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CASE REPORT

The clinical and genetic characteristics of maternally inherited diabetes and deafness (MIDD) with mitochondrial m.3243A > G mutation: A 10-year follow-up observation study and literature review

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Key Clinical Message

Maternally inherited diabetes and deafness (MIDD) is often caused by the m.3243A > G mutation in mitochondrial DNA. Unfortunately, the characteristics of MIDD, especially long-term outcomes and heteroplasmic changes, have not been well described previously. The purpose of this study was to describe the clinical and genetic features of a family with MIDD after 10 years of follow--up.A 33-year-old male patient with typical characteristics of MIDD, including early-onset diabetes, deafness, and low body mass index, was admitted to our department. Further investigation revealed that the vast majority of his maternal relatives suffered from diabetes with or without deafness. A detailed family history was then requested from the patient and a pedigree was constructed. The patient suspected of MIDD was screened for mutations using whole mitochondrial DNA sequencing. Candidate pathogenic variants were then validated in other family members through Sanger sequencing. The patient was diagnosed with MIDD, with inherited m.3243A > G mutation in the mitochondrially encoded tRNA leucine 1 (MT-TL1) gene, after 10 years of symptom onset. The patient was then treated with insulin and coenzyme Q10 to improve mitochondrial function. During the follow-up period, his fasting blood glucose and HbA1c levels were improved and the incidence of diabetic ketoacidosis was significantly reduced.

Shasha Zheng and Juanjuan Wang contributed equally to this work.

Our findings indicate that whole mitochondrial DNA sequencing should be considered for patients suspected of MIDD to improve the efficiency of diagnosis and prognosis.

KEYWORDS

clinical features, diagnosis, genetic testing, m.3243A > G mutation, maternally inherited diabetes and deafness (MIDD), mitochondrial genes, pedigree

1 | INTRODUCTION

Mitochondria play an important role in the production of ATP and are found in all human cells in the body except red blood cells.[1] Mitochondrial diseases are a group of disorders caused by mitochondrial dysfunction. Mitochondrial DNA (mtDNA) is inherited maternally and affects organs that are highly dependent on aerobic metabolism, such as the eye, inner ear, central nervous system, skeletal muscle, and cardiac muscle. Mitochondrial diabetes mellitus, also known as maternally inherited diabetes and deafness (MIDD) syndrome, is an mtDNA mutation disease characterized by progressive islet β-cell secretory dysfunction.[2,3] MIDD is associated with early-onset diabetes and sensorineural deafness, as well as various other systemic features such as cardiomyopathy, nephropathy, and neuropsychiatric symptoms.

MIDD was first reported by J.A. Massen et al. in 1992, who found a large family with mt.3243A > G mutation that suffered from diabetes in the presence of maternal inheritance and most of the mutation carriers complicated with bilateral hearing loss.[4] Since then, a growing body of scientific evidence suggests that a range of other point mutations in the mtDNA may also contribute to the pathogenesis of MIDD, such as mt-tRNA encoding genes, including MT-TI, MT-TS1, and MT-TK, and mt-proteins encoding genes, including MT-ND1, MT-ND4, MT-COX2, and MT-COX3. In addition, nucleotide deletions and depletions have also been described in patients with MIDD.[5] However, these novel mutations are extremely rare compared to the mt.3243A > G. MIDD is considered to be the most common type of monogenic diabetes mellitus, accounting for about 1% of all diabetes mellitus, and its incidence in China is approximately 0.6%.[6]

Due to its low incidence and heterogeneous clinical presentation, MIDD is often misdiagnosed as type 1 or type 2 diabetes. Nonetheless, its treatment is different from the common types of diabetes, and incorrect diagnosis and treatment will accelerate the disease progression and the occurrence of complications. Therefore, correct genetic diagnosis and treatment are crucial for patients with MIDD. This study discussed the clinical manifestations and treatments of a typical patient with MIDD and summarized the disease characteristics through a comprehensive review of the literature.

