Mitochondrial Diabetes: More Than Just Hyperglycemia

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Juvenile-onset diabetes is often branded as type 1 diabetes when a clear family history is absent. A high degree of suspicion regarding other forms of diabetes should be kept in mind when systems not known to be affected by hyperglycemia or associated with type 1 diabetes are involved. Such a scenario is often complicated by the slow evolution of symptomatology and the absence of diabetes in family members. Here, we report on a genetically proven mitochondrial A3243G mutation–related syndromic diabetes in a young patient whose mitochondrial disease–related multisystem symptomatology slowly evolved over the course of a decade.

Case Presentation

Our association with the patient started from his childhood (Figure 1). His first visit to our hospital was for short stature at the age of 9 years. Systemic work-up and growth hormone studies were normal. Familial factors were thought to be responsible. He was noted to have an IQ of 75, with poor performance in school.

At the age of 16 years, he presented to us with diabetes without ketosis or a family history of diabetes. Tests for GAD65 and IA2 antibodies were negative at this stage. Although a trial of oral hypoglycemic agents was instituted, he was soon shifted to insulin therapy because of his poor response.

Two years later, he presented with gastrointestinal symptoms in the form of intermittent diarrhea. Work-up for celiac disease and pancreatic insufficiency, including upper and lower endoscopies with biopsies, was normal. Fortunately, the diarrhea subsided, which was attributed by the family to dietary manipulation, especially restriction of wheat products. At around this time, sensorineural hearing loss was documented. The combination of these symptoms led to a consideration of mitochondrial diabetes. However, fundus evaluation for characteristic pigmentary changes was normal.

Also around this time, his mother, who was then 42 years of age, and his sister, who was older than him by 3

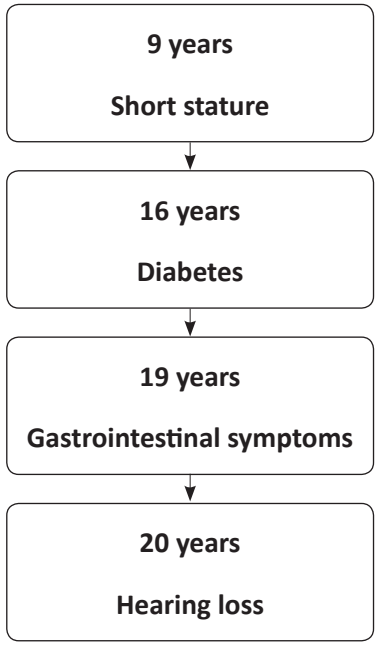

FIGURE 1. Chronology of symptoms in the patient.

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years, were both found to have diabetes. Both of these first-degree relatives had apparently normal hearing, although formal audiometric testing was not performed. The sister suffered from episodes of palpitation and was later diagnosed as having Wolff-Parkinson-White (WPW) syndrome with paroxysmal supraventricular tachycardia. Genetic testing was performed for the proband at this stage and revealed the classical A3243G mutation (Figure 2).

In the past year, our patient developed muscle pains and cramps without demonstrable weakness. His creatine phosphokinase was normal. Evaluation with electromyography (EMG) showed evidence of early myopathy. Electrocardiography showed features suggestive of preexcitation syndrome, as may occur in WPW (Figure 3). A trial of a vitamin E-levocarnitine combination proved beneficial, with significant alleviation of the cramps. The patient's parents and sister declined genetic testing.

The patient's relevant investigations are summarized in Table 1.

Questions

1. What are the characteristics of mitochondrial diabetes?
2. When should mitochondrial diabetes be suspected in a juvenile patient?
3. How can suspected mitochondrial diabetes be confirmed?
4. Once confirmed, how is mitochondrial diabetes treated?

