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Maternally inherited diabetes and deafness (MIDD) syndrome with m.3243A>G mutation associated with renal failure — a case report

ABSTRACT

Maternally-inherited diabetes with deafness (MIDD) is a rare form of monogenic diabetes that results, in most cases, from an A-to-G transition at position 3243 of mitochondrial DNA (m.3243A>G). The clinical presentation of m.3243A>G mutation is variable, ranging from mild to severe phenotypes. Diabetes is often accompanied by sensorineural deafness, cardiomyopathy, neuromuscular, psychiatric disorders, macular dystrophy and renal failure (kidney manifestations in adults presenting with this mutation remain poorly defined).

The study presents a case of a 40-years-old woman with a history of bilateral sensorineural deafness, renal failure and diabetes that was diagnosed due to increasing muscle weakness during exercise. MIDD was diagnosed based on the clinical picture and the results of laboratory studies including genetic testing. As far as we know, glomerulopathy with incomplete distal renal tubular acidosis has never been described before as a cause of renal failure in MIDD patients. (Clin Diabetol 2020; 9; 6: 475–478)

Key words: mitochondrial diabetes, sensorineural deafness, m.3243A>G mutation, renal failure, incomplete distal renal tubular acidosis

Introduction

The relationship between the m.3243A>G mutation and maternally inherited diabetes mellitus and deafness syndrome (MIDD) was first described in 1992 by Ballinger et al. [1] Another disease associated with this mitochondrial mutation is MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) which has been described by Pavlakis et al. [2]. The prognosis for MIDD is better than in the case of MELAS syndrome and for other subtypes of diabetic mitochondrial disease. Such a number of presented phenotypes is attributed to the diverse distribution of defective mitochondria in tissues, which is associated with the level of heteroplasm. The age of the patient seems to be decisive in the development of symptoms. Diabetes is not a very common symptom in patients with the m.3243A>G (mtDNA) mitochondria mutation, it occurs only in 15% of cases [3]. However, the m.3243A>G mutation is found in only 1% of patients with diabetes in Europe [4]. In the course of MIDD syndrome, there may be development of: maculopathy, neuromuscular disorders, mental disorders and renal failure. In a multicenter study carried out in France, as

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many as 43% of MIDD patients with the m.3243A>G mutation had myopathy, 28% had kidney symptoms, 18% had neuropsychiatric symptoms, and only 15% had cardiomyopathy [5, 6].

The abnormality of glucose metabolism in MIDD is associated with a gradual decrease in insulin excretion due to reduced ATP production in pancreatic β cells with abnormal mitochondria. In MIDD, diabetes develops and hearing loss usually occurs in mid-adulthood. Most often, the disease is diagnosed between the second and fifth decades of life. This rare cause of diabetes should be suspected in the case of maternal inheritance and concomitant deafness [7]. Additional tests show normal or reduced levels of C-peptide and normal autoimmune markers [6, 8]. Most often, hearing loss occurs before diabetes. Coexistence of deafness and mitochondrial diabetes in patients with the m.3243A>G mutation is found in 60% of cases [8]. It is also suggested that after exceeding a certain threshold of mutated mtDNA, there is a disturbance in mitochondrial protein synthesis and oxygen consumption, which results in a decrease in the level of ATP (adenosine triphosphate). This may cause disturbances in the balance of ion concentrations, resulting in accelerated and disproportionate cell death in the cochlea [9]. Factors such as the percentage of mutated mitochondria in different tissues and the failure threshold of each organ are responsible for the development of organ-specific symptoms [10]. Kidney manifestations in adults with m.3243A>G mutation remains poorly defined. Here, we report a case of glomerulopathy with incomplete distal renal tubular acidosis as a cause of renal failure in MIDD patient.

Case presentation

A 40-year-old woman was admitted to the Department of Neurology, in June 2012 due to 4-year history of progressive, generalized muscle weakness and pains (the symptoms increased during exercise), initially raising suspicion of peripheral polyneuropathy.

The patient had a bilateral progressive hearing loss since 1993, she also complained of tinnitus and sporadic vertigo. In 2009 and 2012 she underwent a cochlear implantation procedure for the left and right ear, respectively.

Renal failure was diagnosed in 2002, and diabetes in 2005. She received insulin, thiazide diuretic and angiotensin inhibitor for treating hypertension since 2005. There was no history of strokes, epilepsy and mental retardation. The family history revealed diabetes in her mother and hearing loss in her daughter.

