Maternally Inherited Diabetes and Deafness (MIDD) - a Series of Case Reports

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Case Report

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Abstract

Maternally inherited diabetes and deafness (MIDD) is a rare form of diabetes, caused by a mutation in the mitochondrial DNA (mtDNA) which impairs mitochondrial function by decreasing the efficiency of the Leucine Transfer ribonucleic acid (tRNA) in adding amino acids to developing proteins. MIDD has a prevalence of 0.5–3% among diabetic population but almost always misdiagnosed and managed as either Type 1 or Type 2 diabetes mellitus, which adversely impacts their long term outcome. So it is important to differentiate these cases early enough and to institute correct treatment. We report on 3 cases of MIDD which was confirmed by genetic testing and five of their first degree relatives with similar clinical presentation. A heteroplasmic missense mutation in the MT-TL1 gene (chrm: 3243A > G mitochondrial DNA) was detected in all three patients but genetic confirmation was not possible in their relatives for want of patient consent for genetic study. To our knowledge, this is the largest series of MIDD reported from India.

Introduction

Maternally inherited diabetes and deafness (MIDD) (OMIM#520000) is a rare type of diabetes caused by a mitochondrial DNA mutation. MIDD was first identified in 1992 and has a prevalence of 0.5–3% in the diabetes population [3], [5]–[7]. It is often misdiagnosed as Type 1 or Type 2 diabetes. The most common cause of MIDD is point mutation, an A to G transition at the 3243 position of mitochondrial DNA (m.3243A > G), which encodes for the Leucine transfer RNA.[1], [2]. Clinical features includes Diabetes, low BMI, sensorineural hearing loss [1]–[3] and macular pattern dystrophy [3]. The age at which diabetes sets in MIDD may range from 12 to 67 years of age [4]. So far there is only one single case report from India. Here we report a series of three cases confirmed by genetic studies and five of their first degree relatives in their maternal lineage.

Case reports:

We present three cases of diabetes mellitus referred to the ‘Dr Suresh’s Diabcare India Diabetes Centre', for diabetes management which were diagnosed as MIDD on genetic studies.

Case No. 1:

A 23-year-old female with diabetes whose age at onset was 18 years old presented with fluctuating blood sugar and hearing loss that preceded the diabetes. She was on insulin treatment and her height was 143 cm, weight 37 kg, and BMI was 18.1 kg/m2. Her blood pressure was 100/60 mmHg. Investigations revealed that her random blood sugar level was 301 mg/dL, the creatinine level 0.7 mg/dL, the albumin-creatinine ratio 18 mg/gm, and the Vitamin D level 18 IU (low). Her fasting C-peptide concentration was 0.1 ng/ml (low) and GAD 65 Ab was negative. Her ophthalmological examination showed no evidence of diabetic retinopathy. Her mother, maternal aunt, and maternal cousin all were diabetics.

Case No. 2 & 3:

The next two cases are a mother and her son. This case involves a 45-year-old female with diabetes and hearing loss who developed diabetes at the age of 27 and her 27-year-old son, who had diabetes at the age of 21. She had two diabetic siblings and one son; her father was not diabetic. Her mother died when she was young, so her mother's diabetic history was not known. The mother and son were 147 cm and 161.5 cm tall, weighed 48.2 kg and 46.7 kg, and had BMIs of 22.3 kg/m2 and 17.9 kg/m2, respectively. Investigations revealed that her FBS was 79 mg/dL, PPBS of 191 mg/dl, fasting C peptide of 0.5 ng/ml (low), GAD 65 Ab negative, creatinine of 0.9 mg/dl, and an albumin-creatinine ratio of 13 mg/gm (normal). The ECG revealed T inversion in the inferolateral leads. An ophthalmological examination revealed retinal pigmentary epithelial (RPE) changes in both eyes and mild non-proliferative diabetic retinopathy (NPDR) in the right eye. The son's blood tests showed FBS 215 mg/dl, PPBS 565 mg/dl, C-peptide 0.9ng/ml (low), GAD 65 Ab was negative, creatinine 1.1 mg/dl, and an albumin-creatinine ratio of 11 mg/gm.His blood pressure was 104/70 mmHg. His ECG, ECHO and TMT were normal.

