0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(12):4737–4742

doi: 10.1210/jc.2006-1498

CLINICAL CASE SEMINAR

Maternally Inherited Diabetes and Deafness in a North American Kindred: Tips for Making the Diagnosis and Review of Unique Management Issues

Lois E. Donovan and Naomi E. Severin

University of Calgary Department of Medicine, Division of Endocrinology and Metabolism, Calgary, Alberta, Canada T2R 0X7

Context: Mutations in mitochondrial DNA are rare etiologies of adult-onset diabetes mellitus (DM) that merit identification to 1) prevent iatrogenic lactic acidosis, 2) prompt appropriate screening of affected patients and their families, 3) provide genetic counseling, and 4) provide an opportunity to investigate strategies for preventing diabetes.

Objective: The objective of this study is to raise awareness of this rare form of adult-onset nonobese DM so that these patients are identified and provided with appropriate care.

Patients: We describe a kindred in which four of seven siblings have adult-onset DM and sensorineural hearing loss with a confirmed genetic mutation at position 3243 in the tRNA. Two other siblings in this kindred demonstrate different phenotypes of mitochondrial disease.

Intervention: The proband was treated with coenzyme Q10 for 1 yr.

Outcome Measures: Outcome measures included stress thallium exercise testing and audiometry testing.

Results: After 1 yr of treatment of with coenzyme Q10, repeat stress thallium testing demonstrated improvement in the exercise tolerance of the proband from 7–12 min. Audiometry testing did not demonstrate a change in the rate of hearing decline.

Conclusion: Maternally inherited diabetes and deafness is a rare cause of DM that is important to diagnose because of the unique management issues and associated comorbidities. This work highlights clues to the identification of this rare monogenic form of adult-onset diabetes. **(*J Clin Endocrinol Metab* 91: 4737–4742, 2006)**

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). Maternally inherited diabetes and deafness (MIDD) is a rare form of diabetes first described in 1992. 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). MIDD has been reported and studied in Europe, Australia, and Asia. We describe a North American family where six of seven siblings are affected by MIDD or MELAS.

First Published Online October 3, 2006

Abbreviations: BMI, Body mass index; CK, creatinine kinase; CoQ10, coenzyme Q10; CSII, continuous sc insulin infusion device; DM, diabetes mellitus; GDM, gestational DM; HbA1c, hemoglobin A1c; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome; MIDD, maternally inherited diabetes and deafness; ROS, reactive oxygen species; WPW, Wolf-Parkinson-White syndrome.

Case Reports

The proband is a 44-yr-old woman of ideal body weight [body mass index (BMI) = 22 kg/m^2] with an 11-yr history of DM requiring insulin. She presented with complaints of poor recovery from exercise and was referred for consideration of a continuous sc insulin infusion device (CSII).

The patient was initially diagnosed with gestational diabetes (GDM) requiring insulin at 32-wk gestation during her first pregnancy, at the age of 23. During her second pregnancy at age 25, GDM recurred. Placenta accreta occurred at delivery of her second child. Glucose tolerance normalized after both pregnancies, and she was not diagnosed with DM until 8 yr later at age 33.

Her presumed type 2 DM was initially managed with glyburide. This was poorly tolerated so she was switched to insulin. At the time of consultation, her total daily insulin requirements were 60 U and her hemoglobin A1c (HbA1c) was 8.8% (upper limit of the nondiabetic range, 6.1%). The patient had never experienced any episodes of diabetic ketoacidosis or severe hypoglycemia. She has no diabetic retinopathy; however, she does exhibit retinal pigmentation in keeping with macular pattern dystrophy. Her microalbumin

to creatinine ratio was 32.9 mg/mmol (normal range < 3.4 mg/mmol), and old medical records documented unexplained stable proteinuria predating her onset of DM by 8 yr. She reported mild numbness and tingling in her feet and hands.

The proband was diagnosed with Wolf-Parkinson-White syndrome (WPW) at age 19 and had experienced several episodes of tachycardia resulting in loss of consciousness. Her last episode occurred approximately 8 yr before the time of consultation. In the spring of 2003, when she complained of fatigue, elevated creatinine kinase (CK) and CKMB were documented. Concurrent troponin was negative, ruling out cardiac ischemia as the etiology of her elevated CK and raising suspicion of skeletal muscle breakdown. A stress thallium test demonstrated only fair exercise capacity in this physically active young woman. She stopped exercise after 7 min because of fatigue and reached a maximum heart rate of 151 beats per minute.

