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Screening, Evaluation and Management of Monogenic Form of Diabetes: A Hospital Based Experience

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ABSTRACT

Background: Maternally inherited diabetes with deafness is rare diabetes caused by a mitochondrial DNA defect. 85% of cases are associated with m.3243A N G mutation. The phenotypic heterogeneity of MIDD may be the consequence of different levels of mutated mtDNA among mitochondria in a given tissue. 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. **Methods:** We screened a total of 125 patients with diabetes and after careful history and examination, family history and screening, focused examination by ENT and an ophtho specialist and imaging of brain along with fundus photography, we found out a total of 7 patients with monogenic diabetes. **Results:** Out of 125 patients screened ,there were 5 females and 2 males.5 out of 7 patients were having maternal history and were diagnosed after 4 to 12 years of diabetes duaration.5 out of 7 patients had neurological involvement and 4 out of 7 patients had hearing impairment.5 out of 7 patients had retinal findings on fundus photography. **Conclusion:** Recognizing this etiology of DM should promote family screening, genetic counseling, screening of associated comorbidities, avoidance of metformin, and cautious use of statins.

Keywords: Diabetes Mellitus, Deafness.

INTRODUCTION

Much like finding a needle in a haystack, the identification of patients with monogenic forms of diabetes mellitus (DM) is challenging and potentially costly. Nonetheless, the importance of identifying such individuals with monogenic forms of diabetes has been underscored by the recognition that response to therapy is different from individuals with type 1 and type 2 DM.[1] Metformin, the most commonly used first-line medication for type 2 DM, may cause lactic acidosis in individuals with pathogenic mitochondrial DNA mutations.[2,3] 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).[4] 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.[5,6] It is a mitochondrial disorder that is characterized by progressive insulinopenia and sensorineural hearing loss, most commonly caused by a genetic mutation at position 3243 in the tRNA. This is the same mutation that results in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS). 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.[7]

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MATERIALS AND METHODS

We screened a total of 125 patients with diabetes and after careful history and examination, family history

and screening, focused examination by ENT and an ophtho specialist and imaging of brain along with fundus photography, we found out a total of 7 patients where the index case was a 30 year old female who presented with recurrent pregnancy loss, episodic vomiting, hearing impairment and diabetes mellitus. The investigative workup showed moderate to severe sensorineural hearing loss. On investigations of patients family, other relatives were found to have diabetes and mild bilateral sensorineural loss. The genetic analysis was planned.

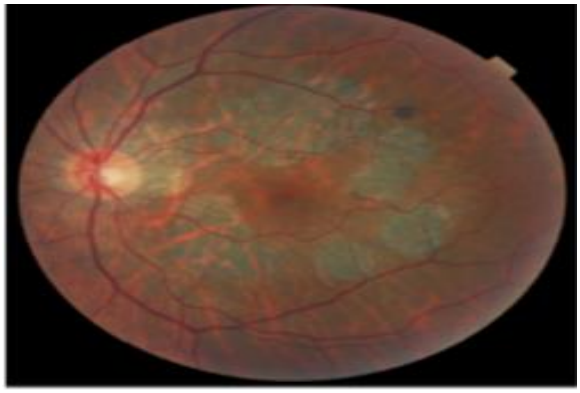
Total number of diabetes patients screened	125 patients
ENT and Ophtho examination	68 patients
Audiogram, Fundus photography	34 patients
MRI/CT examination	20 patients
Positive family history	7 patients
Elevated CK and LDH levels	7 patients

RESULTS

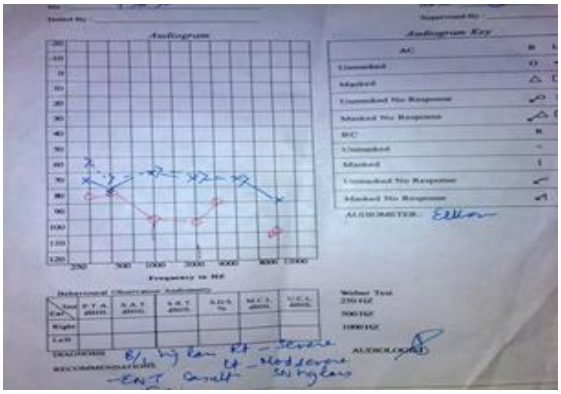
A total of 125 patients were screened for monogenic diabetes and 7 patients were found out to be having MIDD. There were 5 females and 2 males.5 out of 7 patients were having maternal history and were diagnosed after 4 to 12 years of diabetes duaration.5 out of 7 patients had neurological involvement and 4 out of 7 patients had hearing impairment.5 out of 7 patients had retinal findings on fundus photography.Rest of characters of various patients are shown in tabulated form.

