




ORIGINAL ARTICLE

Five non-mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes phenotype adult patients with m.3243A>G mutation after kidney transplantation: follow-up and review of the literature

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ABSTRACT

Background. Renal involvement in patients with the m.3243A>G mutation may result in end-stage renal disease (ESRD) requiring renal replacement therapy. Although kidney transplantations have been performed in a small number of patients, short- and long-term follow-up data are lacking.

Methods. We describe five patients with the m.3243A<G mutation who received a kidney transplant, including follow-up data up to 13 years. We also summarize all cases ($n = 13$) of kidney transplantation in m.3243A>G carriers described in the literature.

Results. Proteinuria with or without renal failure was the first clinical presentation of renal involvement in 13 of 18 (72%) patients. Focal segmental glomerulosclerosis (FSGS) was found in 9 of 13 (69%) biopsies. Sixteen of 18 (84%) patients developed hearing loss. All patients were diagnosed with diabetes mellitus, of whom eight (44%) developed the disease after transplantation. All patients with reported follow-up data (13/18) had stable kidney function from 6 months to 13 years of follow-up after transplantation.

Conclusions. Renal involvement in carriers of the m.3243A>G mutation most commonly leads to proteinuria and FSGS and may lead to ESRD. Proper recognition of the mitochondrial origin of the renal disease in these patients is important for adequate treatment selection and suitable supportive care. This case series and review of the available literature on long-term follow-up after kidney transplantation shows it is feasible for non-mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes phenotype carriers of the m.3243A>G mutation to be considered for kidney transplantation in case of ESRD. These patients should not be excluded from transplant solely for their mitochondrial diagnosis.

Keywords: encephalomyopathy, kidney transplantation, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, m.3243A>G mutation, maternally inherited diabetes deafness (MIDD), mitochondrial disease, mitochondrial myopathy

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INTRODUCTION

Solid organ transplants are rarely performed in adult and paediatric patients with primary mitochondrial disease. It is unclear whether the underlying genetic disease has a significant impact on post-transplant morbidity and mortality.

Mitochondria

Mitochondria play an important role in cellular energy supply via the oxidative phosphorylation system (OXPHOS) producing adenosine triphosphate. Mitochondrial dysfunction can result from mutations in either nuclear DNA or mitochondrial DNA (mtDNA). The 37 genes of the mitochondrial genome encode for 22 transfer RNAs (tRNAs), 2 ribosomal RNAs and 13 subunits of the OXPHOS complexes I, III, IV and V. Nuclear genes encode the remaining 75 structural proteins of the OXPHOS [1, 2]. Human mitochondria number per cell varies.

m.3243A>G mutation

The acronym MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) was first used in 1984 by Pavlakis *et al.* [3] to describe a group of patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. In 1990, the adenine to guanine transition at position 3243 of mtDNA (m.3243A>G) in the MT-TL1 gene-encoding tRNA^{LEU(UUR)} was found as the molecular basis for this disease [4, 5]. The m.3243A>G mutation in the MT-TL1 gene is the most common cause of MELAS syndrome, therefore the mutation is also known as the MELAS mutation. As this particular mutation—in the literature it is still referred to as the MELAS mutation—causes many different phenotypes, non-mitochondrial experts might get confused and draw inappropriate conclusions by searching literature with the term MELAS instead of m.3243A>G or alternative descriptions. This is exemplified by the fact that the mutation is also associated with diseases and conditions like maternally inherited diabetes deafness (MIDD) [6], hypertrophic cardiomyopathy [7], macular dystrophy [8], focal segmental glomerulosclerosis (FSGS) [9], chronic progressive external ophthalmoplegia [10], gastrointestinal involvement [11], increased risk of obstetric complications [12] and oligosymptomatic variants of MELAS [13].

