CASE REPORT

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The Tip of the Iceberg in Maternally Inherited Diabetes and Deafness

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ABSTRACT

Maternally inherited diabetes and deafness (MIDD) is not only a disorder of the pancreas and ears but a multisystem mitochondrial disorder syndrome. Hypogonadism, however, has not been reported as a phenotypic feature of MIDD. We report a single case of a patient with MIDD which manifested clinically at 41 years old. In addition to diabetes and deafness, he manifested with seizures, ataxia, myopathy, and hypogonadism. We used established methods for the routine workup of this patient. MIDD is indeed a multisystem condition. A previously undescribed phenotypic feature of MIDD may be hypogonadism.

Maternally inherited diabetes and deafness (MIDD) is a syndromic mitochondrial disorder (MID) characterized by type 2 diabetes and hearing impairment.[1] In up to 85% of cases, MIDD is due to the mitochondrial (mt)DNA mutation m.3243A>G,[2] but other mtDNA mutations may also cause MIDD.[3] Though MIDD was originally described to affect only the pancreas and ears,[4] during the following years it turned out that it is a mitochondrial multiorgan disorder syndrome (MIMODS) rather than restricted to two organs [Table 1].[5–24] In addition to the central nervous system (CNS) and the endocrine organs, MIDD may manifest with affection of the peripheral nerves, ears, vestibular system, eyes, heart, gastrointestinal tract, and kidneys. Here, we describe a patient with MIDD who presented with infertility in addition to other previously described features of MIDD [Table 1].

CASE REPORT

Our patient, a 44-year-old Caucasian male (height 185 cm, weight 88 kg) was referred for a first tonic-clonic seizure during general anesthesia for surgery of a right-sided inguinal hernia. Despite this event, anesthesia and surgery were continued without further complications. His history was noteworthy for deafness since birth, requiring hearing devices since aged five. Additionally, his history was positive for otitis media at age nine months, dysarthria since early childhood (attributed to deafness), diabetes since age 41 years, mild creatine kinase (CK) elevation, emphysema, nicotine abuse, and hyperlipidemia. Infertility in the patient was diagnosed by history, clinical exam, hormone testing, and semen analysis. His family history was positive for diabetes and impaired hearing in his mother. His maternal grandmother was wheel-chair bound because of muscle weakness. More detailed information about other family members was not available since he was an adopted child.

Clinical neurologic examination at age 44 years revealed bilateral hypoacusis and mild left-sided ataxia. Blood chemical investigations showed a glycated hemoglobin (HbA_{1c})of 12.4% (n < 6.0%) and hyperlipidemia. Ultrasound of the abdomen was non-informative. Colonoscopy was normal. The patient was assumed to have multisystem MIDD. The patient did not consent to a muscle biopsy or genetic workup to confirm the diagnosis.

DISCUSSION

Our patient with putative MIDD is interesting for two reasons. First, he presented with a phenotypic feature, hypogonadism, which has not been reported previously [Table 1]. Hypogonadism in the form of infertility was attributed to MIDD since urologists

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Table 1: Phenotypic manifestations of maternally inherited diabetes and deafness (MIDD).

Organs affected	Present case	Literature	Reference
Central nervous system			
Cerebral atrophy	-	+	5
Cerebellar atrophy	-	+	6
Cerebellar ataxia	+	+	7
Basal ganglia calcification	-	+	8
Leukoencephalopathy	-	+	9
Nystagmus	-	+	9
Cerebrospinal fluid protein↑	-	+	9
Cerebrospinal fluid lactate ↑	-	+	6
Neuropsychological deficits	-	+	6
Depression	-	+	5
Seizures	+	+	10
Peripheral nervous system			
Myopathy	+	+	11
Rhabdomyolysis	-	+	9
Ptosis	-	+	12
Polyneuropathy	-	+	9
Ears			
Hypoacusis, anacusis	+	+	13
Vestibular system			
Impaired vestibule-ocular reflex	-	+	9
Eyes			
Pigmentary retinopathy	-	+	14
Macular degeneration	-	+	15
Optic atrophy	-	+	9
Central retinal vein occlusion	-	+	16
Retinal/choroidal atrophy	-	+	17
Endocrine system			
Diabetes	+	+	9
Hypoaldosteronism	-	+	18
Short stature	-	+	19
Hypogonadism (low testosterone)	+	-	Present case
Heart			
Arterial hypertension	-	+	14
Cardiomyopathy	-	+	20
Heart failure	-	+	21
Gastrointestinal tract			
Pancreatitis	-	+	10
Intestinal pseudo-obstruction	-	+	22
Constipation	-	+	23
Diarrhea	-	+	23
Kidneys			
Renal failure	-	+	12
Glomerulosclerosis	-	+	24

↑: *elevated.*

excluded other causes and since MIDs, except MIDD, have been previously reported to be associated with hypogonadism.[25] Hypogonadism has been found in mitochondrial encephalopathy, lactic acidosis, stroke-like episodes, chronic progressive external ophthalmoplegia, mitochondrial neuro gastro-

intestinal encephalopathy, Kearns-Sayre syndrome, and several non-specific MIDs. Urologists diagnosed his infertility but did not offer any effective treatment. An argument against diabetes as the cause of infertility is that diabetes did not occur earlier than aged 41 years, but infertility was diagnosed earlier. Since cerebral imaging was normal and his history was negative for birth trauma, traumatic brain injury, meningitis, or juvenile febrile seizures, they were attributed to the suspected underlying MID. A further argument for attributing seizures to the suspected MIDD is that epilepsy has been reported as a CNS manifestation of a MID.[26]

Second, for years the patient was not regarded as having a MID as his family history was incomplete because of difficulties taking it and since nobody regarded the clinical presentation of the patient as indicative of a MID and since it is not well-known that MIDD is not only characterized by diabetes and deafness but in fact a multisystem disease as most of the MIDs. MIDs potentially affect all body tissues and turn into a MIMODS during the disease course. The multisystem nature of MIDD is well documented. Organs described to be affected by MIDD include the CNS, peripheral nervous system, eyes, ears, vestibular system, skeletal muscle, endocrine system, heart, and intestines [Table 1].[2] The patient did not complain about sleep disorder, which has been reported as a manifestation of diabetes.[27] Since MIDD may manifest with myopathy, including rhabdomyolysis, muscle biopsy may show features of a MID and biochemical investigations of the muscle homogenate may show decreased activity of some or all complexes of the respiratory chain.

CONCLUSION

This case shows that MIDD is indeed a multisystem MID, that the phenotypic spectrum of MIDD is broader than previously reported, and that hypogonadism may be an additional manifestation of the MIDD.

Disclosure

The authors declared no conflicts of interest.

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