2 | MATERIALS AND METHODS

2.1 | Participants

Patient information, such as the age of disease onset, complications, and family history was obtained from patient's interview and medical records. Information from a total of 24 family members, including 15 females and 9 males, aged 20–80 years from four generations, was collected to construct the pedigree. Classification and diagnosis of diabetes were in accordance with the latest guidelines of the American Diabetes Association.[7] This study was approved by the ethics committee of the Central Hospital of Wuhan. Peripheral blood was collected from the proband, his mother, and two daughters. Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

2.2 | Sample preparation and whole mitochondrial DNA sequencing

Total DNA was extracted from peripheral blood using a TIANGEN DNA Extraction Kit (TIANGEN, Beijing, China). Sample preparation and pretreatment for next-generation sequencing were performed using the SureSelect XT Low Input Reagent Kit Agilent (G9703A) according to the manufacturer's instructions. MtDNA sequencing was carried out on an HiSeq2500 system (Illumina), including MT-DLOOP, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-CYB, MT-CO1, MT-CO2, MT-CO3, MT-ATP6, MT-ATP8, MT-TA, MT-TR, MT-TN, MT-TD, MT-TC, MT-TE, MT-TQ, MT-TG, MT-TH, MT-TI, MT-TL1, MT-TL2, MT-TK, MT-TM, MT-TF, MT-TP, MT-S1, MT-TS2, MT-TT, MT-TW, MT-TY, MT-TV, MT-RNR1, and MT-RNR2. The resulting sequences were compared to the updated Cambridge sequence (GenBank accession number:

NC_012920). Blast homology searches were performed using the programs available on the National Center for Biotechnology Information website and were compared to the wild-type sequence. Areas containing putative novel variations were amplified and re-sequenced on both strands to exclude possible polymerase chain reaction artifacts.

2.3 | Sanger sequencing

The presence of the identified variants in the proband and his family was confirmed by direct Sanger sequencing of the polymerase chain reaction products, and the variants also occurring in other family members with diabetes were selected for further analysis. The presence of the mt.3243A > G variant in the proband and his family (mother) was confirmed by direct Sanger sequencing of the polymerase chain reaction products. The MT-TL1 gene was amplified in a polymerase chain reaction assay using the forward primer 5′-CCGGAGTAATCCAG GTCGGT-3′ and the reverse primer 5′-CAGCATTCCCC CTCAAACCT-3′. The polymerase chain reaction conditions were set as follows: 95°C for 5 min; followed by 35 cycles of, 95°C for 1 min, 60°C for 30 sec, and 72°C for 1 min; with a final extension at 72°C for 10 min. The polymerase chain reaction products were assessed by direct Sanger sequencing (Xiangyin Medical Testing Center, Hangzhou, China).

2.4 | Treatment adjustments

Patients' treatment plans were adjusted based on genetic test results and previously reported findings. For example, insulin was administered to the proband, and melbine was discontinued.

3 | RESULTS

3.1 | Medical history

A 33-year-old male was admitted to our department for poor glycemic control and deafness for 11 years and abdominal pain and vomiting for 1 day. The patient was diagnosed with type 1 diabetes at the age of 22 years. During the course of the disease, the patient repeatedly experienced dry mouth, polydipsia, polyuria, fatigue, weight loss, limb spasms, abdominal pain, and vomiting, and was repeatedly hospitalized for ketosis. His previous hospital records showed that the commonly evaluated islet autoantibodies (anti-GAD, IAA, ICAA, Anti-IA2, and Znt8) were not identified, and oral hypoglycemic drugs were found to be ineffective.

Figure 1 shows the pedigree chart of the proband's family. His family history indicated that the patient's mother had diabetes and his father was a healthy individual with no family history of diabetes. His grandmother (I-2), grandaunt (I-3), granduncle (I-4), mother (II-1), five aunts (II-2, II-3, II-4, II-5, and II-8), one uncle (II-6), and