Renal involvement in the m.3243A>G carriers

Renal involvement is often seen in patients carrying the m.3243A>G mutation. In children, renal involvement is seen in up to 50% of patients. Proximal tubular dysfunction, including Fanconi syndrome, is the most frequent clinical and pathological finding in biopsies [14]. In general, renal disease is part of a severe multi-organ disease in children with the m.3243A>G mutation, often with a poor prognosis [15]. In adults, ~30% of the m.3243A>G mutation carriers have renal involvement [16]. The course of renal involvement varies from mild proteinuria to end-stage renal disease (ESRD) requiring renal replacement therapy. Pathological findings correspond with FSGS in ~79% of patients [17]. Other findings are tubular dysfunction and severe hyaline changes within cytoplasm of smooth muscle cells of afferent arterioles and small arteries [17, 18].

Two interesting hypotheses have been described about the pathophysiology of the development of renal disease in patients with mitochondrial disease. First, the role of

podocytes [17, 19, 20]. These are terminally differentiated cells that are unable to segregate mutant mtDNA between daughter cells so they are unable to undergo regenerative proliferation in response to cell loss. The second hypothesis suggests that vascular changes may contribute to the development of FSGS. The damaged vessel wall is characterized by hyaline changes in the cytoplasm of smooth muscle cells in afferent arterioles and small arteries showing signs of necrosis and apoptosis. In the end, vascular damage results in the loss of renal autoregulation [18]. Dysfunction of mitochondria in smooth muscle and vascular endothelial cells might cause early vascular damage [9].

When renal disease occurs, comorbidity includes (sensorineural) hearing loss, cardiomyopathy and diabetes mellitus. In previous literature, patients were misdiagnosed with Alport syndrome although they did not have haematuria [21]. In patients with the m.3243A>G mutation, steroid treatment for proteinuria or nephrotic syndrome is ineffective and may induce or progress the development of myopathy and diabetes [9, 17, 22]. This may be due to the fact that symptoms are caused by mitochondrial alterations and nephron loss of vascular origin. After a period of time, some patients require renal replacement therapy. So far, only 13 patients carrying the m.3243A>G mutation that received a kidney transplant have been described [17, 18, 21, 23–25]. In this article we describe five patients from our Nijmegen cohort of carriers of the m.3243A>G mutation who received a kidney transplant, with special attention on the follow-up. Second, we review the patients in previously reported case reports who received a kidney transplant. Finally, we discuss the effects and possible side effects of kidney transplantation in these patients.

MATERIALS AND METHODS

Patients

In the Radboud Center for Mitochondrial Medicine, patients harboring the m.3243A>G mutation that underwent kidney transplantation were identified. The mitochondrial diagnoses were confirmed by DNA analysis using blood and urine samples. Five unrelated adult patients received a kidney transplant. We describe their cases using information from their medical records.

Mutation analysis and quantification of heteroplasmy levels

Heteroplasmy levels were determined in urinary epithelial cells in all participants using Pyrosequencing technology (Pyrosequencing, Uppsala, Sweden) as described earlier by Lowik *et al.* [9]. The pyrosequence reaction of the m.3243A>G mutation had a precision of 1.5% and the mutation was detected from a heteroplasmy level of $\geq 5\%$ [26].

Literature research

The search for available literature on kidney transplantation in patients with the m.3243A>G mutation was performed using online databases (PubMed, Cochrane, Web of Science) using the following keywords: MELAS, MIDD, renal transplantation, kidney transplantation, A3243G, m.3243A>G mutation, renal insufficiency, chronic kidney disease. We also included Medical Subject Headings terms if possible. Additional relevant articles were found using the references from the retrieved articles.

RESULTS

Case reports

Case 1. The first patient is a 47-year-old female who first presented with renal symptoms during pregnancy at the age of 31 years. A caesarean section was performed due to signs of pre-eclampsia and foetal distress at 27 weeks amenorrhoea. Simultaneously she was diagnosed with nephrotic syndrome. Renal biopsy showed FSGS. The nephrotic syndrome was treated with prednisone, cyclophosphamide and plasmapheresis without any improvement. Four years later the patient was diagnosed with mitochondrial disease due to the m.3243A>G mutation, with a heteroplasmy level in leucocytes of 25%. She developed diabetes, possibly provoked by the high doses of prednisone. Haemodialysis was started at the age of 35 years. Three years later the patient received a kidney transplant from a post-mortem donor. Afterwards she showed no signs of rejection or side effects due to the immunosuppressive medication. Shortly after transplantation, the diabetes became persistent and was hard to regulate properly. Besides the renal complications of the m.3243A>G mutation, the patient also suffers from minor perceptive hearing loss, maculopathy, severe hypercholesterolaemia with intolerance for statins and possibly related sensorimotor axonal polyneuropathy. Recently she developed hypertrophic cardiomyopathy. Eight years after transplantation, kidney function is still stable without any signs of proteinuria. For immunosuppressive therapy, she uses prednisone and mycophenolate mofetil.