Table 1: Clinical Parameters

Parameters	Case 1	Case 2	Case 3
Age of Onset(yrs.)	18 yrs.	27 yrs.	21 yrs.
Rx at Presentation	Insulin	Insulin	Insulin
Hearing Loss	Yes, Preceded Diabetes Mellitus	Yes, Preceded Diabetes Mellitus	Yes, Preceded Diabetes Mellitus
Family History of Diabetes Mellitus	Mother, Maternal Aunt, Maternal Cousin Sister	Mother died early, 2 sisters Diabetes Mellitus, 1 Son MIDD	Mother MIDD, 2 Maternal Aunts Diabetes Mellitus
Body Mass Index	18.1 kg/m2	22.3 kg/m2	17.9 kg/m2
C-peptide /GAD 65 Ab	0.1ng/mL, GAD: Negative	0.5ng/mL, GAD : Negative	0.9 ng/mL, GAD : Negative
ECG/ECHO/TMT	All Normal	ECG: T inversion in the inferolateral leads, ECHO & TMT: Normal	ECG: Mild ST elevation in V2 &V3 ECHO & TMT: Normal
Nephropathy/Retinopathy	No/No	No/ RPE Changes+ Mild NPDR	No/No

Diagnostic Intervention

Clinically all the three patients were suspected to have MIDD because of the maternal inheritance and the peculiar clinical history. All the 3 samples were sent for genetic analysis to the Madras Diabetes Research Foundation (MDRF) Chennai.

Genetic testing:

Genetic test done at MDRF confirmed MIDD by the detection of heteroplasmic missense mutation in the MT-TL1 gene namely, A to G transition at 3243 position (m.3243A>G) encoding for the Leucine transfer RNA in all patient's DNA samples. All the patients were informed about their diagnosis of MIDD and they were treated with insulin and Mitochondriotropic agents like Co-enzyme Q10, L-Carnitine and vitamin E and their symptoms and diabetes were brought under control.

Treatment

All the MIDD patients were initiated on multi dose insulin therapy along with Mitochondriotropic agents like Co-enzyme Q10, L-Carnitine and vitamin E and subjective improvement was shown by all the patients at the time of reporting.

Discussion

We found only one previous report of MIDD from India, which was a single case report from Uttar Pradesh of a 47-year-old woman with diabetes and deafness, as well as perifoveal atrophy in both eyes. In that case an A3243G mutation in the MTTL1 gene was discovered. [8] We here report three cases of genetically proven MIDD and their five diabetic relatives with same maternal lineage and identical clinical features (whose genetic testing could not be done due to lack of consent) bringing our total case count to eight.

In MIDD, diabetes occurs due to reduced glucose-responsive insulin production and secretion by the beta cells without involvement of autoimmune processes[4]. Initially they can be treated with life style modification and oral hypoglycemic agents, but may need insulin within 2 years of diagnosis. 75% of patients with MIDD may develop hearing loss as a result of the involvement of bilateral VIIIth cranial nerves which present before the onset of diabetes. Half of patients with hearing loss may experience a rapid decline in their hearing, while others may experience a gradual decline over years.

MIDD patients are usually short-statured and lean. Myopathy affects 43% of MIDD patients and typically affects proximal muscles manifesting as exercise-induced muscle cramps or weakness. Cardiomyopathy and diabetic retinopathy were seen in 15% and 8% respectively [3]. Prior to diabetes or deafness 28% of MIDD patients may develop renal disease with focal segmental glomerulosclerosis, which can progress to end stage renal failure [3]. Hence, good blood pressure control and regular monitoring of renal function are required as part of their treatment.

Right diagnosis, proper treatment and regular monitoring of MIDD should be initiated at an early stage itself since complications may lead to renal disease or mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS syndrome). The mainstay of hyperglycemic management is insulin therapy as oral anti-hyperglycemic agents like sulfonylureas may worsen beta cell dysfunction and precipitate insulin dependency. Biguanides can cause lactic acidosis in these patents, they are to be avoided [4]. Imeglimin, a novel experimental drug targeting mitochondrial bioenergetics and improving mitochondrial function may prove to be beneficial for MIDD patients[8]. Administration of mitochondriotropic agents like Co-enzyme Q10 and L-Carnitine have been proposed for treatment. Also use of antioxidants like Vitamin E can be employed as adjuvants in the management of MIDD [9].

In summary, this is the largest series of MIDD reported from India. MIDD can be easily misdiagnosed as type 1 or type 2 diabetes. Long term outcome of MIDD patients depends mostly on the timely diagnosis and early initiation of insulin and other ‘Mitochondriotropic’ agents. The main challenge faced by physician in diagnosing MIDD is the lack of universal availability of genetic testing. But the strength of our study is that we could diagnose all cases of MIDD using genetic testing.

Declarations

1. Funding’ and/or ‘Competing interests: Genetic study was funded by ICMR through Dr. V Radha’s project "Investigations of the Association of Mutations in MODY and NDM by Translational Genomic Research."

2. Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Committee of Dr Suresh’s Diabcare India.

3. Consent to participate’ and/or ‘Consent to publish: Informed consent was obtained from all individual participants included in the study and the participant has consented to the submission of the case report to the journal.

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Figures

Figure 1

Electropherograms showing the presence of heterozygous known variation 3243A>G mitochrodrial gene