The patient was started on a CSII. She had a marked improvement in her glycemic control such that her HbA1c fell to 7.3% 5 months after initiation of CSII. Glycemic control subsequently deteriorated as indicated by a HbA1c of 9.3% 1 yr after she started CSII. She was also started on coenzyme Q10 (CoQ10), 300 mg daily. The patient reported a marked improvement in energy level and exercise recovery. Her duration of exercise on maximal exercise testing improved dramatically from 7–12 min. The proband is a rancher in a rural setting. She has always had to be physically active on her ranch. Her chores often include lifting 50- to 70-pound hay bails onto trucks for up to 30 min two times each day. Before initiating CoQ10 she complained of "aching muscles" throughout the day and night. Since initiating CoQ10 therapy, her "muscle aching now rarely occurs, and when it does it is mild."

Bilateral sensorineural hearing loss was documented at age 37, has been progressive, and has resulted in the reliance on hearing aids. Unfortunately, hearing tests 1 yr after initiating CoQ10 demonstrated no improvement.

The proband's C-peptide was low at 0.18 nmol/liter, and anti-glutamic acid decarboxylase and islet cell antibodies were negative. Her bicarbonate was normal. Her resting lactate levels have always been within the normal range of 1.3–1.6 (0.5–2.2 mmol/liter). Genetic testing on whole blood confirmed the tRNA A3243G mutation.

The proband is one of seven siblings born to unrelated parents, five of whom have deafness and four of whom have DM (Fig. 1). She is third generation Canadian with English ancestry. Her maternal grandmother was born in Durham, UK. The mother of the proband did not have diabetes diagnosed during her lifetime. She died of a myocardial infarction at the age of 56. GDM is suspected in the mother of the proband because the birth weights of her last three children ranged from 9–11 pounds. Information on the maternal grandmother of the proband is very limited. She was known to have short stature (4 feet, 11 inches), obesity, and hypertension, and died of congestive heart failure at an unknown age. The father of the proband was obese and was diagnosed with type 2 DM at age 66. The eldest brother of the proband had cataracts removed at the age of 9 yr. He developed DM at age 28 and hearing loss at age 34. The next eldest brother developed DM at 42 and hearing loss at 38. The next brother (age 50) is not known to have diabetes; however, has just developed hearing loss in the last year as well as sick sinus syndrome. The only sibling that does not currently have diabetes or deafness is a brother, age 48. He lacks the tRNA A3243G mutation on testing of whole blood. All other living siblings and children of the proband have confirmed tRNA A3243G mutation on testing of whole blood.

A sister, born 1 yr before the proband, developed a seizure disorder and progressive hearing loss in the 18 months before her death at age 19. She died of a ruptured brain aneurysm. Unfortunately, her old medical records could not be found; however, one remains suspicious that her "seizure" activity could have represented acute episodes of lactic acidosis and stroke-like syndrome. The younger sister of the proband was diagnosed with developmental delay at age 6. She has a profound hearing deficit that began at age 23. She developed proteinuria and impaired renal function at age 39, followed by diabetes at age 40. Her glycemic control responded well to insulin secretagogues for the first 2 yr after diagnosis, but she has become insulin-requiring now, 3 yr after the onset of DM. Most recently, she has developed congestive heart failure secondary to a presumed mitochondrial cardiomyopathy. All four siblings with adult-onset diabetes have BMI values between 18–22 kg/m^2. The two children of the proband, aged 19 and 21, remain healthy with documented normal glucose tolerance, hearing, and urinalysis.

Discussion

What is MIDD?

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. This is the case with our kindred.

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 (Table 1). The cardiac conduction abnormalities, GDM, placenta accreta, proteinuria, and neuropathy of this proband are abnormalities that have been described in other MIDD cases (4). Onset of the diabetes phenotype usually occurs between ages 15–70 with a mean age of 32.8–38.8 yr (3). The mean duration of diabetes before insulin dependence is only 3.9 yr (5). In our patient, the onset of diabetes was at age 33, and she progressed to insulin dependence within 1 yr. She developed GDM at age 23.

