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Exceptional Case

EXCEPTIONAL CASE

Diabetes, deafness and renal disease

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Abstract

Deafness, kidney disease and diabetes are not a usual association, neither is a family history of these diseases. We present the case of a 47-year-old woman with non-nephrotic proteinuria, no haematuria, normal renal function, sensorineural hearing loss, recently diagnosed diabetes and maculopathy. There was a maternal family history of deafness, diabetes and renal disease. Renal biopsy revealed focal and segmental glomerulosclerosis (FSGS), leading to the pursuit of an m.3243A > G mitochondrial mutation and diagnosis of maternally inherited diabetes and deafness. The association of FSGS with mitochondrial diseases is not well known among nephrologists. Its timely diagnosis is important to avoid exposure to ineffective and unnecessary immunosuppression.

Key words: diabetes mellitus, FSGS, gene expression, maternally inherited diabetes and deafness, renal biopsy

Background

Deafness and kidney disease as well as diabetes and kidney disease are associations of which the nephrologist is well aware. However, the concomitance of the three is not usual, neither is a family history of these diseases.

Case report

A 47-year-old Caucasian woman with a history of progressive bilateral sensorineural deafness and hypertension was referred to the nephrology outpatient clinic due to persistent non-nephrotic-range proteinuria (1–2 g/day). Renal function was normal and no haematuria was found. At this time, the patient was also diagnosed with dyslipidaemia and diabetes mellitus, and she was started on statins and metformin. Her body mass index (BMI) was normal and ophthalmologic evaluation showed macular dystrophy but no signs of diabetic retinopathy. Careful analysis of the medical family history revealed a background of diabetes, deafness and renal disease, with diabetes and deafness reported in five out of eight affected individuals (Figure 1).

Despite anti-proteinuric measures, the patient's proteinuria progressed to being overtly nephrotic and a renal biopsy revealed focal and segmental glomerulosclerosis (FSGS) not otherwise specified (NOS) with 2/8 glomeruli with global sclerosis and 3/8 with segmental sclerosis. Immunofluorescence identified deposits of C1, C3 and C4 (++) and IgM (+++) in the segmental lesions; non-sclerotic glomeruli showed no deposits. Skin biopsy showed a normal immunostaining pattern for alpha-5 chains of type IV collagen, virtually excluding the diagnosis of X-linked Alport syndrome. While genetic study for maternally inherited diabetes and deafness (MIDD) was underway, the patient developed symptomatic nephrosis. Prednisolone 1 mg/kg/day was started and maintained during 8 weeks with no response and with side effects leading to progressive downward taper. Completion of the genetic study revealed mutated

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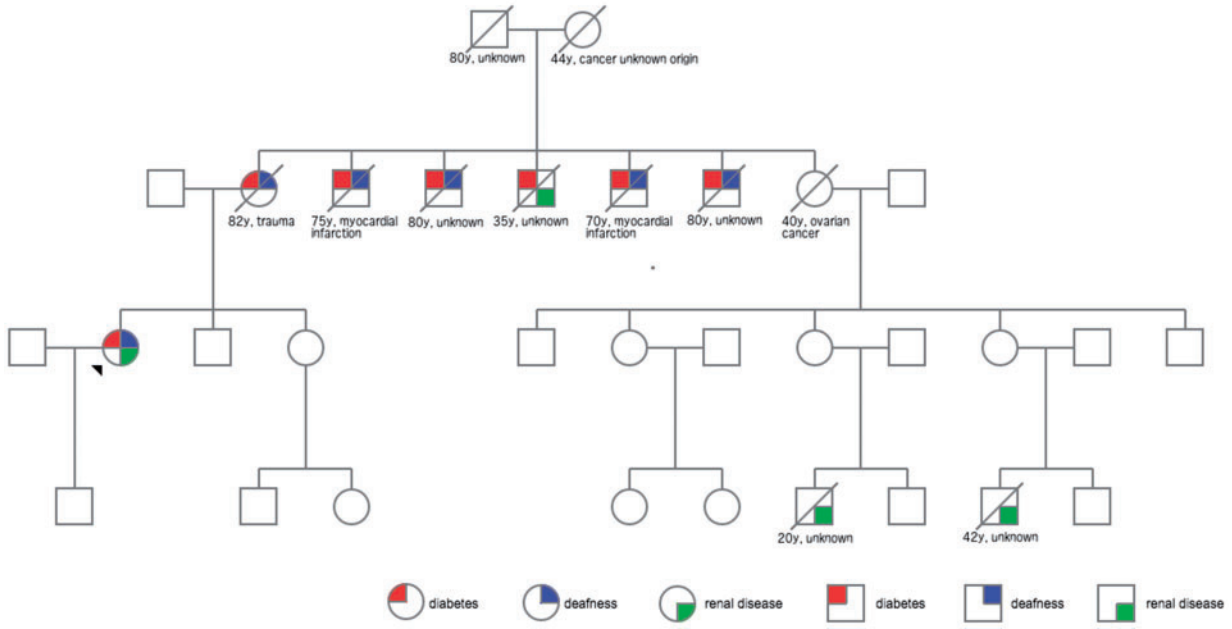

