LETTER TO THE EDITOR

Kidney transplantation in m.3243A>G carriers has outcome implications

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With interest we read the article by de Laat et al. about five patients with a mitochondrial disorder (MID) due to the variant m.3243A>G in MT-TL1 clinically manifesting as multisystem disease, with kidney failure as the most prominent feature leading to end-stage renal disease (ESRD) and requiring kidney transplantation [1]. The study has a number of shortcomings.

We do not agree that renal involvement in MIDs may only manifest as renal insufficiency with proteinuria, focal segmental glomerulosclerosis (FSGS) or potentially ESRD. In addition to renal insufficiency, FSGS or ESRD kidney involvement in MIDs may also manifest as renal cysts, nephrolithiasis, Fanconi syndrome, renal malignancy or renal infarction secondary to primary mitochondrial cardiomyopathy with atrial fibrillation [2].

Patients receiving a kidney transplant usually require long-term steroids or immunosuppressants. Long-term immunosuppression may be complicated by focal or systemic side effects. One of these possible side effects is muscular compromise (e.g. steroid myopathy, myopathy due to sirolimus) [3]. Since patients carrying the m.3243A>G variant frequently manifest in the skeletal muscle, it is crucial to assess the muscle status prior to transplantation and to monitor muscle function after starting the immunosuppression during follow-up. Thus, we should know how many of the five included patients had clinical or subclinical muscle manifestations prior to transplantation and in how many immunosuppression either triggered muscle involvement or worsened pre-existing muscle disease.

In all five included patients, blood and urine heteroplasmy rates were low. We should know how the authors explain that the m.3243A>G variant was pathogenic and if heteroplasmy rates were also determined in the explanted kidneys. Determining heteroplasmy rates in clinically affected organs or tissues is crucial, as heteroplasmy rates are usually higher in affected than unaffected tissues. Patient 3 had undergone muscle biopsy, thus, it is conceivable that she had undergone determination of heteroplasmy rates in the muscle.

Missing is an extensive family history in all five cases. We should know in how many of the patients the MID was inherited and in how many it occurred spontaneously. According to previous data, mitochondrial DNA-related mutations are transmitted via the maternal line in 75% of cases [4], therefore it is conceivable that the variant was inherited from the mother in most or all five patients. Knowing the family history is crucial for determination of the outcome and for genetic counselling of the index patients and their first-degree relatives.

Patient 4 presented with epilepsy. Since some of the antiepileptic drugs (AEDs) are not only mitochondrion-toxic but may also cause renal insufficiency (e.g. topiramate, clobazam and perampanel [5]), we should know which AEDs this patient received and if they potentially contributed to kidney dysfunction.

Patients carrying the m.3243A>G variant frequently present with stroke-like episodes (SLEs) [6]. Interestingly, none of the five patients was described as having SLEs [1]. Thus, we should know if cerebral imaging was carried out to see if there were remnants of previous SLEs or if there were other manifestations of central nervous system involvement in a MID.

In conclusion, the report by de Laat et al. has a number of shortcomings that need to be addressed before drawing final conclusions. Heteroplasmy rates should have been determined in the explanted kidneys to confirm the pathogenicity of the culprit variant.

NOTE FROM THE EDITORIAL OFFICE
Dr de Laat et al. had no further comments on this letter.

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AUTHORS’ CONTRIBUTIONS
J.F. contributed to design, literature search, discussion, first draft and critical comments. The author read the journal’s position on issues involved in ethical publication.

CONFLICT OF INTEREST STATEMENT
The results presented in this article have not been published previously in whole or part, except in abstract format.

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