The mean age of onset of hearing impairment is 33.2 yr. Hearing loss is progressive and nearly universal (5, 6). Our patient was diagnosed with hearing impairment at age 37. This kindred underscores that there is no order to the development of diabetes and hearing loss. Both can be diagnosed simultaneously or many years apart (5, 6). The variable age of onset of diabetes and hearing loss in MIDD may

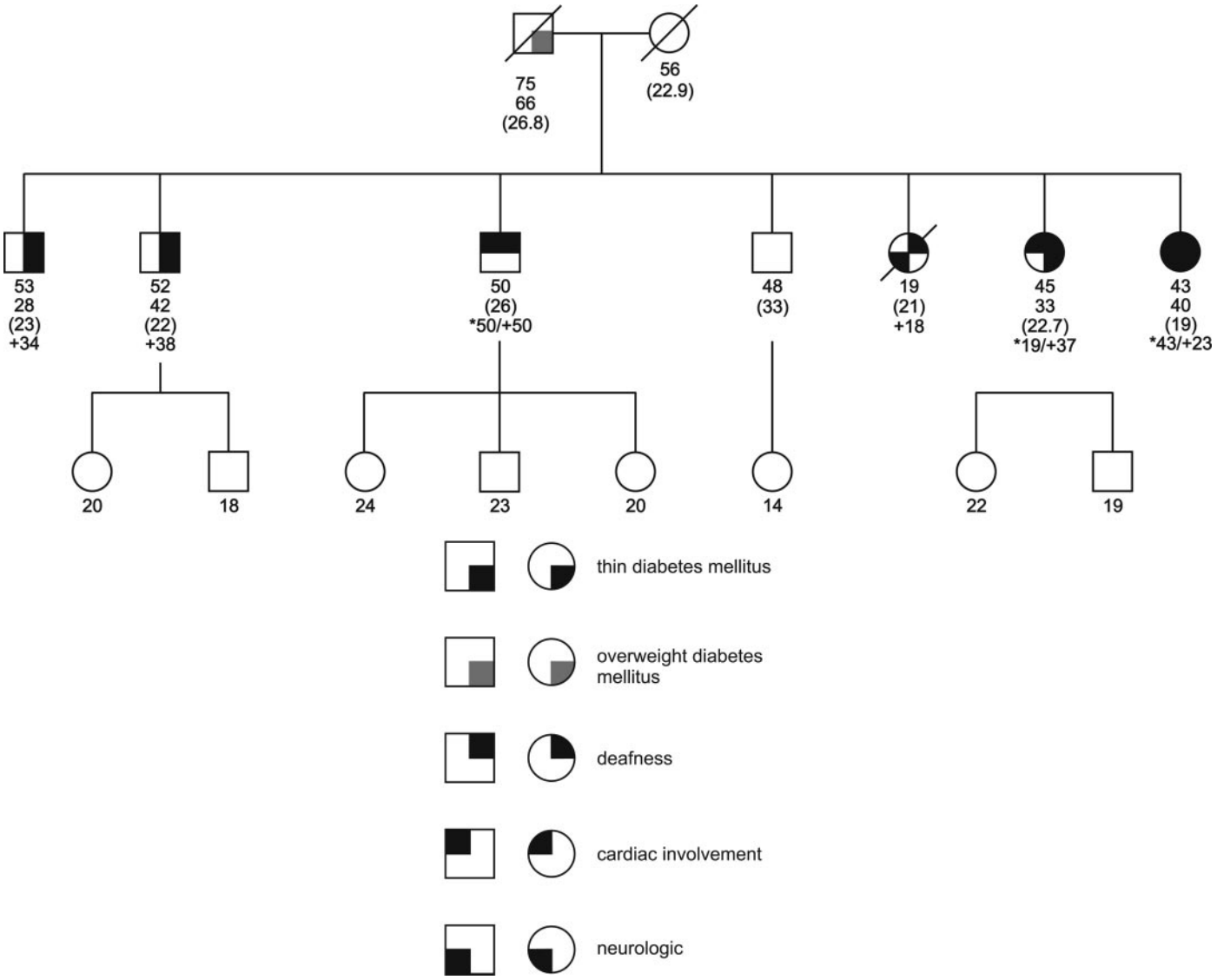

FIG. 1. Pedigree. The number immediately below the *square* (male) or *circle* (female) is the current age of the individual or age at death. The *unbracketed number* below this is the age at diagnosis of DM. The *bracketed number* below that is/was the BMI. *, The age of onset of cardiac disorder. +, The age of onset of hearing loss.

explain why the mother of the proband was not known to have either disorder before her death at the age of 56.