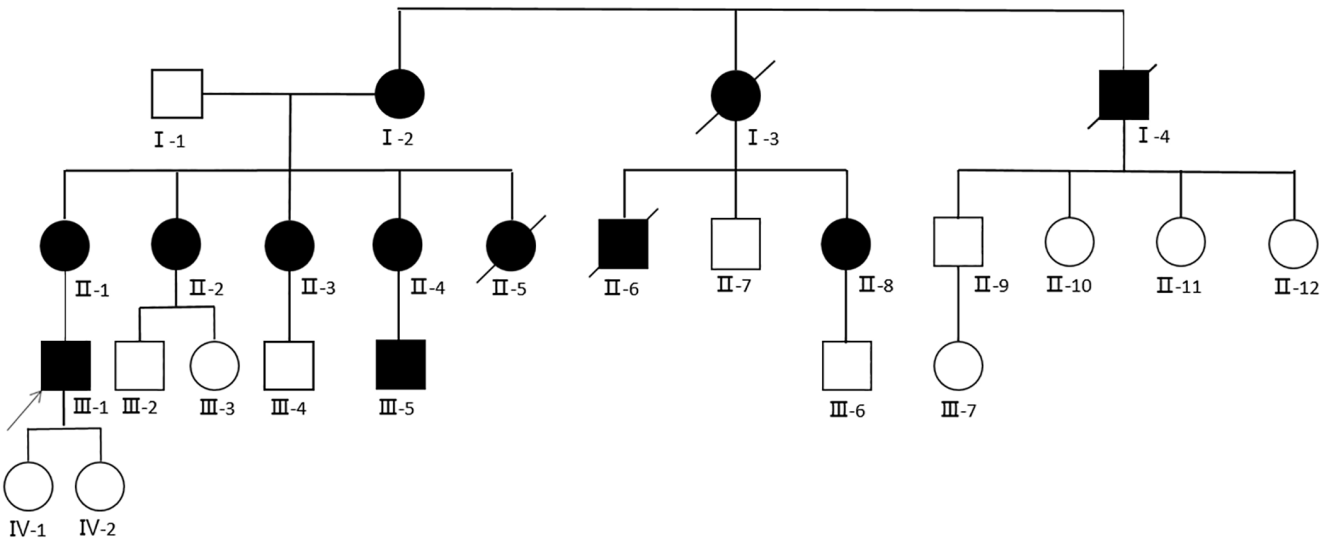

FIGURE 1 Pedigree of the patient's family. Generations were indicated on the left, and the numbers under the individuals represented identification numbers for each generation. Males were represented as squares, while females were represented as circles. The black arrow indicates the proband (III-1). Individuals with diabetes were labeled with black symbols, and death was indicated by an oblique line. The proband (III-1) had a diagnosis of type 1 diabetes mellitus at the age of 22, and his grandmother (I-2), grandaunt (I-3), granduncle (I-4), mother (II-1), five aunts (II-2, II-3, II-4, II-5, and II-8), one uncle (II-6), and one cousin (III-5) were diagnosed with type 2 diabetes mellitus at the age of 40, 40, 45, 50, 50, 30, 40, 40, 50, 40, and 28 years, respectively.

one cousin (III-5) had similar presentations, while the offspring of the granduncle (II-9, II-10, II-11, and II-12), his grandfather (I-1), one uncle (II-7), and five cousins (III-2, III-3, III-4, and III-6) did not. The proband's family had more females than males, and none of the male's offspring was diagnosed with diabetes. These findings suggested that an extensive history of early-onset adult diabetes in the maternal lineage.

3.2 | Clinical characteristics

The clinical characteristics of diabetic patients within the proband's family are presented in Table 1 and Table 2. A total of five medical records of the proband were collected from 2013 to 2022. The proband's laboratory analysis results revealed poor glycemic control, and he was frequently hospitalized for diabetic ketosis or ketoacidosis. Physical examination showed that the patient was lean, with a weight of 52 kg, a height of 1.70 m, and a body mass index (BMI) of only 17.99 kg/m^2. His fasting and 2-h C-peptide levels decreased from 0.6 and 3.0 ng/mL in 2014 to 0.32 and 0.63 ng/mL in 2022, indicating a worsening of islet β-cell secretory dysfunction. No diabetes autoantibodies were detected in the 2022 examination. Blood tests showed a slightly elevated lipid profile and elevated uric acid levels, possibly due to ketoacidosis. In 2022, an ultrasound examination of the liver, kidney, pancreas, bladder, ureter, spleen, and gallbladder showed normal morphology, but complications of the eye and lower extremity artery indicated rapid progression. The patient was first diagnosed with glaucoma in 2013, which was later corrected to diabetic retinopathy in 2014.