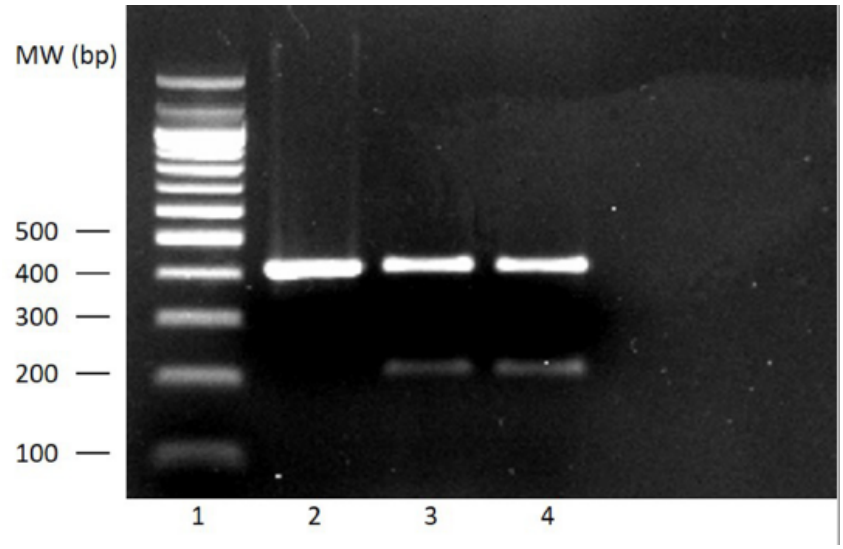

FIGURE 2. Detection of mitochondrial A3243G mutation by PCR-RFLP (polymerase chain reaction–restriction fragment length polymorphism). A restriction digest analysis for the A3243G mtDNA mutation was performed. PCR product encompassing the *tRNALeu* gene was digested with ApaI before running analysis on 3% agarose gel. The figure shows *1*) lanes, *2*) wild-type, *3*) positive control (a known patient with the A3243G mutation as detected by PCR-RFLP), and *4*) the patient in this case study.

Discussion

Mitochondrial diabetes often presents as an unremarkable form of diabetes, mistaken for either type 1 or type 2 diabetes depending on the severity of insulinopenia. Studies from Europe have described prevalence rates of >5% in patients presenting with a type 2 diabetes phenotype (1); it has not been well studied in patients with a type 1 phenotype. This form of diabetes is not commonly reported in young Indian patients (2); however, it is not uncommon in other parts of Asia (3). The average age of onset of diabetes in a Japanese study was 28.9 ± 11.2 years, whereas in our case, the age of onset of diabetes was 16 years, which is a bit younger than the known data.

Often, there are other clues that point toward a mitochondrial etiology, including deafness (92.2%) (3),

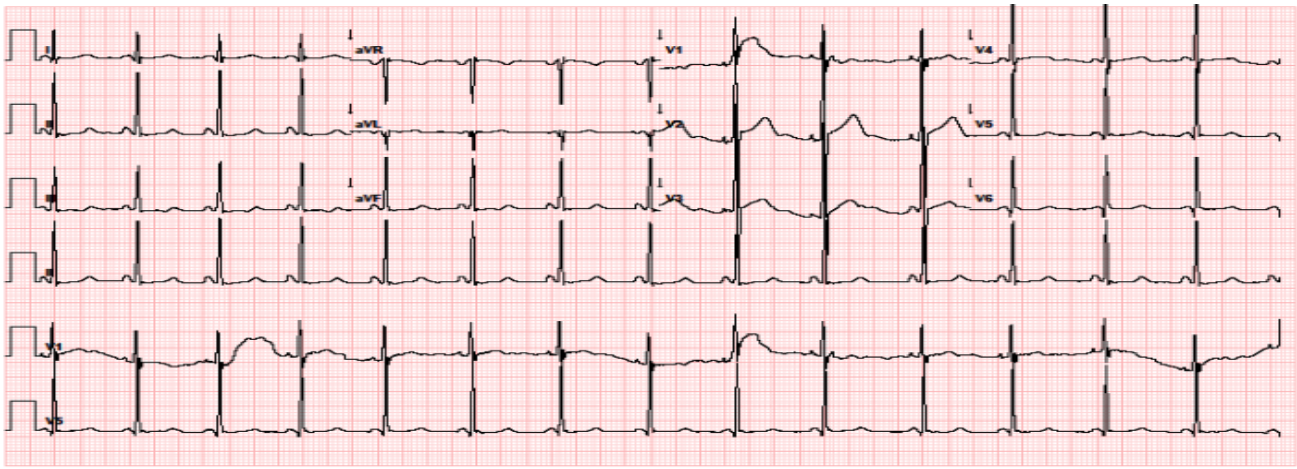

FIGURE 3. Electrocardiogram showing Wolff-Parkinson-White pattern.

TABLE 1. Patient's Laboratory Investigations

Parameters	Patient's Values	Reference Range
Thyroid-stimulating hormone, μIU/mL	1.42	0.7–5.97
Free thyroxine, ng/dL	1.13	0.7–1.48
IGF-1, ng/mL	181	74–388
GAD65, IU/mL	2.27	Cutoff: 5.0
IA2, IU/mL	6.18	Cutoff: 8.0
Lactate, mmol/L	4.5	0.5–2.2
Cortisol (8:00 a.m.), μg/dL	14.5	3.7–19.4
Luteinizing hormone, μIU/mL	2.92	1.14–8.75
Follicle-stimulating hormone, μIU/mL	0.81	0.95–11.95
Testosterone, ng/mL	4.91	1.56–8.77
Adrenocortotropic hormone, pg/mL	98	7.2–63.3
Creatine phosphokinase, U/L	153	0–171
A1C, %	8.4	Normal <6.5%
Stool fat	Negative	
Computed tomography scan of brain	Normal	
Multidetector computed tomography of the abdomen	No abnormality detected	
Two-dimensional echocardiogram	Myxomatous mitral valve, prolapsed anterior mitral leaflet with trivial mitrial regurgitation	
Endoscopy with duodenum biopsy	Normal	