On evaluation, the patient appeared alert. In the neurological examination, slight muscle weakness of the lower limbs was found, as well as the weakening of deep reflexes. No cranial nerve damage, exteroceptive and proprioceptive sensation disturbances or symptoms of the cerebellar syndrome were observed.

In the course of neurological examination, computed tomography of the lumbar spine was performed and revealed no significant deviations. In addition, cerebral spectroscopy magnetic resonance was performed, showing a relatively increased concentration of lactates in all brain tissue (indicating a mitochondrial disease). Elevated concentration of lactic acid was found in the blood serum (lactic acid = 2.3 mmol/L). The echocardiogram examination and chest X-ray did not show abnormalities. Based on ophthalmic examination the hypertensive and diabetic maculopathy was excluded.

Due to the diagnosed renal failure accompanied by hypomagnesemia with unclear aetiology (previously undiagnosed), a decision was made to extend the nephrological evaluation.

In additional examinations (within 3 months), a doubled level of albumins excreted in the urine was also found, while the general urinalysis revealed inactive urine sediment. The patient did not agree for renal biopsy. Abdominal ultrasonography showed hypoechogenic renal pyramids with single parapyramidal calcifications. Due to the diagnosed hypomagnesemia in the blood serum and the suspected magnesium loss via the kidneys, the fractional excretion of magnesium in the urine was calculated based on the magnesium and creatinine concentration (measured in the serum and urine). Fe_{Mg}% (fractional excretion of filtered magnesium) amounted to 0.3%, which indicates a non-renal cause of hypomagnesemia (decreased delivery of food, malabsorption in the intestines). In addition, there were no other markers of proximal tube dysfunction (hypophosphatemia, hypouricemia or hypokalaemia in the blood serum). On the other hand, the increased concentration of low-molecular-weight alpha-2 macroglobulin protein seems to result from the energy dysfunction of proximal tube cells (extremely rich in mitochondria).

Based on the increased excretion of albumin in the urine, decreased excretion of citrates in the urine and an abnormal urinary pH, the patient was diagnosed with the chronic kidney disease in the course of glomerulonephritis and the incomplete distal tubular acidosis (due to the suspicion of a mitochondrial disease, the ammonium chloride loading test was omitted) (Table 1).

Mutation detection/genetic analyses

Due to suspected genetically transmitted disorder, genetic test was performed in the proband and her daughter. Total DNA was isolated from blood, hair follicles, urine sediment, nails and buccal mucosa smear

Table 1. Clinical characteristics in patient with mutation A3243G

BMI [kg/m^2]	20.0
HbA_{1c} [4.8–5.9%]	**6.4**
Magnesium [1.6–2.6 mg/dL]	**1.4**
Potassium [3.5–5.1 mmo/L]	4.6
Sodium [135–145 mmol/L]	136
PTH [17.3–72.9 pg/mL]	33.8
Phosphorus [2.6–4.5 mmol/L]	3.9
Calcium [8.6–10.2 mg/dL]	9.6
Lactic acid [0.3–1.7 mmol/L]	**2.3**
Uric acid [2.4–5.7 mg/dL]	4.0
Serum creatinine kinase [0.7–1.2 mg/dL]	1.7
eGFR using MDRD [> 60 mL/min/m^2]	40
Alfa–1 mikroglobulin [< 20 mg/dL]	12.4
Alfa–2 makroglobulin [< 2 mg/dL]	2.55
Albumin in DUC [< 30 mg/24 h]	**117.0**
Urine specific:	
Gravity [1.016–1.022 g/L]	1.020
pH [4.8–6.4]	**6.0**
Leukocytes	Negative
Glucose	Negative
Erythrocytes	Negative
Electrolyte excretion in 24 h — urine collection:	
Citrates in DUC [0.4–3.4 mmol/24 h]	**0.16**
Oxalate in DUC [0.04–0.32 mmol/24 h]	0.22
Sodium [40–220 mmol/24 h]	83.0
Potassium [25–125 mmol/24 h]	28.0
Magnesium [32–307 mg/24 h]	**2.0**
Fe_{Mg}%	0.03
Uric acid [0.5–1.0 g/24 h]	**0.1**
Calcium [100–250 mg/24 h]	**3.0**
Phosphorus [0.8–2.0 g/24 h]	**0.2**
Venous blood gas:	
pH [7.35–7.45]	**7.29**
$HC03^-$ [21–25 mmol/L]	23.9
BE [from –2 to 2]	–2.5

