CASE REPORT

MIDD or MELAS: that's not the question

MIDD evolving into MELAS: a severe phenotype of the m.3243A>G mutation due to paternal co-inheritance of type 2 diabetes and a high heteroplasmy level

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ABSTRACT

Maternally inherited diabetes and deafness (MIDD) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) are different syndromes, but are caused by the same m.3243A>G mutation in mitochondrial DNA. Why some patients develop MIDD while others MELAS is unknown, but may be related to heteroplasmy level. Progression from MIDD to MELAS has not been described. Here we report a patient with MIDD who over time developed severe insulin resistance and symptoms and signs consistent with MELAS. The most likely explanation here was paternal co-inheritance of type 2 diabetes in combination with a high heteroplasmy level. The present case showing evolution of MIDD to MELAS supports the concept that both syndromes can be regarded as two phenotypes of the same disease.

KEYWORDS

Insulin resistance, m.3243A>G mutation, MELAS, MIDD, heteroplasmy

INTRODUCTION

Maternally inherited diabetes and deafness (MIDD) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) are both caused by a maternally inherited m.3243A>G mutation in the mitochondrially encoded tRNAleucine 1 (UUA/UUG) gene.[1,2] MIDD accounts for 0.5-3% of diabetes mellitus (DM) and is characterised by decreased insulin secretion and sensorineural hearing loss.[3,4] In contrast, MELAS is a more severe syndrome, characterised by stroke-like episodes, encephalopathy, myopathy and lactic acidosis in blood and/or cerebral spinal fluid.[1,5,6] Both syndromes are associated with a broad spectrum of other symptoms, including depression, heart disease (cardiomyopathy) and Alport-like renal disease.[3-6] It is not clear why some patients develop MIDD, and others MELAS, but it has been suggested that the level of heteroplasmy (the presence of a mixture of mutant and normal mtDNA in a cell) plays a role.[6-8] Although some papers have reported neuromuscular involvement in MIDD,[3,9] progression from MIDD to MELAS has not been described in Caucasians.
Here we describe a male patient with the m.3243A>G mutation and an MIDD phenotype who over time developed a strikingly progressive insulin resistance and eventually evolved into MELAS. This case illustrates that mitochondrial diseases are multisystem disorders and that clinical signs and symptoms might alter over time. Apart from that it emphasises the importance of considering genotyping in DM patients, especially when the patient is young, has a positive family history or additional signs suggesting MIDD or MELAS.

CASE REPORT

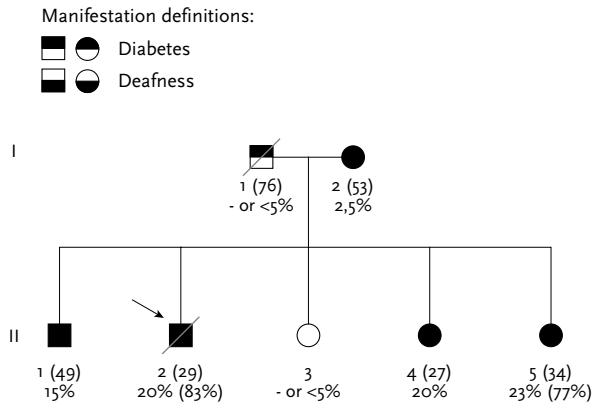
The proband -body mass index 24 to 27 throughout adult life- was diagnosed with hypertension and DM at 29 years, and sensorineural deafness at 33 years. His family,

which we have described previously, showed a high coseggregation of DM and deafness.[10] The m.3243A>G mutation was detected by targeted mutation analysis, with a blood leucocyte heteroplasmy of 20% in the proband (*figure 1*). His mother suffered from insulin-dependent DM and deafness, his father had type 2 DM treated with oral medication. The clinical course in the second generation was variable, ranging from no symptoms at all (II-3) to progressive disease in II-1, II-4 and the proband, who showed the most severe clinical picture.

His diabetes was characterised by progressive insulin resistance, for which he needed increasing doses of a rapid-acting insulin analogue ranging from 60 units per day at age 40, to 420 units at age 62. Nevertheless the Hba1c had exceeded 86 mmol/mol over the last ten years. To reach normoglycaemia, he was finally hospitalised monthly, for one week, to be treated with intravenous insulin up to 200 units per day. During these weeks he felt much better, especially concerning complaints of progressive muscle pain for which he eventually needed morphine. Ankle-brachial index was normal and he had no peripheral neuropathy or rhabdomyolysis. Serum triglyceride levels exceeded 10 mmol/l despite treatment with gemfibrozil and acipimox. Atorvastatin was stopped because of the myalgia. There was only mild background retinopathy and no renal failure or proteinuria.