Interestingly, these 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. Indeed, in our proband and her sister, proteinuria predated the diagnosis of DM. The renal lesions observed in MIDD include focal segmental glomerulosclerosis with hyalinized glomeruli and myocyte necrosis in afferent arterioloes and small arteries (6, 7). Macular pattern dystrophy is a retinal lesion that is commonly seen in MIDD (8). 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 (6). The proband was diagnosed with WPW at age 19. Furthermore, the same genetic mutation can result in MELAS. Both the MIDD and MELAS phenotypes can be seen within the same family as is the case in this family (5). Finally, the natural history of MIDD is widely variable, as demonstrated in the family described here, ranging from a currently unaffected male at the age of 48 to a rapidly progressive disease that resulted in the death of a sister at age 19, 1.5 yr after the onset of "seizures" and hearing loss.

Pathophysiology

An understanding of 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 in MIDD (9). Several studies have shown that insulin resistance is not the main culprit, but

TABLE 1. Reported clinical manifestations of A3243G mitochondrial mutation

Reported clinical manifestations
DM
Sensorineural hearing loss
Cardiac issues
Conduction abnormalities (WPW, atrial fibrillation, sick sinus syndrome)
Cardiomyopathy (dilated and hypertrophic)
Congestive heart failure
Neurological disorders
MELAS
Mitochondrial myopathy
Basal ganglia calcifications
Cerebellar ataxia
Oculomotor palsy
Weakness and exercise intolerance
Neuropsychiatric disorders
Mental retardation
Dementia
Depression
Psychosis
Ophthalmic disorders
Macular pattern dystrophy
Cataracts
Renal disorders
Focal segmental glomerulosclerosis with hyalinized glomeruli
Myocyte necrosis in afferent arterioles and small arteries
Complications of pregnancy
Placenta accrete
Preterm labor

rather that pancreatic β-cell function is impaired (10). The A to G substitution leads to dimerization of the mutant tRNA molecule and impaired aminoacylation (11). Cybrid cell lines derived from MELAS patients containing the A3243G mutation have shown a significant decrease in mitochondrial protein synthesis (12, 13). 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 (7). 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.

However, the question remains why there is such clinical heterogeneity and why the insulin deficiency does not manifest until later in life. 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 (14–17). 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 (18). These cells are also more susceptible to damage from ROS. As such, one hypothesis is mitochondrial mutations lead to progressive insulinopenia as well as increased ROS, which then causes further damage to both the mitochondrial DNA and cell components, which may then exacerbate impaired insulin secretion. The buildup of ROS may also lead to premature and progressive β-cell death, also leading to worsening insulin secretion and hyperglycemia. Interestingly, there is no evidence that the level of heteroplasmy coincides with clinical presentation (19). Investigations are also currently underway to determine the role that the A3243G mutation has on additional signaling molecules important for insulin secretion (4).

Management issues unique to MIDD

The A3243G mutation primarily results in a secretory defect, rather than a defect in insulin sensitivity; therefore, 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 (5). It should be noted that metformin, aside from being less effective, may actually be harmful because of the 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 (5). Of special note for females with MIDD is the predilection for complications of pregnancy, as there have been reports of preterm labor and placenta accreta (20). 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 (21).

The unique pathophysiology of MIDD has spurred investigations into mitochondrial-based therapeutics. CoQ10 is an electron carrier in the respiratory chain of the mitochondria (see Fig. 2). 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 (22). We know that mutant mitochondria show enhanced release of free radicals and impairment of the mitochondrial respiratory chain, which, in turn, leads to the dysfunctions mentioned above (23). 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 (24–28). Suzuki *et al.* (29) 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. Another report by Silvestre-Aillaud *et al.* (30), investigating CoQ10 and L-carnitine, found no such improvements. However, they only treated one patient, and follow-up was limited to 6 months. CoQ10 has also been investigated in type 2 diabetics, where it has been found to improve blood pressure and HbA1c but had no effect on oxidative stress as assessed by F2-isoprostane levels (31). Certainly type 2 diabetics do not exhibit the same degree of mitochondrial dysfunction as those with MIDD.

CoQ10 has been used in other mitochondrial disorders at a dosage of up to 3000 mg/d without any side effects (32).

