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Case report

Maternally inherited diabetes and deafness (MIDD): Diagnosis and management

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ABSTRACT

Maternally inherited diabetes with deafness is rare diabetes caused by a mitochondrial DNA defect. 85% of cases are associated with m.3243A > G mutation. It is important to diagnose this form of diabetes because of the unique management issues and associated comorbidities. A very strong family history of diabetes, deafness and presence of retinal dystrophy should prompt an investigation for MIDD. Microvascular complications out of keeping with duration of diabetes are another clue to the diagnosis. Retinal and renal manifestations of mitochondrial disease may be confused for diabetic complications. Glutamic acid decarboxylase (GAD) autoantibody negativity in a nonobese diabetic is another clue. Cardiac conduction defects and GDM may also raise suspicion as to the diagnosis. Recognizing this etiology of DM should promote family screening, genetic counseling, screening of associated comorbidities, avoidance of metformin, and cautious use of statins. We report a 77 years old lady with MIDD who was being followed up as insulin requiring type 2 diabetes. We then identified 5 more patients with MIDD in the same clinic. They all had A3243 mutation with characteristic clinical presentation. The pharmacological approaches discussed in the paper are unlikely to work in these patients as they were diagnosed late.

1. Introduction

Mutations in mitochondrial DNA (mtDNA) are rare etiologies of adult-onset diabetes mellitus (DM). These monogenic forms of diabetes comprise various forms of maturity onset diabetes of the young (MODY) and mitochondrial diabetes, also called "maternally inherited diabetes and deafness" (MIDD) (Chinnery, 2000). Nuclear gene defects can be inherited in an autosomal recessive or autosomal dominant manner. Mitochondrial disorders may be caused by defects of nuclear DNA or mitochondrial DNA (mtDNA). Mitochondrial DNA defects are transmitted by maternal inheritance. MIDD is a rare form of diabetes and was first described in 1992 (Reardon et al., 1992; van den Ouweland et al., 1992). In MIDD, diabetes seems to be due primarily to a defect in insulin secretion, while insulin sensitivity is unaltered. Diagnosis is based on the presence of one or more of the following criteria: 1) maculopathy; 2) hearing impairment; 3) maternal heritability of diabetes/impaired fasting glucose and a normal body mass index. Other associated findings include deafness due to bilateral sensorineural hearing loss in 85–98% of cases and the presence of a pattern macular dystrophy in around 80% of cases. The commonest mutation in MIDD results from an A to G substitution at position 3243 (m.3243A > G) of the mitochondrial DNA encoding the gene for tRNA. Other mitochondrial DNA point mutations have been associated with MIDD but these are extremely rare (Maassen, Hart LM1, Van, et al., 2004; Murphy, Turnbull, Walker, & Hattersley, 2008).

We report a 77 years old lady with MIDD due to 3243 mutation. She was being followed in a hospital diabetic clinic as insulin requiring type 2 diabetes. In last 10 years we have identified 5 more patients with diabetes and deafness associated with the same mutation. All these patients were attending an adult diabetes clinic as insulin requiring type 2 diabetes mellitus (T2DM). In 2 patients the retinal dystrophy was diagnosed macular degeneration. Hearing impairment was not considered as a part of the presentation of the disease in these patients and family history was not documented. All cases were treated with metformin at some stage and also received statins which could be harmful in such patients. The clinical characteristics of these cases are summarized in Table 1. To our knowledge the features detailed are unique to these patients. Identification of these patients allowed correlation of the clinical findings, institute surveillance for new symptoms and discussion of long term prognosis and treatment

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Table
Clinical characteristic of the patients with MIDD.

