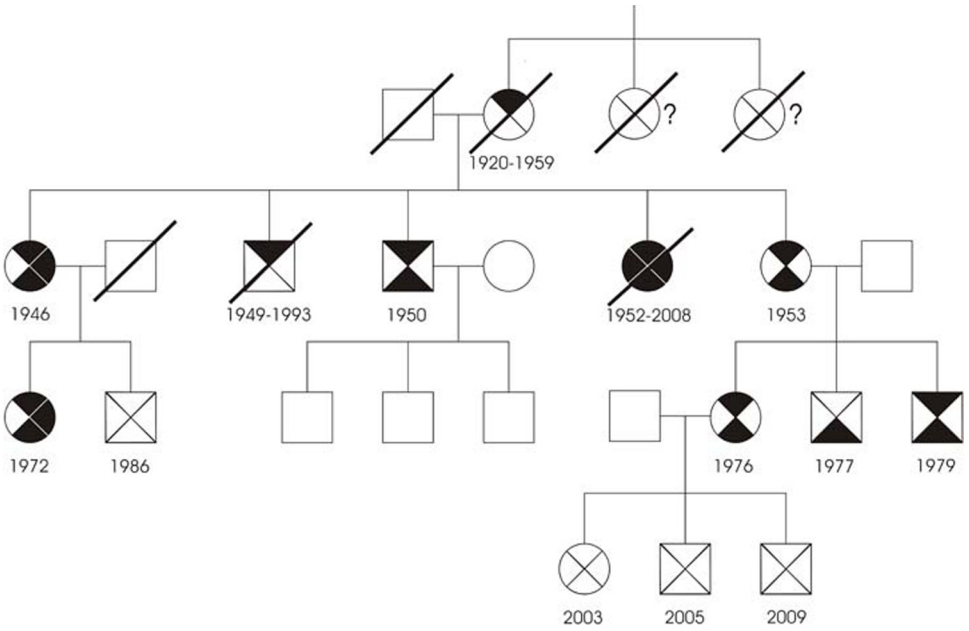

Figure 2 Family tree. Circles represent women, squares represent men. In family members at risk for mitochondrial disorder the date of birth and, if appropriate, date of death are indicated. Fully or partially filled symbols represent individuals showing disease-specific symptoms and each closed quarter stands for a single clinical manifestation: the upper quarter for diabetes mellitus; the right quarter for cardiomyopathy; the lower quarter for hearing loss; the left quarter for neuropsychiatric disorder. The question mark stands for death of unknown origin at young age. The fully filled circle represents our index patient.

A3243G transition is high (>85%) but the age at diagnosis varies considerably (median 37, ±11 years).[5] Moreover, the correlation between the level of heteroplasmy in peripheral blood leucocytes and the severity of the clinical phenotype is weak and the mutation might even be undetectable in leucocytes of affected individuals.[6] Hence, in family members at risk for carrying the mtDNA mutation, a regular screening for organ dysfunction seems to have a higher impact on

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the patient management than genetic testing itself. So far, in our patient's family the A3243G transition has been independently proven in only one individual of the third generation with gestational diabetes and sensorineural hearing loss. Cardiopathy is known to be another important feature of mitochondrial disease. In a report of 113 Japanese patients with the A3243G mutation, cardiomyopathy was found in 30.4% of all individuals with a mean age at diagnosis of 42.2 years.[7] In another study from a Finnish group which screened 39 individuals with a A3243G mutation for possible cardiac involvement, a left ventricular hypertrophy (LVH) was diagnosed in 56% of all patients.[8] In this cohort the risk for developing a LVH was mainly related to the severity of the clinical phenotype. These data highlight the need for cardiac monitoring, which should begin early in patients carrying a A3243G mutation As a general rule, it seems reasonable to start screening for a cardiopathy at the age of 30–35 years. Screening should start even earlier if there is a known premature onset of cardiopathy in the patient's family or if there are clinical signs of cardiac dysfunction or arrhythmia in an individual patient. Screening at baseline must include at least an electrocardiogram (ECG) and a transthoracic echocardiogram. Despite the progress made in the elucidation of molecular mechanisms underlying mitochondrial disorders, therapeutic options are still limited and often symptomatic. There is some data supporting the use of metabolites or cofactor supplements especially coenzyme Q10 (CoQ10) and L-carnitine. CoQ10 is an antioxidant and mitochondrial cofactor that plays an important role in the mitochondrial respiratory chain. Primary CoQ10 deficiency leads to neurological, myopathic and renal disease.[9] A case report in an individual with the A3243G mutation described improvement of left ventricular function after starting treatment with CoQ10 and worsening of cardiac function after the medication was stopped.[10] A small open-label study demonstrated slowing of disease progression in respect to hearing loss, loss of pancreatic β cell function and decrease in exercise tolerance in individuals with the A3243G transition taking CoQ10.[11] The assumed positive effect of coenzyme Q in mitochondrial cytopathy is an important finding, as it might influence patient management beyond CoQ10 prescription. For example, one might be more reluctant to use statins, a commonly prescribed type of drug in patients who are diabetic as they are known to lower endogenous CoQ10 levels in some individuals.[12] While there is ongoing debate on the risk and benefit of statins in MIDD, there is consensus that metformin should be avoided as it might increase the risk of lactic acidosis.

At present, there is still no cure for mitochondrial disorders but different strategies for genetic treatment are currently under investigation.[13 14] However, until such an approach will be available for clinical trials, supportive measures, CoQ10, genetic counselling and screening for organ dysfunction in affected individuals and families remain the mainstays of patient care.

Learning points

- A mitochondrial disorder should be considered in unexplained hypertrophic cardiomyopathy, especially in patients who are diabetic.
- Obtaining a family history is a simple and valuable diagnostic procedure.
- The diagnosis of a mitochondrial disorder can influence treatment options for diabetes.

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Competing interests None.

Patient consent Obtained.

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