pigmentary retinopathy, short stature, cardiac disease in the form of cardiomyopathy (30.4%) (3), conductive tissue disease (27.8%), gastrointestinal symptoms, renal abnormalities, hypogonadism (<20%), and myopathy (10.4%) (3). Hearing loss manifests several years before diabetes. Hence, screening for hearing loss has a good diagnostic value. Hypertrophic cardiomyopathy is the usual form of cardiomyopathy in these patients. Patients can also have muscle involvement in the form of proximal myopathy or exercise-induced muscle cramps or weakness.

The most common mitochondrial mutation associated with mitochondrial diabetes is A3243G mutation (4). This was initially identified in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Distinct from MELAS, which presents at a younger age, maternally inherited diabetes and deafness (MIDD) tends to present in the third or fourth decade of life.

Various theories have been proposed for the pathogenesis of mitochondrial diabetes. Mitochondrial mutation leads to reduced ATP production in pancreatic β-cells, alters the ATP/ADP ratio that determines the opening probability of the K_{ATP} channel involved in insulin secretion, thereby affecting glucose-induced insulin secretion, leading to diabetes (5,6). Mitochondrial function itself contributes to the process of insulin secretion, and its dysfunction leads to diabetes. Another proposed mechanism for diabetes is higher lactate flux to the liver, fueling gluconeogenesis because of mitochondrial dysfunction in the muscle and leading to increased hepatic glucose production. Mitochondria are a main free radical generator, apart from regulating many compounds such as calcium, glutamate, cytochrome C, and lactate (7–10). Hence, distinct mutations of these molecules may differentially affect their concentrations and express different clinical manifestations in patients.

Mitochondrial diabetes is almost exclusively maternally transmitted. Different mutations in the mitochondrial genome have different clinical presentations based on the organ systems affected. An important concept in explaining the pathogenic pathway of MIDD is heteroplasmy. This is a state in which the patient has mutated mitochondrial DNA mixed with normal mitochondrial DNA in the cells. As the percentage of heteroplasmy increases, the severity of clinical phenotype varies. Heteroplasmy values show large variations between individual tissues, with a tendency toward high heteroplasmy values in nondividing tissue compared with rapidly dividing cells (11).

Diagnosis of mitochondrial diabetes rests purely on genetic analysis of the patient to identify mutation with clinical suspicion of the syndrome. The investigation of a suspected mitochondrial disease requires an integrated approach, incorporating clinical, histochemical, biochemical, and molecular biological investigations. Every patient should get an electrocardiogram to look for cardiomyopathy. Serum lactate, pyruvate, and creatinine kinase are tests required. Nerve conduction studies are needed to diagnose axonal or mixed axonal-demyelinating neuropathies, and EMG should be performed to rule out myopathies (12).

Mitochondrial diabetes is progressive; hence, treatment must begin very early in the disease process. Diabetes initially can be managed with diet and oral antidiabetic agents, but

within a few years, patients become insulin dependent. Metformin is generally contraindicated because of the risk of lactic acidosis. Currently, use of vitamin-based and cofactor-based mitochondrial therapies remains experimental. Such therapies include coenzyme Q, riboflavin, creatine, L-carnitine, L-arginine, and folinic acid and have shown variable benefit (13–15).

Clinical Pearls

- Although classically described as presenting in the third and fourth decades of life, mitochondrial diabetes can present in juvenile patients, often without a known family history at presentation.
- Unexplained multisystem affection should raise suspicions regarding a non–type 1 diabetes etiology for juvenile diabetes.
- Juvenile diabetes even without a relevant family history should prompt a search for a mitochondrial etiology. Short stature and nerve deafness are important clues.
- Maternal diabetes can sometimes be diagnosed after diabetes has developed in a child, as in this case.
- The evolution of clinical symptomatology in this case exemplifies the need for vigilance in following up with patients who have an apparent diagnosis of type 1 diabetes.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

M.P.R. collected the data and wrote the manuscript. P.V.P. wrote the manuscript. N.B., U.V.M., and N.A. contributed to the discussion. H.K. reviewed and edited the manuscript. V.N. researched the data and contributed to the discussion. A.S.M. contributed to writing the manuscript. P.V.P. is the guarantor of this work and, as such, had full access to all the data presented and takes responsibility for the integrity of the data and the accuracy of the case presentation.

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