The patient's grandmother (I-2), grandaunt (I-3), granduncle (I-4), mother (II-1), five aunts (II-2, II-3, II-4, II-5, and II-8), one uncle (II-6), and one cousin (III-5) were diagnosed with type 2 diabetes mellitus (T2DM) at the ages of 40, 40, 45, 50, 50, 30, 40, 40, 50, 40, and 28 years, respectively. The medical history interview reviewed that all diabetic patients within the family had early-onset diabetes and only a few of them (I-2, II-1, and II-8) could achieve optimal glycemic control with oral hypoglycemic agents alone. In addition to the proband (III-1), his grandmother (I-2), grandaunt (I-3), granduncle (I-4), mother (II-1), and two aunts (II-4 and II-8) had hearing impairment, and his mother reported that the disease onset was very early. The proband (III-1), his grandmother (I-2), and his mother (II-1) also had complicated myoclonus while, some patients within the family had diabetes alone (II-2, II-3, II-5, II-6, and III-5). The above information suggested that the occurrence of diabetes in this family was distinctive and maternally inherited, and the disease presentation varied among family members.

3.3 | Genetic analysis

Based on the clinical symptoms and maternal clustering characteristics in the proband's family, we performed sequencing analysis of the whole mtDNA in the proband. The proband exclusively had a heteroplasmic m.3243A > G mutation in the MT-TL1, with a mutation frequency of 31.46% (Figure 2A and Table 3). This mutation was detected in his mother (II-1) but was absent in the other two family members (his daughters IV-1 and IV-2) suggested by the Sanger sequencing (Figure 2B–D). Further genetic testing confirmed that these family members should also be diagnosed with MIDD.

3.4 | Precise treatment based on patient's genotype

In this study, the patient was misdiagnosed for 10 years before the discovery of the m.3243A > G mutation in the MT-TL1 gene in his family. Although the diagnosis was clear, the clinical management of MIDD remains a complicated issue. After a thorough literature review and information we gathered from the patient's family, we recommended that everyone in his family should receive individualized management. For instance, the patient himself should receive insulin administration because he had defective insulin secretion from the pancreatic β-cells, as suggested by the m.3243A > G mutation in the mtDNA. According to the literature, we added coenzyme Q10 to improve the mitochondrial function and avoided drugs that may damage mitochondrial function, such as metformin and statins. During the follow-up, the incidence of diabetic ketoacidosis was found to be significantly reduced, and his fasting blood glucose as well as HbA1c levels were evidently improved. Cochlear implantation was also recommended to the patient to improve the hearing. Long-term follow-up and careful mutant mtDNA testing were recommended for the patient's maternal relatives with MIDD.

4 | DISCUSSION

In the present study, we described the clinical and genetic features of a rare case of MIDD in a proband characterized by early-onset diabetes, deafness, low BMI, and maternal relatives with diabetes. Accurate diagnosis, made possible by genetic sequencing that revealed the m.3243A > G mutation in the mitochondrially encoded tRNA leucine 1

TABLE 1 Physical and laboratory examination findings of the proband.