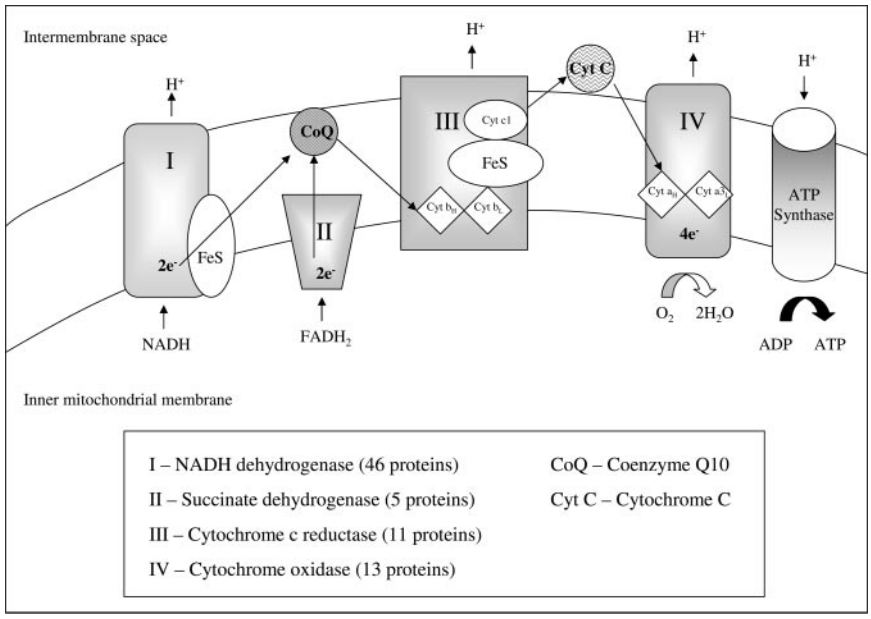

FIG. 2. The electron transport chain showing where CoQ10 is involved.

One study that used up to 3000 mg of CoQ10 per day observed that serum plasma levels of CoQ10 reached a plateau at a dosage of 2400 mg/d (32). A CoQ10 dosage of 300 mg per day was used in a double-blind placebo-controlled crossover design trial of 23 patients with heart failure (33). They demonstrated improved functional capacity and left ventricular contractility without any side effects. Studies of oral CoQ10 at doses of 100 mg/d in heart failure have had variable success. We chose a dose of 300 mg/d of CoQ10 for our patient, which cost her approximately $54 U.S. per month.

Because CoQ10 level is decreased with statins, cautious use of statins is advised in the setting of mitochondrial disorders. Theoretically, one could predict a higher rate of lactic acidosis and intolerance to statins in MIDD; however, this has not been reported.

A variety of combinations of 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 (34). One author found that CoQ10 was the only component of a cofactor mixture that improved ATP syntheses in lymphocytes (34). These other cofactors provide potential for future therapy in MIDD.

Finally, as MIDD is a mitochondrial disorder that is inherited from the mother in a dominant fashion, all progeny are at risk of developing some features of the disorder. The highly variable phenotype makes it very difficult to predict to what extent family members may be affected; however, one study in Dutch patients with the A3243G mutation showed an incidence of diabetes or IGT of 100% by age 70 (4). 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.

Tips for identifying patients with MIDD

In retrospect, the diagnosis of MIDD in this proband appeared simple, especially when a detailed family history was taken. The presentation of many of this proband's mitochondria dysfunction (*i.e.* WPW, GDM, and proteinuria) occurred in time, before the recognition and naming of this disorder in 1994.

A very strong family history of DM and deafness should prompt an investigation for MIDD. Microvascular complications out of keeping with duration of diabetes are another clue to the diagnosis, as the retinal and renal manifestations of mitochondrial disease may be confused for diabetic complications. Glutamic acid decarboxylase autoantibody negativity in a nonobese diabetic is yet another clue. Cardiac conduction defects and GDM may also raise suspicion as to the diagnosis; however, screening for MIDD in such individuals who have these disorders in isolation has not been productive (20).

Conclusions

MIDD, although rare, is an important diagnosis to make. Recognizing this etiology of DM should promote family screening, genetic counseling, screening of associated comorbidities, avoidance of metformin, and cautious use of statins. CoQ10 supplementation in MIDD requires further study as support for this agent is limited to an open label study and anecdotal case reports. Given that cost is the only known side effect of CoQ10 and that no other proven therapeutic options are available for MIDD, we believe that a therapeutic trial of CoQ10 should be considered in individuals that can afford CoQ10 after informed consent is obtained.

Acknowledgments

Received July 12, 2006. Accepted September 27, 2006.