Fig. 1. Partial pedigree of the patient's family, specifically reporting diabetes, deafness and renal disease. Squares represent males, circles represent females. The arrowhead indicates the proband and deceased individuals are identified by slashes. Age and cause of death is presented next to each deceased family member. None of the affected individuals had history of cerebrovascular, ophthalmological, cardiac or neuromuscular complications attributable to the m.3243A > G mutation. In agreement with the maternal inheritance of MIDD, none of the offspring of the proband's five maternal uncles manifested diabetes, deafness or renal disease.

m.3243A > G mitochondrial deoxyribonucleic acid (mtDNA) in heteroplasmy. The ultrastructural renal study, not done initially, identified enlarged dysmorphic mitochondria with loss of cristae (Figure 2). Additional studies revealed hypertrophic myocardiopathy. No further immunosuppression was prescribed, metformin and statins cessation was encouraged and coenzyme Q10 was started. At this moment, under supportive antiproteinuric therapy and coenzyme Q10, the patient maintains normal renal function with serum creatinine of 78 μmol/L (0.9 mg/dL) and proteinuria reduced from 2–3 g to 655 mg/day.

Discussion

Mitochondrial diseases constitute a rare group of disorders where renal involvement is rare, although possible. This is the case of MIDD, a mitochondrial disease in which patients present with diabetes and sensorineural hearing loss. Diabetes in most patients presents insidiously, mimicking type 2 diabetes, although up to 8% of MIDD cases can present as type 1 depending on the severity of insulinopaenia. In MIDD, as insulin sensitivity is normal, metformin is less effective than in type 2 diabetic patients and can be detrimental due to an increased risk of lactic acidosis. Almost all organs can be involved in MIDD, namely causing cardiomyopathies and pigmented macular dystrophy [1, 2]. Although tubular cells are the most frequent renal targets [1], renal involvement has been reported mostly in the form of FSGS [2]. In MIDD-related FSGS, no subtype is predominant and the patient usually has non-nephrotic-range proteinuria with scarce response to antiproteinuric measures. Almost half of patients are on dialysis 10 years after diagnosis [1]. Due to the association of renal disease and deafness sometimes patients are misdiagnosed with Alport syndrome [3]. The absence of haematuria in MIDD can aid in the differential diagnosis between these two entities. In 85% of cases, the genetic cause for MIDD is the m.3243A > G point mutation in mtDNA [4]. Additionally, prevalence of MIDD between diabetic patients has been estimated in 0.5–2.8%, highlighting MIDD as an important differential diagnosis in diabetic patients with renal disease. Maternal inheritance, absence of diabetic retinopathy, a normal BMI and typical retinal dystrophy may lead to suspicion of MIDD. Although MIDD is the most common clinical presentation, the phenotypic spectrum associated with the m.3243A > G mutation also includes mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, chronic progressive external ophthalmoplegia and cardiomyopathy. The molecular basis of the phenotypic diversity of mitochondrial disorders is not well understood, but the phenomenon of mtDNA heteroplasmy (i.e. co-occurrence of the mutant allele and the wild-type allele in mitochondria), leading to varying ratios of wild-type to mutant mtDNA in different tissues, might be a major factor.