Clinical features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	77	60	68	65	52	65
Sex	F	F	M	F	M	F
Duration of diabetes (years)	41	47	32	15	16	7
Diagnosis of MIDD (years)	12	12	8	4	7	3
BMI at diagnosis of MIDD	18	24	17	28	26	29
HbA1C at diagnosis (%)	9.8	7.8	9.4	8	8.2	7.9
Treatment	Insulin	Insulin		Insulin	Insulin	Insulin
Hearing impairment	Sensorineural bilateral	Yes	Yes	Yes	Yes	No
Retinal dystrophy	Yes	Yes	Yes	No	Yes	Yes
Neurological involvement	Cerebellar signs	No	No	Learning disabilities	No	No
Thyroid disease	Hyperthyroidism	No	No	No	Subclinical hyperthyroidism	Hypothyroidism
Maternal history	Yes	Yes	Yes	No	Yes	No
Creatinine kinase (30–180 U/L)	68	221	na	196	152	49
Serum lactate (0.5–2.2 mmol/L)	1.2	na	na	na	na	na
MRI brain/CT	High signal lesions in white matter cerebellar atrophy		Calcification of basal ganglia Involutional changes in advance for this patient's age	na	na	na
Muscle biopsy	Yes ragged red fibers	no	no	no	no	no
Mutation	A3243G	A3243G	A3243G	A3243G	A3243G	A3243G
other	Stasis dermatitis pustular dermatosis of scalp	Fibro-epithelial endometrial polyp	Cardiac pacemaker	Gall stones high cholesterol recurrent UTIs	Heart disease required stenting	Hyperlipidemia

Abbreviations: UTIs = urinary tract infections, na = not available.

options. Oral hypoglycemics and statin was stopped and patients were changed to more appropriate treatment with insulin. The diabetic control and muscle aches of all the patients improved after this change. Patients were also given a list of potential harmful drugs. After a detailed family history and counseling genetic testing was offered to the patients and the first degree relatives. Patients were also encouraged to get in touch with Mitochondrial Research Society which offers free support and advice to the families.

2. Case report

The index case is a 77 years old lady who was diagnosed with type 2 diabetes mellitus (T2DM) at the age of 33. Her body mass index at diagnosis was 19 kg/m^2. Her presumed type 2 diabetes was initially managed on diet and Glinbenclamide. She was changed to insulin after 5 years of diagnosis because of poor glycemic control. The patient had never experienced any episodes of diabetic ketoacidosis. She was under regular follow up by the ophthalmologists for hyperpigmented maculae. This was diagnosed as age related macular degeneration (Fig. 1). She had no diabetic retinopathy and no other complication of diabetes such as diabetic nephropathy or neuropathy.

Her past medical history included Grave's thyrotoxicosis that was in remission after treatment with Carbimazole, idiopathic lymphoedema, asthma and bronchopulmonary aspergillosis.

She was diagnosed with bilateral sensorineural hearing loss at the age of 47. During the course of her illness; she developed restless legs and over the next 2 years she noticed gradually worsening unsteady gait. She had clinical evidence of cerebellar ataxia and myopathy. Her MRI brain showed cerebellar atrophy. She had a muscle biopsy and that showed ragged red fibers.

This patient's family history was interesting (Fig. 2). She was one of the two siblings born to unrelated parents. She had 2 children. Her son had no medical history. Her daughter developed diabetes at the age of 45 years. She also had muscle weakness and this was diagnosed as multiple sclerosis. The eldest brother of the patient was diagnosed with type 2 diabetes at the age of 52. He had no macular dystrophy or hearing impairment. Her mother had diabetes, deafness and renal failure. This patient's family history and clinical features were consistent with the diagnosis of MIDD. The patient and her daughter were offered genetic test and both were positive for A3243 mutation.

3. Discussion

An estimated 0.5% to 2.8% of diabetic patients have MIDD (Murphy et al., 2008). Identification of patients with monogenic forms of diabetes mellitus is challenging but important as the response to therapy is different from individuals with type 1 and type 2 DM. The risk to develop diabetes involves a complex interaction between genetic and environmental factors. A number of gene mutations have been identified that represent high penetrance risk genes for diabetes and carriers of these mutations have nearly 100% chance to develop diabetes during their life span. These are the various forms of maturity onset diabetes of the young (MODY) (Stride & Hattersley, 2002) and mitochondrial diabetes also called MIDD (Maassen & Kadowaki, 1996).