Address all correspondence and requests for reprints to: Lois Donovan, 4005, 1213 4th Street S.W., Calgary, Alberta, Canada T2R 0X7. E-mail: loisdon@telus.net.

Disclosure statement: The authors have nothing to disclose.

References

1. **Stride A, Hattersley AT** 2002 Different genes, different diabetes: lessons from maturity-onset diabetes of the young. Ann Med 34:207–216
2. **Jones DL, Greenaway TM** 2004 Beware the thin, deaf "type 2" diabetic: maternally inherited diabetes and deafness with systemic (mitochondrial) manifestations. Intern Med J 34:517–518
3. **Owen MR, Doran E, Halestrap AP** 2000 Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 348(Pt 3):607–614
4. **Maassen JA, Jahangir Tafrechi RS, Janssen GM, Raap AK, Lemkes HH, 't Hart LM** 2006 New insights in the molecular pathogenesis of the maternally inherited diabetes and deafness syndrome. Endocrinol Metab Clin North Am 35:385–396, x-xi
5. **Suzuki S** 2004 Diabetes mellitus with mitochondrial gene mutations in Japan. Ann NY Acad Sci 1011:185–192
6. **Guillausseau PJ, Massin P, Dubois-LaForgue D, Timsit J, Virally M, Gin H, Bertin E, Blickle JF, Bouhanick B, Cahen J, Caillat-Zucman S, Charpentier G, Chedin P, Derrien C, Ducluzeau PH, Grimaldi A, Guerci B, Kaloustian E, Murat A, Olivier F, Paques M, Paquis-Flucklinger V, Porokhov B, Samuel-Lajeunesse J, Vialettes B** 2001 Maternally inherited diabetes and deafness: a multicenter study. Ann Intern Med 134:721–728
7. **Jansen JJ, Maassen JA, van der Woude FJ, Lemmink HA, van den Ouweland JM, 't Hart LM, Smeets HJ, Bruijn JA, Lemkes HH** 1997 Mutation in mitochondrial tRNA(Leu(UUR)) gene associated with progressive kidney disease. J Am Soc Nephrol 8:1118–1124
8. **Massin P, Virally-Monod M, Vialettes B, Paques M, Gin H, Porokhov B, Caillat-Zucman S, Froguel P, Paquis-Fluckinger V, Gaudric A, Guillausseau PJ** 1999 Prevalence of macular pattern dystrophy in maternally inherited diabetes and deafness. GEDIAM Group. Ophthalmology 106:1821–1827
9. **Becker R, Laube H, Linn T, Damian MS** 2002 Insulin resistance in patients with the mitochondrial tRNA(Leu(UUR)) gene mutation at position 3243. Exp Clin Endocrinol Diabetes 110:291–297
10. **Holmes-Walker DJ, Ward GM, Boyages SC** 2001 Insulin secretion and insulin sensitivity are normal in non-diabetic subjects from maternal inheritance diabetes and deafness families. Diabet Med 18:381–387
11. **Wittenhagen LM, Kelley SO** 2002 Dimerization of a pathogenic human mitochondrial tRNA. Nat Struct Biol 9:586–590
12. **King MP, Koga Y, Davidson M, Schon EA** 1992 Defects in mitochondrial protein synthesis and respiratory chain activity segregate with the tRNA(Leu(UUR)) mutation associated with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. Mol Cell Biol 12:480–490
13. **Chomyn A, Martinuzzi A, Yoneda M, Daga A, Hurko O, Johns D, Lai ST, Nonaka I, Angelini C, Attardi G** 1992 MELAS mutation in mtDNA binding site for transcription termination factor causes defects in protein synthesis and in respiration but no change in levels of upstream and downstream mature transcripts. Proc Natl Acad Sci USA 89:4221–4225
14. **Van Dam PS, Van Asbeck BS, Erkelens DW, Marx JJ, Gispen WH, Bravenboer B** 1995 The role of oxidative stress in neuropathy and other diabetic complications. Diabetes Metab Rev 11:181–192
15. **Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, Nicotera T** 1996 Oxidative damage to DNA in diabetes mellitus. Lancet 347:444–445
16. **Lorenzi M, Montisano DF, Toledo S, Barrieux A** 1986 High glucose induces DNA damage in cultured human endothelial cells. J Clin Invest 77:322–325