Although the association of FSGS with mitochondrial diseases is rare, it is essential to any nephrologist to be aware of its existence and to perform a thorough anamnesis and physical exam. Unfortunately, specific treatments are unknown for the majority of mitochondrial diseases, including MIDD [4]. Whereas supplemental oral coenzyme Q has been shown to be effective in mitochondrial diseases caused by mutations on the coenzyme Q10 biosynthesis, in MIDD it has shown conflicting results [1, 5]. The correct diagnosis allows family screening and proper follow-up, and spares the patient the inadequate use of immunosuppression considered for idiopathic FSGS and other potentially harmful therapies such as metformin and statins. Hopefully, the intense research currently underway for these diseases will eventually produce effective treatment possibilities in the near future. This case underlies the importance of considering a mitochondrial disease in a case of deafness, diabetes and renal disease with proteinuria, especially in the presence of a maternal family history of these diseases.

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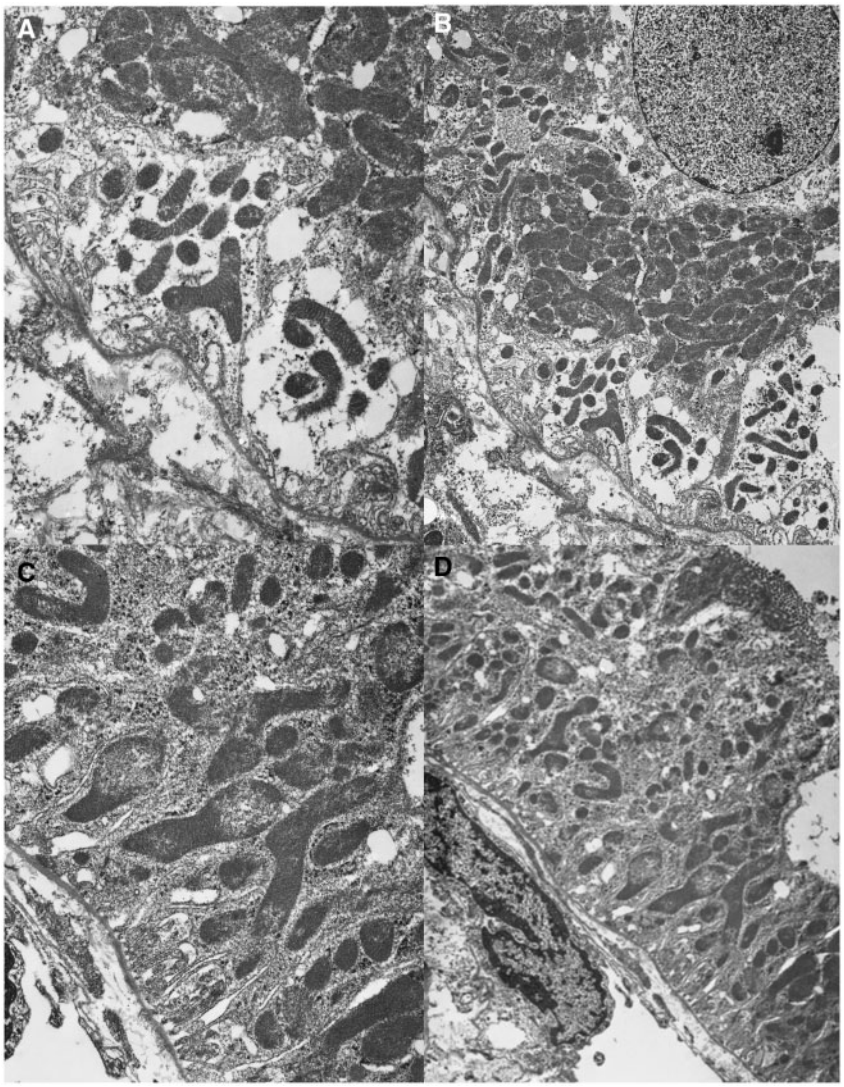

Fig. 2. Ultrastructural study of patient's renal biopsy shows tubular epithelial cells with mitochondrial proliferation (panel B and D, magnification 5000×) and enlarged dysmorphic mitochondria with loss of cristae (panel A and C, magnification 10000×).

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Conflict of interest statement

None declared.

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