Case 2. The second case is a 48-year-old male who first presented with proteinuria at the age of 25 years. Seven years later, proteinuria deteriorated and the patient's creatinine level increased, leading to renal failure. Biopsy was consistent with FSGS. He developed diabetes, which was difficult to manage. At the age of 36 years, the patient received a kidney transplant from his human leucocyte antigen-matched brother. One year post-transplantation, the m.3243A>G mutation was detected, with a heteroplasmy level in leucocytes of 25%. After transplantation and using high doses of prednisone, the patient's diabetes became insulin-dependent and was even more difficult to manage. Six years after transplantation, he was diagnosed with moderate perceptive hearing loss and started using hearing aids. In the same period, the ophthalmologist found mild cataract and retina pigment epithelial alterations, but no signs of diabetic retinopathy. Ten years after transplantation, the patient is still using cyclosporine and prednisone. He has left ventricle hypertrophy and obstructive sleep apnoea. His kidney function is stable without any signs of proteinuria.

Case 3. The third patient is a 41-year-old female. She developed pancreatitis at a young age with recurrent episodes. Kidney dysfunction became apparent at the age of 17 years. Kidney biopsy showed signs of chronic ischaemia. At the age of 20 years, the patient was diagnosed with mitochondrial disease based on a complex I enzyme deficiency in muscle; at that time genetic investigation was not performed. At the age of 27 years, the patient was diagnosed with ESRD. Later that year, at the age of 28 years, she received a kidney transplant from a post-mortem, heart-beating donor. Before leaving the hospital, renal function was normal and there was no sign of proteinuria. Two years after transplantation, cyclosporine was stopped without complications. She is still using prednisone and mycophenolate mofetil as immunosuppressants. Four years after transplantation,

the patient started to develop non-insulin-dependent diabetes, but it was not until 8 years post-transplantation that mtDNA investigation confirmed the m.3243A>G mutation at the age of 36 years, with a heteroplasmy level in leucocytes of 35%. The patient's mother and sister were also diagnosed with the m.3243A>G mutation.

Case 4. The fourth patient is a 57-year-old female. As a child, the patient was treated for epilepsy until she was 10 years old. At the age of 31 and 33 years, the patient gave birth to two children. During both pregnancies she suffered from haemolysis, elevated liver enzymes and low platelets syndrome. At the age of 40 years, proteinuria was detected (2.2 g/L). The patient also developed sensorineural hearing loss and started to use hearing aids. In the same year, she also developed diabetes mellitus, which was treated at first with oral medication. At the age of 41 years, renal failure, proteinuria and hypertension were present. Kidney biopsy 3 years later showed immunoglobulin A (IgA) nephropathy and no signs of Alport disease. At the age of 49 years, the renal failure and proteinuria were treated with prednisone, but did not improve, necessitating peritoneal dialysis. Simultaneously the patient's diabetes became insulin dependent. At the age of 52 years, the patient received a kidney transplant from a postmortem, heart-beating donor. Follow-up after 2 years showed severe left ventricle hypertrophy and diastolic heart failure that remained stable 4 years after transplantation. Four years post-transplantation, the m.3243A>G mutation was found, with a heteroplasmy level in leucocytes of 6%. In the same year, the patient was diagnosed with central scotoma causing visual problems. Currently the kidney function is stable with mild microalbuminuria. She is using prednisone and tacrolimus as immunosuppressants.