The index patient was 30 year old female presenting with recurrent pregnancy loss, hearing impairment and diabetes mellitus.This normotensive female, labelled as DM - 2 for last 2 years, was initially managed with OHAS and diet control, but presently was on insulin and was being evaluated for recurrent pregnancy loss in the form of two 2 nd trimester abortions and one live birth who died after 4 days of delivery with exact cause of death could not be ascertained. She also has progressively worsening hearing impairment for last 6 years for which she has never sought a medical advice. On family screening, it was found that she had two brothers. Her mother was screened for diabetes with fasting blood glucose found to be 254 mg/dl and HbA1C 10.1% . She was also subjected to pure tone audiometry which revealed mild bilateral symmetrical sensorineural hearing loss for high frequency. Clinical examination of patient revealed height of 149cm (<3rd centile), US/LS=0.98, weight 45 kgs and a BMI of 20.22 kg/m2. The systemic examination was essentially normal and fundal examination did not reveal any abnormality. Lab investigations did not reveal any abnormality except for persistent mild metabolic acidosis with low serum lactate levels. Pure tone audiometry of the patient revealed right sided severe and left sided moderately severe high frequency sensorineural hearing loss. Upper GI endoscopy which was done in view of intermittent episodes of vomiting was normal. Echocardiography and electromyography was also normal. MRI brain showed basal ganglia calcification.

Clinical features	Case 1	2	3	4	5	6
Age	65	60	45	55	45	45
Sex	F	F	M	F	M	F
Diabetes duration	24	22	21	12	12	16
MIDD Dx	18	14	21	21	13	16
BMI at MIDD Dx	19	23	19	24	25	23
HbA1c at Dx	8.9	7.9	9.1	8.4	8.8	7.9
Treatment	insulin	insulin	SU	SU	insulin	SU
Retinal dystrophy	yes	yes	no	yes	no	yes
Hearing impairment	SNHL bilateral	+	+	+	-	-
Neurological involvement	no	Cerebellar signs	No	Learning disabilities	Cerebellar signs	no
Thyroid disease	Subclinical hyperthyroidism	hypothyroidism	N	N	N	Hyperthyroidism
Maternal involvement	yes	no	yes	no	yes	No
MRI/CT	Basal ganglia calcification	Cerebellar atrophy	White matter changes	N	N	N



Retinal pigmentation, DR and dystrophy



Audiogram of Index case (SNHL)

DISCUSSION

An estimated 0.5% to 2.8% of diabetic patients have MIDD (8). MIDD is a genetic disorder characterized by diabetes and hearing loss that is caused by a mitochondrial gene mutation. Mitochondrial DNA is exclusively maternally inherited so all offspring of an affected mother inherit the genetic defect. MIDD is most commonly caused by an A to G substitution at position 3243 in the tRNA leucine gene. 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) and mitochondrial diabetes also called MIDD.[1,9] There is a wide variety in the phenotypic expression of this disorder. A mix of wild-type and mutant DNA in the same cell is called heteroplasmy. Varying degrees of heteroplasmy between individuals and in different tissues may partly explain the varied phenotype that results from this genetic disorder Reported clinical manifestations of A3243G mitochondrial mutation:[10]

DM, Sensorineural Hearing Loss, Cardiac Issues: Conduction Abnormalities (WPW, Atrial Fibrillation, Sick Sinus Syndrome) Cardiomyopathy (Dilated And Hypertrophic) CHF. Neurological Disorders MELAS Mitochondrial Myopathy ,Basal Ganglia Calcifications, Cerebellar Ataxia, Oculomotor Palsy, Weakness And Exercise Intolerance, Neuropsychiatric Disorders Mental Retardation, Dementia, Renal Disorders, Focal Segmental Glomerulosclerosis With Hyalinized Glomeruli, Depression, Psychosis, Myocyte Necrosis In Afferent Arterioles And Small Arteries. Ophthalmic Disorders Macular Pattern Dystrophy, Cataracts