	Year				
Symptoms	**2013**	**2014**	**2019**	**2021**	**2022**
BMI, kg/m^2	17.30	17.30	17.30	17.30	17.99
Random urine glucose	Unknown	3+	3+	1+	4+
Ketones in urine	Unknown	3+	2+	2+	Neg
Fasting plasma glucose, mmol/L	–	6.95	–	–	10.60
Fasting C-peptide, ng/mL	–	0.6	–	–	0.32
2-h fasting C-peptide, ng/mL	–	3.0	–	–	0.63
HbA1c, %	10.9	13.1	15.4	12.8	11.8
Albumin, g/L	Normal	Normal	Normal	Normal	38.6
Globulin, g/L	Normal	Normal	Normal	Normal	25.2
Alanine aminotransferase, U/L	Normal	Normal	Normal	Normal	11.3
Aspartate aminotransferase, U/L	Normal	Normal	Normal	Normal	11.1
Creatinine, μmol/L	Normal	Normal	Normal	137.0	69.0
Uric acid, μmol/L	Normal	441.4	595.3	648.0	424
TG, mmol/L	Normal	Normal	3.11	5.00	1.88
TC, mmol/L	Normal	Normal	Normal	6.38	3.77
HDL-C, mmol/L	Normal	Normal	0.83	Normal	1.00
LDL-C, mmol/L	Normal	Normal	Normal	3.125	2.22
CRP, mg/L	–	Normal	–	Normal	0.03
Anti-GAD	–	–	–	–	Neg
IAA	–	–	–	–	Neg
ICAA	–	–	–	–	Neg
Anti-IA2	–	–	–	–	Neg
Znt8	–	–	–	–	–
Drug therapy	Lispro mix 25 + Acarbose	BIAsp30	BIAsp30	Apidra+IDegAsp +Voglibose	IDegAsp +carbose

Note: The results of biochemical parameters upon proband's admission to the hospital. –, no detection; unknown, tests were conducted but the results are unknown.

Abbreviations: +, positive; BMI, body mass index; CRP, C-reactive protein; GAD, glutamic acid decarboxylase antibody; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IAA, insulin autoantibodies; LDL-C, low-density lipoprotein cholesterol; Neg, negative; TC, total cholesterol; TG, triglyceride.

(MT-TL1) gene, resulted in a significantly reduced incidence of diabetic ketoacidosis during 10-year follow-up.

MIDD is a group of clinically heterogeneous diseases caused by dysfunction of the mitochondrial respiratory chain and oxidative phosphorylation.[8] MIDD often causes early-onset diabetes and sensorineural deafness, but various presentations from other organs or systems can occur, such as ophthalmic disease,[9,10] myopathy, encephalopathy, cardiac disease, gastrointestinal diseases[11] and renal disease.[12] The heterogenity of presentation may be related to the mitochondrial DNA heteroplasmy. However, the same mutation can cause different phenotypes or can be "silenced" eternally. In our case, although the mutation was screened in only four individuals, two were found to carry the mutation. Based on the genetic characteristics of MIDD, it is reasonable to assume that other people with diabetes within the family may also carry the same mutation and that there may also be some unidentified asymptomatic carriers. Among the 12 diabetics identified within the family, only three were males. In addition, seven of them had hearing impairment, three had myoclonus, three were lean, and five had diabetes only. Most of the patients were diagnosed with diabetes around the age of 40 years, but a few had a much earlier disease onset. In this family, the proband (III-1), his grandmother (I-2), and his mother (II-1) had myoclonus. As mentioned by the proband, his myoclonus only occurred in the lower extremities infrequently and is often accompanied by pain after exercise.

Similar presentations have been reported in the literature. The proband was initially diagnosed with T1DM due to the early age of onset (<30 years old), lean body,

TABLE 2 Disease characteristics of different patients within the family.

	Age at onset (years)	Gender	symptom	Therapies	Ending
I-2	40	F	Diabetes, lean, hearing impairment, myoclonus	OAD	Alive
I-3	40	F	Diabetes, hearing impairment	Unknown	Dead
I-4	45	M	Diabetes, hearing impairment	Unknown	Dead
II-1	50	F	Diabetes, lean, hearing impairment, myoclonus	OAD	Alive
II-2	50	F	Diabetes	Insulin injection	Alive
II-3	30	F	Diabetes	Insulin injection	Alive
II-4	40	F	Diabetes, hearing impairment	Insulin injection	Alive
II-5	40	F	Diabetes	Unknown	Dead
II-6	40	M	Diabetes	Unknown	Dead
II-8	50	F	Diabetes, hearing impairment	OAD	Alive
III-1	23	M	Diabetes, lean, hearing impairment, myoclonus	Insulin injection	Alive
III-5	28	M	Diabetes	Insulin injection	Alive

Abbreviation: OAD, oral anti-diabetic drug.