Case 5. The fifth patient is a 43-year-old female who was diagnosed with diabetes at the age of 13 years. At the age of 21 years, her first pregnancy was complicated by an intrauterine fetal death. At the age of 23 years, a healthy daughter was born with a planned caesarean section. She developed diabetic retinopathy and nephropathy at the age of 28 and 29 years, respectively. The patient suffered from hypertrophic cardiomyopathy, leading to heart failure at the age of 35 years. Two years later, haemodialysis was started. In the same year, the patient received a kidney transplant from her brother complicated by a non-ST segment elevation myocardial infarction acute coronary syndrome 3 days later. One month later, creatinine levels were increasing, showing signs of transplant rejection for which treatment with intravenous methylprednisolone was started. During the treatment, a second acute coronary syndrome occurred. Later she was admitted to the hospital because of sepsis caused by a *Staphylococcus aureus* infection. After treatment with flucoxacillin, creatinine levels increased and treatment with methylprednisolone was started again. Kidney function was not improving, and for that reason she was treated with antithymocyte globulin (ATG) four times. During this treatment, the patient suffered from a third acute coronary syndrome. A year after the ATG treatment, the immunosuppressive treatment was switched from triple therapy to sirolimus and azathioprine. At the age of 40 years, 3 years after transplantation, the m.3243A>G mutation was found as part of a family survey, after her niece was diagnosed with the same mutation. The heteroplasmy level in leucocytes was 16%. Further genetic investigation within the family showed that the patient's sister and mother of the niece also carried the m.3243A>G mutation. Almost 5 years after transplantation, the patient has stable

moderate kidney function (Modification of Diet in Renal Disease estimated glomerular filtration rate 17 mL/min/1.73 m²) without any signs of proteinuria.

Summary of characteristics of all patients

In the literature, we found six articles describing cases of patients with the m.3243A>G mutation who received kidney transplantation. The characteristics of our patients and the previously reported cases are summarized in Table 1. All patients successfully received kidney transplantation. We found that proteinuria with or without renal failure was the first clinical presentation of renal involvement in 13 of 18 (72%) patients. FSGS was found in 9 of 13 (69%) biopsies. Sixteen of 18 (89%) patients developed hearing loss. All patients were diagnosed with diabetes mellitus, eight of whom (44%) developed the disease after transplantation. All patients for whom follow-up data were reported (11/18) had stable kidney function at 6 months to 13 years of follow-up.

DISCUSSION

We describe five not yet reported patients with the m.3243A>G mutation who received a kidney transplant. We also summarized 13 cases of patients with the same mitochondrial mutation described in the literature so far, providing an overview of 18 post-kidney transplantation patients carrying the m.3243A>G mutation. While mitochondrial disease patients may have a shortened life expectancy due to progression of their underlying disease, successful kidney transplantation, when feasible, allows for additional years of likely functional survival.

Clinical phenotype and follow-up

MELAS syndrome is one of the possible phenotypic presentations of the m.3243A>G mutation in the *MT-TL1* gene and probably one of the most acknowledged. However, in previous reports about the phenotypic expressions in carriers of the m.3243A>G mutation, MELAS syndrome represents only a small proportion of the clinical spectrum [13, 27]. Although all 18 patients described in this article carried the m.3243A>G mutation, none had the typical phenotypic presentation of MELAS syndrome with stroke-like episodes. The phenotypic spectrum of the 18 patients described in this article is clinically heterogeneous. In 72% of patients, proteinuria with or without renal failure was the first renal symptom. All patients developed diabetes, and nearly all developed hearing loss (which combined is known as MIDD). Other symptoms that were present include retinal dystrophy, cardiomyopathy and myopathy. Three of 14 women had obstetric complications, including pre-eclampsia and foetal death. In these cases, the obstetric complications were the first sign of mitochondrial disease, especially the first presentation of renal involvement in the form of proteinuria and hypertension. In general, the classic MELAS phenotype is associated with a poor outcome [28]. This could be seen as a reason to withhold kidney transplant in these patients if they develop ESRD. However, in this study we report on 18 cases of patients carrying the m.3243A>G mutation, with a non-MELAS phenotype, with an average follow-up of 5.6 (range 0.5–13) years after transplantation. This indicates that in a selection of patients carrying the m.3243A>G mutation, kidney transplantation is feasible.