In clinical practice mitochondrial diabetes presents as unremarkable type 1 or type 2 diabetes depending on the severity of insulin deficiency. It has been reported that approximately 8% of MIDD cases present as type 1 diabetes with acidosis and ketonuria but majority will present with insidious onset as T2DM. Our patient was diagnosed with MIDD nearly 15 years after her initial diagnosis of type 2 diabetes as her presenting symptoms were not severe. Her age at the time of diagnosis of diabetes was 33 years. The age of onset of diabetes in MIDD is variable but commonly before 40 years of age. As in this case normal insulin sensitivity and low or normal BMI is usual in MIDD phenotypes rather than obese phenotype typically seen in T2DM (Guillausseau, Dubois-Laforge, Massin, et al., 2004). Our patient had bilateral progressive sensorineural deafness. The hearing loss tends to be more common and severe in men. It is thought to be due to atrophy of cochlear striae vascularis (Chinnery et al., 2000).

This patient also had classical retinal pattern dystrophy. This was initially labeled as age related macular degeneration. About 86% of MIDD cases will have specific macular dystrophy and pigmented retinal lesions. Our patient had no evidence of diabetic retinopathy. MIDD patients generally do not typically have severe diabetic retinopathy. This has been reported to be regardless of the duration of diabetes or sub-optimal glycemic control. Prevalence of diabetic retinopathy is thought to be about 8% lower than that expected after mean 12 years duration. It may be due to the fact that hypertension is not typically associated with MIDD. This typical retinal dystrophy detected on routine diabetic screening may lead to suspicion of MIDD. Vision is usually maintained in a high percentage of patients (Klein, Klein, Moss, et al., 1984; Rath et al., 2008).

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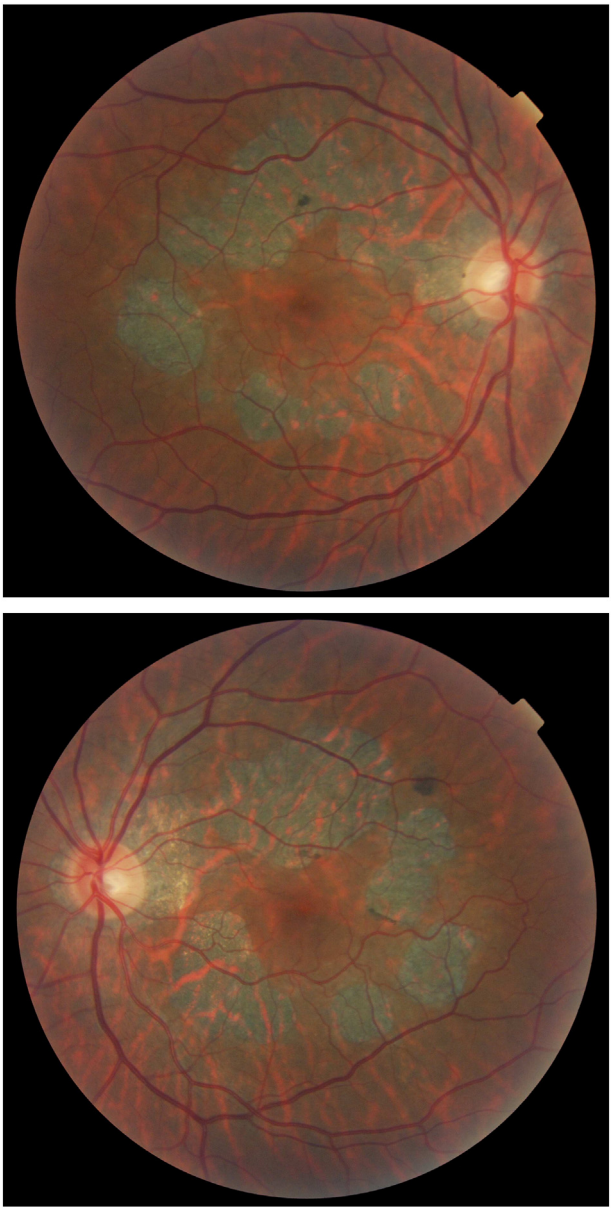

Fig. 1. Retinal photographs right and left eye. Classical retinal dystrophy and hyperpigmentation with little evidence of diabetic retinopathy.

