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Exceptional Case

A deaf mother and son with diabetes and renal failure

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Abstract
Chronic renal failure is a well-known complication of long-standing diabetes. Moreover, audiological abnormalities are a common feature of patients with end-stage renal disease. Severe deafness, however, is not a typical symptom in most patients with chronic renal failure and likewise in patients with diabetes mellitus. In this case report, we describe a young patient with insulin-dependant diabetes mellitus, severe deafness requiring hearing aid and chronic renal failure outlining typical clinical features of the maternally inherited diabetes with deafness syndrome. Genetic testing confirmed the presence of the m.3243A>G mutation.

Keywords: deafness; maternal inherited diabetes with deafness; renal failure

Introduction

Maternally inherited diabetes with deafness (MIDD) is a rare monogenic form of diabetes mellitus caused by the m.3243A>G mutation in the mitochondrial genome [1]. In clinical practice, bilateral hearing impairment due to a decreased perception of high-tone frequencies >5 kHz and familial clustering with maternal transmission of diabetes are characteristic features of MIDD. Macular pattern dystrophy, myopathy, cardiomyopathy, neuropsychiatric abnormalities and renal dysfunction are other clinical comorbidities often associated with the disease. Although phenotypic expression is variable with gradually developing symptoms, most patients will have insulin-dependant diabetes and sensorineural hearing loss by the ages of 30–40 years [2]. From the clinical point of view, MIDD shares some characteristic symptoms with the Alport's syndrome though diabetes is not a typical feature of the diagnosis [3]. Prior to definitive diagnosis, patients with MIDD are classified as having Type 1 or Type 2 diabetes owing to the clinical variability and grade of insulin deficiency. Monogenic forms of diabetes comprise various forms of the maturity-onset diabetes of the young (MODY) as well. Besides familiar clustering of diabetes in patients with MODY, there is no characteristic high-tone frequency loss, no progressive loss of insulin secretion and, particularly, no other systemic comorbidity [4]. At last, final proof is provided only by genetic analysis.

In this case report, we describe a young patient with a long-standing insulin-dependant diabetes and severe deafness requiring a hearing aid which started already before diabetes manifestation. A diagnosis of MIDD had not yet been made but was the suspected diagnosis given his typical familial and medical history. Our patient was admitted as an emergency case after suffering from syncopation and was evaluated by the nephrology service due to hyperkalaemia in new-onset renal failure.

Case summary

A 45-year-old male patient was admitted to the hospital as an emergency case after suffering from a first syncopation. His past medical history was remarkable for insulin-dependant diabetes classified as Type 2 diabetes. Diabetes was diagnosed at the age of 35 years and treated with fixed doses of long- and short-acting insulin (30% solved insulin and 70% isophan insulin). This rather simplified insulin regimen was chosen owing to his severe hearing impairment leading to worse training results and consequently to worse blood glucose control.

Profound bilateral hearing loss requiring a hearing aid started at the age of 30 years. Furthermore, the patient developed hypertension with 41 years of age. His family history was notable with regard to his mother, who died at the age of 58 years suffering from diabetic nephropathy and on maintenance haemodialysis. Interestingly, severe and progressive hypacusis was present in her case as well (Figure 1). The patient's sisters, however, were reportedly healthy and childless. At that point, a diagnosis of MIDD was suspected based on the former medical and familial history and genetic testing was recommended.

Clinical examination revealed a body mass index of 18.5 kg/m^2, blood pressure 120/70 mmHg, pulse rate 90 beats/minute, soft systolic murmur Grade 2 and complete bilateral deafness in the absence of his hearing aid. No peripheral oedema or visual impairment was present at admission and likewise lung auscultation and percussion were normal.
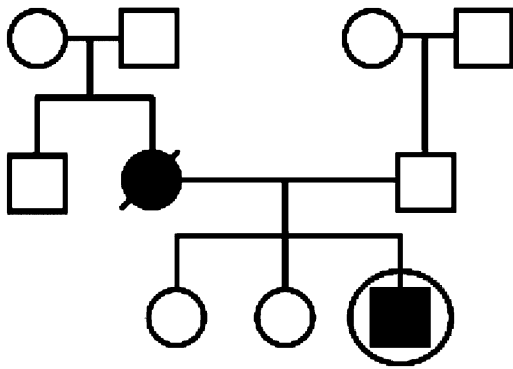
Fig. 1. Family pedigree: open symbols indicate subjects without diabetes; quadrangles indicate male and circles female subjects. Black quadrangle with circle indicates the patient tested positive for MIDD, black circle his mother deceased at the age of 58 years.

His home medications included fixed doses of long- and short-acting insulin (30% solved insulin and 70% isophan insulin, 10 U twice daily), amlodipine, ramipril and hydrochlorothiazide for treatment of hypertension.