Biopsy

Nine of 13 (69%) patients' kidney biopsies showed FSGS. Diabetic glomerulopathy was not found at all. In the article of Guery [17], FSGS was diagnosed in 79% of the biopsies. Hirano et al. [29] detected FSGS in 9 of 16 (56%) patients. But the spectrum of possible lesions is more variable, including tubulointerstitial nephropathy, bilateral enlarged cystic kidneys [17], chronic interstitial nephritis [29], IgA nephropathy [30], neoplasm [22], cystic renal disease [31] and chronic ischaemia in one patient from our own case series.

Related donors

Family members as potential donors should be up for discussion. Two of our patients (Cases 2 and 5) received kidney transplantation from a brother and both patients were diagnosed with the m.3243A>G mutation several years after transplantation. It is recommended to be aware of the diagnosis of mitochondrial disease in case of multisystemic problems, such as renal disease, cardiac failure, diabetes and deafness. The presence of the mutation in potential related donor candidates should be ruled out before transplantation, as the risk of transmission of the mutation in the maternal lineage is very high [26].

Anaesthetics during transplantation

A recently published study summarized important considerations of the systematic effects of MELAS syndrome for anaesthetics during kidney transplantation surgery [25]. They recommend standard evaluation of electrolyte abnormalities and the possible onset of diabetes, as these are common comorbidities. Because of the increased risk for cardiomyopathy and conduction abnormalities, they recommend a preoperative electrocardiogram and a low threshold for an echocardiogram. Neuromuscular blockade (such as propofol) should be administered carefully, because reports have described prolonged effects of neuromuscular-blocking agents in patients with mitochondrial diseases [32]. During surgery, patients may be at an increased risk for malignant hyperthermia. Administration of glucose-containing fluids is also recommended to prevent hypoglycaemic and catabolic episodes in response to the stress of surgery.

Diabetes

It is not the transplantation itself but the post-transplant therapy with high doses of prednisone that may provoke or progress the development of diabetes in these patients. All 18 patients were diagnosed with diabetes, 8 of whom (44%) developed diabetes following transplantation. The non-insulin-dependent diabetes in four patients became insulin dependent after transplantation. This results in the current use of insulin in 12 of 18 (67%) patients. It should be noted that treatment with metformin is contraindicated in patients with mitochondrial disease because of the elevated risk for lactic acidosis.

Recognition of the m.3243A>G mutation carriers

Studies have suggested that renal involvement might be the first sign of mitochondrial disease [17, 33]. Recognition of the disease is difficult when only renal symptoms are present. Other symptoms such as deafness and diabetes may lead to the proper diagnosis. However, in some cases they can be misleading, for example, in the case of Alport syndrome. It is important

Table 1. A summary of the characteristics of patients who received a renal transplantation