During the course of her disease this patient developed progressive neurological deficit in the form of ataxia and muscle weakness. Neuromuscular disorder in the form of myopathy that is more pronounced in the proximal muscles is well documented in MIDD. Ragged red fibers as reported in our patient on muscle biopsy are typically seen in MIDD and are thought to be pathognomonic of mitochondrial disease (Lien et al., 2001). MIDD affects different tissues with variable effects but metabolically active tissues are more affected than less metabolically active organs. MIDD can also cause cardiomyopathy and renal disease (Azevedo et al., 2010).

Although extremely rare, endocrine pathologies such as growth hormone deficiency, ACTH deficiency, hypoparathyroidism and ovarian dysfunction have also been reported. Other rare endocrine manifestations in association with MIDD include hypothalamic hypogonadism and secondary hypothyroidism (Balestri & Grosso, 2000).

Diabetes in MIDD is characterized by progressive insulinopenia thus requirement of insulin is inevitable. Our patient required insulin within 5 years of initial diagnosis to control her hyperglycemia. Studies have shown that nearly 46% of MIDD cases progress to require insulin within 10 years of treatment (Whittaker et al., 2007). Unless there is a high index of suspicion the diagnosis is usually made later in the course of diabetes as in this case. A suspicion for mitochondrial diabetes is provided by strong familial clustering of diabetes. This is also seen in MODY but mitochondrial diabetes is distinguished from MODY on the presence of maternal transmission in conjunction with hearing impairment or macular dystrophy. MIDD is a mitochondrial disorder that is inherited from the mother in a dominant fashion and all progeny are at risk of developing some features of the disorder. An affected woman transmits the trait to all her children. Affected men do not pass the trait to any of their offspring as sperm mitochondria are shed before entry of the sperm nucleus in to egg. All mitochondrial in the zygote are contributed by the egg cell. The highly variable phenotype makes it very difficult to predict to what extent family members may be affected.

There is no single diagnostic test for this condition. Clinical vigilance, awareness and multiple investigations are needed for accurate diagnosis. Lactate to pyruvate ratios may be helpful in diagnosis and monitoring but a normal lactate level does not exclude a mitochondrial disease. Many patients may have episodes of lactic acidosis followed by periods when blood lactate level is normal. A high cerebrospinal fluid (CSF) lactate level is more sensitive but again may not be always helpful. Furthermore CSF lactate may remain high several days after a prolonged seizure or meningitis. Muscle biopsy is extremely helpful and may show ragged-red fibers that are characteristic of mitochondrial disorders. Mitochondrial genetic studies confirm the diagnosis of MIDD. The proportion of mutant mitochondrial DNA (mtDNA) in any cell or tissue may vary from 0% to 100% and this may change in time. Heteroplasmy probably explains some of the variation in phenotype found in patients with same mutations. The level of mtDNA is lower in blood than in muscle and may fall with age. In majority of the cases blood sample is adequate for the diagnosis of the disease. The penetrance of diabetes is high and is estimated to be over 85% in carriers of m.3243A > G (Murphy et al., 2008). All first-degree family members should be screened for the mutation and provided with genetic counseling. Furthermore, for those carrying the mutation, routine surveillance regarding glucose tolerance, kidney function, hearing, and cardiac function should be considered (Haas, Chir, Parikh, Falk, et al., 2008; Maassen, Jahangir Tafrechi, Janssen, et al., 2006).