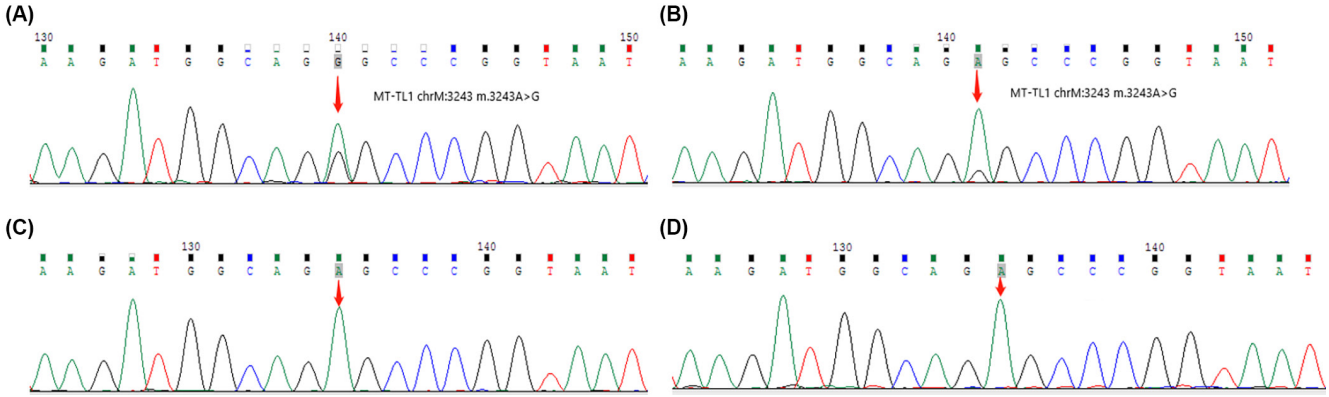

FIGURE 2 Sanger sequencing chromatogram. Arrows indicated the changed position of the mutation in the MT-TL1 gene. (A) Proband (III-1), mutant type; (B) the proband's mother (II-1), mutant type; (C) the proband's daughter (IV-1), wild type; and (D) the proband's daughter (IV-2), wild type.

TABLE 3 Detection details of the proband mt.3243A > G mutation site.

Chr	Mutation	Gene	Group	Homo/hete	sum_depth	alt_depth	alt_rate
ChrM	m.3243A > G	MT-TL1	tRNA	hete	5000	1573	34.16%

poor glycemic control, low fasting C-peptide level, and repeated ketoacidosis. Unfortunately, the patient's progressive hearing problem was largely neglected due to the fact that he was repeated hospitalizations for life-threatening ketoacidosis. Careful review of the patient's medical history and physical examination revealed that his hearing problem and diabetes had developed around the same period, and many of his maternal relatives had experienced the same situation. Further genetic testing confirmed our suspicion that the patient had MIDD with the mt.3243A > G mutation. In conclusion, the clinical features of MIDD can be characterized as follows[1]: Maternal inheritance. Almost all offspring of female patients carry the mutation, but not all of them have presentations. The offspring of male patients generally do not carry this mutation.[2] The vast majority of individuals have diabetes with the onset before the age of 40, but rarely in adolescents.[3] Most patients have normal or lean body mass, with an average BMI of less than 20 kg/m^2.[4] Most patients have negative results for islet autoantibodies.[5] Abnormalities in glucose metabolism associated with multiorgan damage. Special attention

should be paid to patients with early-onset diabetic retinopathy. According to the literature, the most common ophthalmologic feature of MIDD is typical macular retinal dystrophy.[13] Most patients with macular disease have a history of diabetes for more than 5 years and the onset is always after the age of 40 years. Early-onset diabetes and poor glycemic control may contribute to the progression of diabetic retinopathy.

The diagnosis of MIDD in suspected patients needs to be confirmed by genetic testing such as Sanger sequencing, gene chip sequencing, and high-throughput gene sequencing. Blood leukocytes are most frequently used for detection but misdiagnosis may occur due to their higher heterogeneity compared to blood leukocytes, muscle, urine,[13] and buccal mucosa.[14] Although the patient mentioned in this report had an apparent phenotype and several family members carried the mt.3243A > G mutation, his blood test results showed no mutation, which may be attributed to the heterogeneity of the specimen.