Patient	Author	Sex	First renal symptom (age ^a)	Biopsy (age ^a)	Age ^a at RTx (donor)	Hearing loss (age ^a)	Age ^a of onset DM (therapy)	Age ^a at diagnosis	Heteroplasmy (%) ^b	Post-transplantation ^c
Case 1	This report	F	NS (31)	FSGS (31)	38 (PM)	Yes	35 (OM; IP)	35	25/28	8; KF stable, PR ⁻
Case 2	This report	M	PR (25)	FSGS (32)	36 (HLA)	Yes (42)	32 (OM; IP)	37	26/11	10; KF stable, PR ⁻
Case 3	This report	F	Loss of renal function	Chronic ischaemia (17)	28 (PM)	No	32 (OM)	35	35/44	13; KF stable
Case 4	This report	F	PR (40)	IgA-nephropathy	52 (PM)	Yes (40)	41 (I)	56	17/31	4; KF stable, MA ⁺
Case 5	This report	F	Nephropathy (29)	-f	36 (HLA)	No	13 (I)	40	16/31	5; KF stable, PR ⁻
1	Jansen et al. [21]	F	PR + PRF	-f	38	Yes	38 (I)	-f	12/ f	-f
2	Jansen et al. [21]	F	PR + PRF	CLGN (44)	47	Yes	48 (D)	-f	6/ f	-f
3	Jansen et al. [21]	F	PR + PRF	FSGS	25	Yes	25 (OM)	-f	34/ f	-f
4	Jansen et al. [21]	F	PR + PRF	Chronic GS + hyalinized glomeruli	36	Yes	34 (OM; IP)	-f	18/ f	-f
5	Guery [17]	F	PR + ESRD (41)	-f	43	Yes (36)	46 (OM)	-f	e/f	4; SC 63 µmol/L
6	Guery [17]	M	PR (32)	-f	39	Yes	34 (D; IP)	-f	e/f	-f
7	Guery [17]	F	PR (30)	-f	42	Yes (42)	42 (I)	-f	e/f	5; SC 92 µmol/L
8	Guery [17]	F	PR (5)	FSGS (14)	17	Yes	17 (I)	-f	e/f	2; SC 93 µmol/L
9	Doleris et al. [18]	F	PR (18)	FSGS (21)	40	Yes (28)	33 (I)	-f	59/ f	-f
10	Lederer et al. [23]	M	NS + PRF (43) ^d	FSGS + tubulaire atrophy	52	Yes (19)	22 (I)	57	-f	6; SC 1.7 mg/dL
11	Humeidan et al. [25]	F	-f	FSGS	33	Yes	f (D)	-f	-f	-f
12	Seidowsky et al. [24]	M	PRF	FSGS	42	Yes (38)	32 (I)	43	10/ f	4; SC 220 µmol/L, PR 0.55 g/day
13	Seidowsky et al. [24]	F	PRF	FSGS	27	Yes (11)	27 (I)	25	40/ f	0.5; KF stable

^aAge in years.

^bBlood/urine.

^cYears after transplantation.

^dThe patient died at the age of 58 years due to progressive and complicated disease.

^eHeteroplasmy in blood reported between 5% and 25%.

^fData unknown.

F, female; M, male; NS, nephrotic syndrome; PR, proteinuria; PRF, progressive renal failure; IgM-N, IgM nephropathy; CLGN, chronic lobular glomerulonephritis; GS, glomerulosclerosis; PM, post-mortem donor (unrelated); HLA, HLA-matched donor (related); DM, diabetes mellitus; OM, oral medication; IP, insulin; D, diet; KF, kidney function; MA, microalbuminuria; SC, serum creatinine.

to recognize the possible mitochondrial origin of renal failure in a patient. Possible features that may point to a mitochondrial origin of proteinuria and renal failure are unresponsiveness of nephrotic syndrome to steroid therapy, steroid therapy being complicated by diabetes or the presence of other symptoms frequently seen in carriers of the m.3243A>G mutation. Besides neuromuscular symptoms such as myopathy, dementia, epilepsy and migraines, these also include diabetes, deafness, cardiomyopathy, retinal dystrophy and the presence of these symptoms in (maternal) family members. Either alone or combined, these symptoms should make every doctor consider the possibility of the existence of a mitochondrial disease. In general, we would like to recommend a liberal policy in determining the m.3243A>G mutation in patients with renal failure, in combination with hearing problems, diabetes, neurological involvement and/or cardiac failure.

CONCLUSION

Renal involvement in carriers of the m.3243A>G mutation most commonly leads to proteinuria and FSGS and may lead to ESRD. Proper recognition of the mitochondrial origin of the renal disease in all patients is important for adequate treatment selection and suitable supportive care. This case series and review of the literature on long-term follow-up after kidney transplantation shows that it is feasible for carriers of the m.3243A>G mutation, with a non-MELAS phenotype, to be considered for kidney transplantation. These patients should not be excluded from transplant solely because of their mitochondrial diagnosis.

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CONFLICT OF INTEREST STATEMENT

J.A.M.S. is the founding chief executive officer of Khondrion BV.

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