Complications of Pregnancy Placenta Accrete, Preterm Labor

Onset of the diabetes phenotype usually occurs between ages 15–70 with a mean age of 32.8 – 38.8yr.[3] The mean duration of diabetes before insulin dependence is only 3.9 yr.[11] In our patient, the onset of diabetes was at age 28, and she progressed to insulin dependence within 2 yrs. She had recurrent second trimester abortions. Hearing loss is progressive and nearly universal.[11,12] Our patient was diagnosed with hearing impairment at age 24. A sensorineural hearing loss, not always leading to clinically manifest deafness, commonly precedes the onset of diabetes;[13] the age of onset of hearing loss is between 14 and 50 years of age with mean age of 33.2 and mainly affects high frequencies.[14] Cochlear dysgenesis was proposed to be the primary pathology for hearing loss and most patients can benefit from cochlear implants.[15] The most characteristic audiographic feature is that of sloping with flat profile in advanced cases as was seen in our patient.[16] Patients with MIDD are often reported to have advanced microvascular complications. However, impaired renal function and proteinuria from mitochondrial dysfunction is a known phenotype of this genetic disorder. As such, these complications may be misinterpreted as a diabetic microvascular complication. The renal lesions observed in MIDD include focal segmental glomerulosclerosis with hyalinized glomeruli and myocyte necrosis in afferent arterioloes and small arteries Macular pattern dystrophy is a retinal lesion that is commonly seen in MIDD.[12,17,18] This has the appearance of linear pigmentation on the retina surrounding the macula and the optic disc. Neuromuscular and cardiac disorders have been described in 43.1% of MIDD patients including muscle weakness and pain, biopsy-confirmed ragged red fibers, cardiomyopathy, and preexcitation syndrome.[12] Other common associations were not seen in our patient. Nephropathy and spontaneous abortions as was seen in our case have also been reported by other studies.[13]

Pathophysiology: The molecular basis of diabetes in those affected by MIDD is just emerging. Initially it was thought that impaired glucose uptake at the level of the muscle was the main defect inMIDD.[19] Several studies have shown that insulin resistance is not the main culprit, but rather that pancreatic β cell function is impaired.[20] The A to G substitution leads to dimerization of the mutant tRNA molecule and impaired aminoacylation.[21] Cybrid cell lines derived from MELAS patients containing the A3243G mutation have shown a significant decrease in mitochondrial protein synthesis.[22,23] However, cybrid cell lines derived from MIDD patients showed severely reduced cellular respiration despite intact protein synthesis, leading to the hypothesis that the 3243 mutation in MIDD patients may result in enhanced degradation of mitochondrial DNA-encoded proteins.[17] 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 is hypothesized to lead ultimately to the β cell apoptosis. It has been shown that hyperglycemia leads to an increased production of reactive oxygen species (ROS), which may then lead to oxidative damage to membranes, DNA, and proteins.[23–26] It has also been shown that cybrid cells containing the A3243G mutation have greatly increased levels of lipid peroxidation and oxidative stress, independent of glucose level.[27-29]

Management: The treatment with insulin secretagogues such as glyburide is usually first line. The hallmark of this disorder is a progressive loss of insulin secretion; thus, requirement of insulin is usually inevitable. The mean duration from diagnosis of diabetes to insulin dependence is 3.9 vs. 15 yr in type 2 diabetics.[11] It should be noted that

metformin is contraindicated due to increased risk of lactic acidosis in these individuals.[2,3] Patients with MIDD should also be advised to maintain their carbohydrate intake carefully when ill, as some have experienced stroke-like episodes when they lacked carbohydrates on sick days.[11] Pregnant women with MIDD should be carefully 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.[30] 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.[31] As such, CoQ10 has been noted as a possible therapeutic which may enhance insulin secretion and slow hearing loss. Indeed, there have been several studies showing an improvement in clinical symptoms in those with MELAS.[32–36] Suzuki et al.[37] completed a 3-yr open label study in Japan of 86 patients with the A3243G mitochondrial mutation to investigate whether 150 mg of CoQ10 had any effect on insulin secretion, hearing capacity, and blood lactate levels. They found that long-term therapy with CoQ10 significantly slowed progression of the insulin secretory defect and hearing loss, as well as decreased postexercise lactate levels in those with established MIDD. Because CoQ10 level is decreased with statins, cautious use of statins is advised in the setting of mitochondrial disorders. 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. 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. 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.[38] 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.[39] 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.[40]

CONCLUSION

Although the frequency of mitochondrial illnesses is low. 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. Recognizing this etiology of DM should promote family screening, genetic counseling, screening of associated comorbidities, avoidance of metformin, and cautious use of statins.

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