17. **Suzuki S, Hinokio Y, Komatu K, Ohtomo M, Onoda M, Hirai S, Hirai M, Hirai A, Chiba M, Kasuga S, Akai H, Toyota T** 1999 Oxidative damage to mitochondrial DNA and its relationship to diabetic complications. Diabetes Res Clin Pract 45:161–168
18. **Pang CY, Lee HC, Wei YH** 2001 Enhanced oxidative damage in human cells harboring A3243G mutation of mitochondrial DNA: implication of oxidative stress in the pathogenesis of mitochondrial diabetes. Diabetes Res Clin Pract 54(Suppl 2):S45–S56
19. **Lynn S, Borthwick GM, Charnley RM, Walker M, Turnbull DM** 2003 Heteroplasmic ratio of the A3243G mitochondrial DNA mutation in single pancreatic β cells. Diabetologia 46:296–299
20. **Aggarwal P, Gill-Randall R, Wheatley T, Buchalter MB, Metcalfe J, Alcolado JC** 2001 Identification of mtDNA mutation in a pedigree with gestational diabetes, deafness, Wolff-Parkinson-White syndrome and placenta accreta. Hum Hered 51:114–116
21. **Hosono T, Suzuki M, Chiba Y** 2001 Contraindication of magnesium sulfate in a pregnancy complicated with late-onset diabetes mellitus and sensory deafness due to mitochondrial myopathy. J Matern Fetal Med 10:355–356
22. **Frei B, Kim MC, Ames BN** 1990 Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc Natl Acad Sci USA 87:4879–4883
23. **Richter C** 1995 Oxidative damage to mitochondrial DNA and its relationship to ageing. Int J Biochem Cell Biol 27:647–653
24. **Ogasahara S, Yorifuji S, Nishikawa Y, Takahashi M, Wada K, Hazama T, Nakamura Y, Hashimoto S, Kono N, Tarui S** 1985 Improvement of abnormal pyruvate metabolism and cardiac conduction defect with coenzyme Q10 in Kearns-Sayre syndrome. Neurology 35:372–377
25. **Bresolin N, Doriguzzi C, Ponzetto C, Angelini C, Moroni I, Castelli E, Cossutta E, Binda A, Gallanti A, Gabellini S, Piccolo G, Martinuzzi A, Ciafaloni E, Arnaudo E, Liciardello L, Carenzi A, Scarlato G** 1990 Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. J Neurol Sci 100:70–78
26. **Chen RS, Huang CC, Chu NS** 1997 Coenzyme Q10 treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. Eur Neurol 37:212–218
27. **Goda S, Hamada T, Ishimoto S, Kobayashi T, Goto I, Kuroiwa Y** 1987 Clinical improvement after administration of coenzyme Q10 in a patient with mitochondrial encephalomyopathy. J Neurol 234:62–63
28. **Nishikawa Y, Takahashi M, Yorifuji S, Nakamura Y, Ueno S, Tarui S, Kozuka T, Nishimura T** 1989 Long-term coenzyme Q10 therapy for a mitochondrial encephalomyopathy with cytochrome c oxidase deficiency: a 31P NMR study. Neurology 39:399–403
29. **Suzuki S, Hinokio Y, Ohtomo M, Hirai M, Hirai A, Chiba M, Kasuga S, Satoh Y, Akai H, Toyota T** 1998 The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation. Diabetologia 41:584–588
30. **Silvestre-Aillaud P, BenDahan D, Paquis-Fluckinger V, Pouget J, Pelissier JF, Desnuelle C, Cozzone PJ, Vialettes B** 1995 Could coenzyme Q10 and L-carnitine be a treatment for diabetes secondary to 3243 mutation of mtDNA? Diabetologia 38:1485–1486
31. **Hodgson JM, Watts GF, Playford DA, Burke V, Croft KD** 2002 Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. Eur J Clin Nutr 56:1137–1142
32. **Shults CW, Flint Beal M, Song D, Fontaine D** 2004 Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. Exp Neurol 188:491–494
33. **Belardinelli R, Mucaj A, Lacalaprice F, Solenghi M, Seddaiu G, Principi F, Tiano L, Littarru GP,** Coenzyme Q10 and exercise training in chronic heart failure. Eur Heart J, in press
34. **Marriage BJ, Clandinin MT, Macdonald IM, Glerum DM** 2004 Cofactor treatment improves ATP synthetic capacity in patients with oxidative phosphorylation disorders. Mol Genet Metab 81:263–272

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.