MIDD was initially thought to be due to impaired glucose uptake at the level of the muscle but several studies have shown that the pancreatic β-cell function is impaired. The A to G substitution leads to dimerization of the mutant tRNA molecule and impaired aminoacylation (King, Koga, Davidson, & Schon, 1992). 3243 mutation in MIDD patients may result in enhanced degradation of mitochondrial DNA-encoded proteins. The end result is a reduction of functional respiratory enzyme complexes and reduced ATP generation. The altered ATP to ADP ratio may then result in impaired insulin secretion and lead ultimately to the β-cell apoptosis. It has been shown that hyperglycemia leads to an increase in production of reactive oxygen species (ROS), which may then lead to oxidative damage to the cell membranes, DNA, and proteins (Haas et al., 2008).

The prognosis for MIDD is better than that for other subtypes of mitochondrial diseases with diabetes. Oral antidiabetic agents and/or insulin therapy is used to treat the diabetes. Management of MIDD is symptomatic. Treatment for MIDD should be initiated at an early stage, since complications may lead to renal disease. Treatment with Metformin is less effective and may actually be harmful because of the increased risk of lactic acidosis in these individuals. Patients with MIDD should be advised to maintain their carbohydrate intake carefully when ill, as some can experience stroke-like episodes when there is lack of carbohydrates on sick days (Suzuki, 2004).

There is predilection for complications of pregnancy in females with MIDD. There have been reports of preterm labor and placenta accreta. Pregnant women with MIDD should also be carefully

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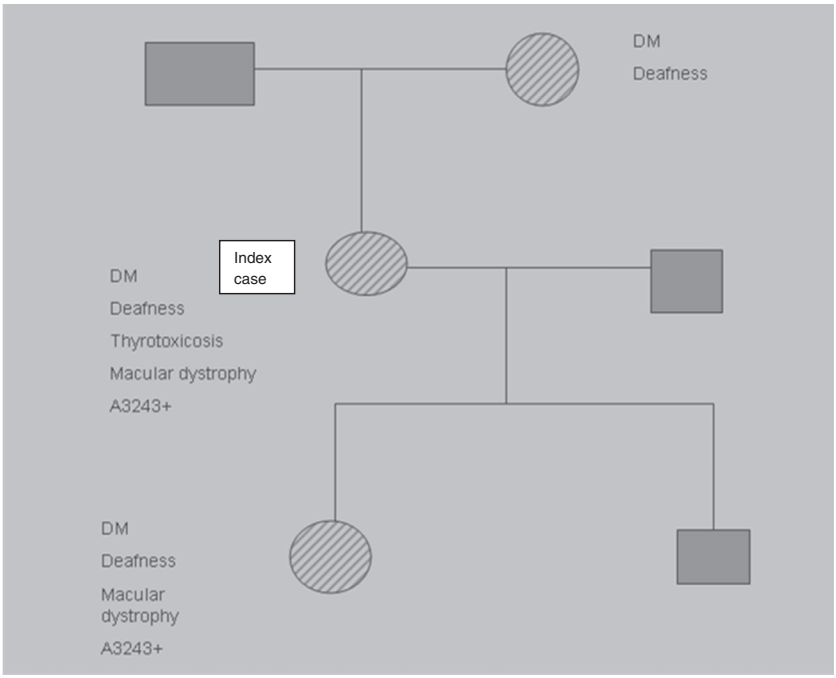

Fig. 2. Pedigree. The *square* is male and a *circle* is a female. Other associated comorbidities are listed in affected females.

monitored in the third trimester, and magnesium sulfate should be avoided, as it competes with calcium in the mitochondrial membranes and may exacerbate muscle damage (Aggarwal et al., 2001; Hosono, Suzuki, & Chiba, 2001).