BMI — body mass index; DUC — daily urine collection; HbA_{1c} — hemoglobin A_{1c}; eGFR — estimated glomerular filtration rate; MDRD — modification of diet in renal disease; FeMg% — fractional excretion of filtered magnesium

Table 2. Level of the heteroplasmy for m.3243A>G mutation

% of the 'G' allele					
Muscle	Blood cells	Hair follicles	Urine	Nail	Cheek mucosa
NA	12.6	33.1	54.7	6.7	5.6

*NA indicates that the sample was not obtained

according to standard protocols. Detection of the m.3243A>G was performed with a Real Time TaqMan assay on Demand (Applied Biosystems, Foster City, CA). Assessment of the heteroplasmy level was based on the PCR-RFLP method as previously described [15]. The analysis revealed pathogenic m.3243A>G mutation in the *MT-TL1* gene ($tRNA^{leu}$). The mutant mtDNA was distributed heteroplasmically in different tissues, with the highest proportion found in the urine sample (Table 2). On the basis of performed analysis the diagnosis of maternally inherited diabetes with deafness, i.e. MIDD syndrome with accompanying glomerulopathy and incomplete distal renal tubular acidosis was established.

Discussion

Some reports suggest a relation between m.3243A>G mutation and renal failure which typically occurs in the mean age of 35 years [11]. Renal biopsy usually reveals focal and segmental glomerulosclerotic (FSGS) changes most often of steroid-resistant type and tubulointerstitial nephropathy. The renal biopsy was not performed in our patient due to the significant reduction of the kidney cortex. Therefore, the precise diagnosis of glomerulopathy could not be made. However, the lack of renal biopsy did not influence the tubular disorders diagnostic as well as the therapeutic procedure.

Changes in renal glomerulus are not specific for those found in diabetes type 2. Diabetes is usually recognized a few years after the diagnosis of renal failure is made. It took place also in our patient - the diagnosis of renal insufficiency was made 3 years prior to diagnosis of diabetes. It means that the increased glucose concentration could accelerate renal disease only after the diabetes was diagnosed. Additionally the decreased number of abnormal mitochondria in renal tubules and podocytes are observed [11]. Patients with dominant damage of renal glomerulus have clinically significant proteinuria. The m.3243A>G mutation is observed in some patients with FSGS of unknown cause in which other systems are not affected. According to Löwik et al. [12] the steroid-resistant nephrotic proteinuria is also common in these patients. On the other hand, Hott et al. [13] reported FSGS with m.3243A>G mutation that proceeded with non-nephrotic proteinuria. Based on the screening examination of m.3243A>G mutation in patients who had a history of maternally inherited diabetes, sensorineural hearing loss, Jansen et al. reported a few patients who incurred from progressive non-diabetic kidney disease [4]. In another patients with possible Alport syndrome, the m.3243A>G mutation was detected [2]. Both proximal and distal tubules were affected due to m.3243A>G mutation. Proximal tubular dysfunction with Fanconi syndrome is the most

frequent presentation due to mitochondriopathy, less often, nonspecific chronic tubulointerstitial disease [14].

Management of patients with MIDD is symptomatic. Pharmacological treatment based on oral antidiabetic agents or insulin therapy and coenzyme Q10 (supplementation has been proposed). Non-pharmacology treatment consists of avoiding excessive physical activity and dehydration. Treatment of MIDD should be initiated at an early stage, since complications may lead to renal disease and electrolyte disturbances in the case of incomplete distal renal tubular acidosis.

Conclusion

It is the first case of a MIDD patient diagnosed with renal failure due to glomerulopathy and incomplete distal renal tubular acidosis. The described case is an example of a diagnostic challenge combined with a diagnosis of mitochondrial aetiology of diabetes. Making an early diagnosis is important because of unique management issues and associated comorbidities.

The genetic test performed in mother and daughter in 2012 confirmed the presence of the same maternal mutation in both patients and allowed the early diagnosis of disease in daughter.

This is particularly important in terms of differentiating the causes of renal failure and its prevention in MIDD patients with m.3243A>G mutation (here exemplified by the patient's daughter).

The diagnosis would not be possible without genetic test. It should be also underlined that the genetic engineering role and usefulness in medicine is increasing.

Competing interests

The authors declare that they have no competing interests.

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