His clinical picture worsened and at age 51 he developed MELAS with stroke-like episodes consisting of transient hemiparesis, headache, aphasia and reduced consciousness. There was no evidence of cerebral ischaemia on repeated CT scans, performed directly or within one week after an episode. An MRI could not be performed because of a cochlear implant. His cognitive function declined during the course of the disease. He suffered from right ventricular failure of unknown cause at age 49. Serum lactate was elevated (3.9 mmol/l) increasing to 4.9 mmol/l after a six-minute walk test, performed at age 60 at the end of a week of intravenous insulin. The walking distance was far below expected (212 m, expected 631 ± 93 m). A muscle biopsy showed decreased mitochondrial energy production, with lowered substrate oxidation and ATP production (19.1 nmol/h. mUCS; normal 34.5-67.5). Many COX-negative fibres were seen, indicating mitochondrial myopathy (*figure 2*). The muscle heteroplasmy level was 84%. He died at age 62 of aspiration pneumonia after a stroke-like episode.

Figure 1. *Pedigree of the family with the m.3243A>G mutation*



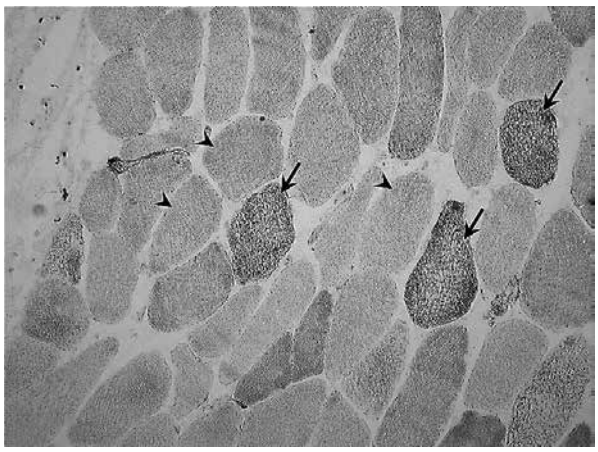
Roman numbers indicate generations. The proband is indicated by an arrow. The first line below the symbol represents identification number, with in parenthesis the age of onset of DM. The second line displays heteroplasmy levels in peripheral blood leucocytes and, in parenthesis, if available, in muscle.

DISCUSSION

Here we describe an MIDD patient who clinically evolved to MELAS over time. This is highly unusual and has not been described before in a Caucasian patient. Observational studies of Caucasian MIDD patients just showed absence of typical MELAS manifestations.[2,3,9] Furthermore, while MIDD has been associated with a predominant insulin secretion defect,[4,6,7] this patient developed extreme insulin resistance over time.

The explanation for these two features may be dual. Firstly, the MIDD phenotype may have evolved into a much more severe MELAS phenotype with severe insulin resistance in addition due to co-inheritance of type 2 diabetes from his father ('double gene dose').[11] A similar, albeit milder, phenotype was observed in the family members II-1 and II-4 who also show progressive insulin resistance,

Figure 2. *Muscle biopsy of the proband with cytochrome c oxidase (COX) staining*



Many COX-negative fibres (arrowheads) and a few COX-positive fibres (arrows) are present, indicating mitochondrial myopathy.

with average daily insulin doses of 250 and 120 units, respectively.

A second potential explanation is the high heteroplasmy level of the m.3243A>G mutation in muscle tissue (84%), which may cause a mitochondrial respiratory chain defect leading to reduced insulin-stimulated glucose metabolism and thus insulin resistance.[7,12,13,14] Mitochondrial dysfunction may also lead to stroke-like episodes, right ventricular failure and the severe hypertriglyceridaemia due to failure to metabolise free fatty acids.[3,4,6,12,14]

The present case demonstrates that a high muscle mutation load of 84% is a better predictor for the severe phenotype than the relatively low blood mutation load of 20%. This also seems the case in II-4, who does not meet all the MELAS criteria, but suffers from severe depression, has cerebral spinal fluid lactic acidosis and myopathy with a muscle heteroplasmy level of 77%. Heteroplasmy levels differ considerably amongst various tissues and the phenotypic variability of the m.3243A>G mutation is, at least in part, due to the varying levels of heteroplasmy.[4,6-8,13,15] Leucocytes are mostly used to determine heteroplasmy levels, in which they can be quite low and also tend to decline upon ageing.[4,15] The mutation load in more slowly dividing tissues such as muscle is higher,[7,15] and has a stronger relationship with phenotype.[4,8,13] Urinary epithelial cells may provide a reliable non-invasive alternative to perform mutation analysis.[16]

Interestingly, this case also demonstrates that muscle pain, which somewhat resembles ischaemic pains, was less severe when glucose control was optimised by intravenous insulin treatment. This observation suggests that muscle pain in MELAS is related to intracellular energy metabolism.

Treatment options, beside symptomatic relief and rehabilitation, are limited to treatment with L-arginine, an important mediator of cerebral vasodilation which can improve frequency and severity of stroke-like episodes, and the antioxidant coenzyme Q10.[6] The latter also acts as an electron carrier in the mitochondrial respiratory chain. It may therefore improve the mutation-associated dysfunction of the respiratory chain in mitochondria, but was not effective in our patient. Metformin is contraindicated because of the risk for lactate acidosis.[6]

CONCLUSION

This case history illustrates the severe and progressive clinical phenotype that may arise from the m.3243A>G mutation. Severe insulin resistance may occur, possibly determined by co-inheritance of type 2 diabetes. Furthermore, we show that MIDD patients may develop MELAS over time, which supports the concept that MIDD and MELAS in fact are two phenotypical expressions of one disease.

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