Pathological admission laboratory data included creatinine 2.3 mg/dL (normal range 0.1–1.3 mg/dL) correlating with a glomerular filtration rate of 35 mL/min according to the Modification of Diet in Renal Disease, total protein urine 1.8 g/24 h (normal < 0.25 g/24 h), potassium 7.98 mmol/L (normal range 3.5–4.8 mmol/L), sodium 133 mmol/L (normal range 135–145 mmol/L), calcium 2.06 mmol/L (normal range 2.1–2.65 mmol/L) and HbA1c 9.1% (normal < 6.1%). The remainder of the laboratory evaluation was normal, islet cell antibodies and antibodies to glutamic acid decarboxylase included.

Abdomen sonography was reportedly normal except for small cystic abnormalities of renal parenchyma and normal-sized kidneys. However, echocardiography revealed a restrictive cardiomyopathy.

To clarify the pathogenesis of the new-onset renal failure, a renal biopsy was performed. Results showed focal glomerular and interstitial scarring interpreted as benign nephrosclerosis along with diabetic glomerulosclerosis with obsolescence of 8 of 14 glomeruli. Immunohistology (IgA, IgG, IgM, C3c, fibrin/fibrinogen) revealed only uncharacteristic deposits of IgM and C3c. Electron microscope evaluation showed an increase of the mesangial matrix in the glomerular capillaries along with an enlargement of the basal membrane. Mitochondrial abnormalities were not noticed. Histologically, a diagnosis of diabetic and hypertensive nephropathy was made owing to poor control of persisting diabetes and hypertension.

Finally, genetic testing revealed the m.3243A>G mutation in 28% of leucocytes in a peripheral blood sample confirming the diagnosis of MIDD.

Discussion

Bilateral hearing impairment and familial clustering of diabetes are the strong clinical indicators for the MIDD syndrome [1]. However, a wide range of additional or distinct clinical phenotypes can be noticed despite sharing the same m.3243A>G mutation in the mitochondrial genome. This is thought to be a result of the degree of heteroplasmy and distribution in different tissues [2, 5]. As was the case in our patient, clinically, the most pathognomonic features, diabetes and hearing loss, usually develop gradually over years making it easier to diagnose MIDD in retrospect.

Besides secondary renal abnormalities due to diabetic nephropathy as in our patient, there is some evidence of a specific renal involvement and failure in MIDD. Nevertheless, no pathognomonic histomorphological abnormalities are described yet but focal segmental glomerulosclerosis seems to occur more often [6]. Sometimes, mitochondrial abnormalities can be seen even directly in podocytes on electron microscopy [6].

As patients with Alport's syndrome share some clinical symptoms with MIDD, genetic testing for the m.3243A>G mutation in patients given the diagnosis of Alport's syndrome revealed a few cases of undiagnosed MIDD [3]. Noteworthy, haematuria is a key feature of Alport's syndrome in contrary to MIDD-associated nephropathy [6].

Even in a Japanese dialysis population with diabetic nephropathy, testing for the m.3243A>G mutation showed an unexpected frequency of the mutation of 5.9%, which is thought to be a selection bias [7]. In Europe, however, the frequency of MIDD in the diabetes population is estimated to be ~1% contrasting with higher frequencies in Japan [8, 9]. Random screening of blood samples intended for measuring HbA1c in Holland quantified a rate of 1.3% of the m.3243A>G mutation [4]. The frequency of mitochondrial DNA mutations in the general population seems to be as high as 1:200 with m.3243A>G as the most common mutation [10], and estimates from diabetic or dialysis subgroups are presumably overrated.

In addition to genetic testing in leucocytes of peripheral blood, urine analysis offers a very suitable method to detect the m.3243A>G mutation and amount of heteroplasmy, which is indeed a better predictor of clinical outcome in patients with neurological symptoms [11].

Of note is the therapeutic implication of metformin in patients with MIDD who are classified with diabetes Type 2. Metformin is contraindicated because of the risk of lactate acidosis in mitochondrial diseases, whereas sulphonylurea or changes in diet are alternative treatment options at the beginning of the disease [4].

Our case illustrates the value of a detailed medical and family history taking as it can help in the diagnosis of rare subtypes of diabetes on clinical suspicion alone. Although having been given a diagnosis of diabetes before an evolving syndromal pattern of deafness, renal failure and syncopation due to a restrictive cardiomyopathy and hyperkalaemia was finally evident. From the clinical point of view, hearing loss, diabetes, renal failure and a positive family history are strong indicators for a diagnosis of MIDD. Consequently, genetic testing should be done at an early stage of the diagnostic process at the time of emerging pathognomonic features in an individual or in the context of familiar clustering.

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