In addition to the clinical phenotype, heteroplasmy plays an important role in determining the severity of MIDD.[15] Mt.3243A > G occurs in a wide range of mitochondrial encephalomyopathies including MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) or MELAS/MERRF (myoclonic epilepsy and red ragged fibers), and overlap syndrome.[16] The proband's grandaunt (I-3), granduncle (I-4), one aunt (II-5), and one uncle (II-6) died of diabetic complications. Whether these complications contributed to their deaths is currently unknown. Compared to his mother, the proband had an earlier age of onset and a more severe presentations, even though the same mutation (A3243G) was identified. A large-scale study conducted in Finland showed that the frequency of the A3243G mutation may gradually increase in subsequent generations,[17] and we suspect that this may be the reason why the proband had a more severe presentation compared to his mother. Another previous study also showed that the frequency of mt.A3243G is negatively correlated with age.[18] A meta-analysis showed that mitochondrial heterogeneity of A 3243G is significantly associated with the incidence of diabetes, i.e., the greater the heterogeneity, the greater the probability of developing MIDD as well as an earlier age of disease onset.[19] In our experience, genetic counseling plays a crucial role in helping asymptomatic patients receive early diagnosis and prevent complications. Unfortunately, we only screened the mt.3243A > G mutation in the patient's mother and children. His other family members should also be screened for this mutation for early identification. Early screening for mutations, especially in patients with low mutation frequency, may improve treatment and prognosis and delay the onset of complications.

Due to the heterogeneity of MIDD, treatment is often challenging. Patients with MIDD tend to be lean and have insufficient energy synthesis, making them unsuitable for strict diets. Endurance training can lead to a decrease in the proportion of the mutant mitochondrial DNA; therefore, an appropriate level of exercise can improve mitochondrial function.[19] However, too strenuous exercise can easily lead to severe lactic acidosis, a fatal condition, in these patients. As for medications, individualized treatment should be considered. Of all the patients within the family, five were treated with insulin and three were treated with oral hypoglycemic agents. The use of different glycemic control regimens may be attributed to the different mutation frequencies in each patient. Although some patients may not need hypoglycemic agents at present or may only need oral hypoglycemic agents, we recommend starting insulin therapy as early as possible because mtDNA mutations may aggravate β-cell apoptosis to impair insulin secretion. As mentioned above, coQ10[20] has been added to the treatment regimen because of its capability to improve mitochondrial energy metabolism. Other drugs that can enhance mitochondrial function, such as lipoic acid[21] and thiamine may also be considered. On the other hand, some commonly used drugs should be avoided in these patients, such as tetracycline, chloramphenicol, sodium valproate, phenytoin, phenobarbital,[22] antiretrovirals,[23] statins, and metformin.[24] Because of the rapid progression of diabetic vascular complications in the proband, we specifically advised the patient not to use statins. Patients who decide to take oral hypoglycemic agents should be instructed to avoid metformin. All of the above treatments are for symptomatic relief or glycemic control, and only gene therapy can be curative. Recombinant RNA molecules have been designed to decrease the amount of the mutant mitochondrial DNA.[25] However, this technique has not been applied in clinical practice and needs further investigation.

In conclusion, MIDD is a complex disease with variable clinical features and is often misdiagnosed. Our findings indicate that whole mtDNA sequencing analysis can be used to detect the m.3243A > G mutation in the mtDNA and should be recommended for suspected patients as early as possible to provide a reference for individualized clinical management.

AUTHOR CONTRIBUTIONS

Shasha Zheng: Formal analysis; writing – original draft. **Juanjuan Wang:** Formal analysis; writing – original draft. **Minxian Sun:** Data curation; formal analysis; methodology. **Pei Wang:** Data curation; formal analysis; methodology. **Wei Shi:** Data curation; investigation. **Zhongzhi Zhang:** Data curation; investigation. **Zhongjing Wang:** Funding acquisition; project administration; supervision;

writing – review and editing. **Hongmei Zhang:** Funding acquisition; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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