Although mitochondrial disease research is robust, adequate treatment of these life-threatening conditions has lagged, as there are no scientifically and ethically rigorous clinical trials. Most of the studies are single-center trials. Most experts use combination of vitamins, optimize patient's nutrition and general health, insulin to control hyperglycemia and try to prevent worsening of symptoms during illness and physiologic stress. Hearing aids or cochlear implants are recommended for the hearing loss. Aerobic exercise and physical therapy is useful to prevent or correct deconditioning and this may improve exercise tolerance. Pharmacological approach is based on removing toxics metabolites, using reactive oxygen species scavengers and administrating vitamins and cofactors which is especially important in case of primary deficiencies of specific compounds such as Coenzyme Q10 (CoQ10). CoQ10 is an electron carrier in the respiratory chain of the mitochondria. In its reduced form as ubiquinol-10, it acts as an antioxidant by protecting membrane phospholipids, serum LDL from lipid peroxidation, and mitochondrial membrane proteins from free radicals. Mutant mitochondria show enhanced release of free radicals and impairment of the mitochondrial respiratory chain, which, in turn, leads to the dysfunctions. CoQ10 has been noted as a possible therapeutic which may enhance insulin secretion, slows hearing loss and improves symptoms of myopathy, painful neuropathy and congestive heart failure in the setting of mitochondrial disease (Liou, Huang, Lin, et al., 2000).

There are many drugs with known detrimental effect on mitochondrial function. These include antibiotics like tetracycline and chloramphenicol; antiepileptics like valproate, phenytoin, antiretroviral agents and metformin. Overall their effects in patients with MIDD are not known. Statin therapy should be avoided in patients especially with myopathy. HMG Co-A reductase inhibitors can reduce both cholesterol and Co-enzyme Q via mevalonate pathway. These patients may have higher rate of lactic acidosis and intolerance to statins resulting in myalgia and may worsen the symptoms of existing myopathy. However, the effect of statin on lowering Co-enzyme Q level is reversible. In addition to CoQ10 and other mitochondrial cofactors including carnitine and vitamins B, C, and K have been shown in different mitochondrial disorders to improve ATP synthetic capacity *in vitro* and positively influence some clinical outcomes (Neustadt & Pieczenik, 2008). Gene therapy is a challenge because of polyplasmy and heteroplasmy, but interesting experimental approaches are being pursued. Preventive therapy through genetic counseling and prenatal diagnosis is becoming increasingly important for nuclear DNA-related disorders (DiMauro & Mancuso, 2007). Pre-implantation genetic (PGD) technique can help to identify mitochondrial diseases. This could either prevent or greatly reduce the chance of child developing this disease.

A major update on treatment of mitochondrial diseases was published in 2012. The conclusion was that there is currently no clear evidence supporting the use of any intervention in mitochondrial disorders. Further research is needed to establish the role of a wide range of therapeutic approaches (Pfeffer, Majamaa, Turnbull, Thorburn, & Chinnery, 2012). Clinical presentation of MIDD is heterogeneous and patients with high heteroplasmy levels have more severe defect in mitochondrial function so the response to any treatment is variable. The diagnosis is often late as in our patients. These patients are unlikely to respond or improve on treatment because of prolonged and severe damage to mitochondria due to late recognition of the disease.

In conclusion MIDD, although rare, is an important diagnosis to make. Of the 1% of diabetes that is caused by a mitochondrial DNA defect, m.3243A > G is the most common subtype causing over 85% of these cases. Other rarer mitochondrial point mutations associated with diabetes occur within tRNA genes either for leucine; lysine; arginine; serine; glutamine and within subunit of respiratory chain complex[39].

A very strong family history of DM and deafness and presence of retinal dystrophy should prompt an investigation for MIDD. Microvascular complications out of keeping with duration of diabetes are another clue to the diagnosis. Retinal and renal manifestations of mitochondrial disease may be confused for diabetic complications. Glutamic acid decarboxylase (GAD) autoantibody negativity in a nonobese diabetic is yet another clue. Cardiac conduction defects and GDM may also raise suspicion as to the diagnosis. Recognizing this etiology of DM should promote family screening, genetic counseling, screening of associated comorbidities, avoidance of metformin, and cautious use of statins. The optimal management of mitochondrial disease

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necessitates early diagnosis, involvement of a multidisciplinary team, careful evaluations of patients, and the anticipation of iatrogenic and noniatrogenic complication.

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