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Letter to the Editor

Transplantation in Mitochondrial Disorders Requires Pheno- and Genotypic Clarification and Considered Selection of Immuosuppression

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We read with interest the article by Anderson *et al*. about a 30-year-old man with mitochondrial encephalopathy, lactic acidosis and stroke-like episode syndrome (MELAS), phenotypically presenting as developmental delay, Wolf-Parkinson-White (WPW) treated by ablation, non-ischemic cardiomyopathy with heart failure, chronic stage III renal disease with left congenital renal atrophy, hypoaldosteronism with fludrocortisone, superior mesenteric artery syndrome and embolic stroke due to left ventricular mural thrombus [1]. The patient underwent combined heart and kidney transplantation, which he tolerated without major side effects and was successfully extubated on postoperative day 7 [1]. The study is convincing, but some points should be discussed.

The first point is that it is unclear how MELAS was diagnosed in the index patient [1]. MELAS is usually diagnosed according to either the Hirano criteria [2] or the Japanese criteria [3]. According to the Hirano criteria, MELAS is diagnosed in the presence of a stroke-like episode (SLE) before the age of 40, seizures or dementia, lactic acidosis, ragged-red fibers, normal early development, recurrent headaches or recurrent vomiting [2]. According to the Japanese criteria, evidence of a genetic defect associated with a MELAS phenotype is required [3]. Therefore, we should know which of these criteria have been applied and which type of genetic defect is responsible for the phenotype. In about 80% of cases, MELAS is due to the mtDNA variant m.3243A>G in MT-TL1. If the index patient carried an mtDNA defect, we should know whether it was inherited from the mother or occurred sporadically. According to the information in the case description, the patient fulfilled neither the Hirano nor the Japanese criteria.

The second point is that the explanted heart and kidneys were apparently not further examined by histologic, immunohistologic, biochemical or genetic methods to determine the extent to which the mitochondria in these two organs were defective. An autopsy of these organs could have clarified whether the cardiomyopathy and renal failure were indeed due to a mitochondrial defect. Renal involvement in MELAS is rather rare and includes proteinurea, renal insufficiency, acute tubular necrosis, focal segmental glomerulosclerosis or renal neoplasia [4].

The third point is that the immunosuppressive regimen used after transplantation has not been specified. Since some immunosuppressants can be mitochondrial toxic [5], they should be carefully selected so as not to cause additional harm to patients with mitochondrial dysfunction.

The fourth point is that it was not specified whether the patient had lactic acidosis or not. Knowing whether there is an elevated level of lactate in the serum or cerebrospinal fluid (CSF) is critical to the choice of medications administered during and after transplantation. Common drugs that increase serum lactate include metformin, acetaminophen, nucleoside reverse transcriptase inhibitors, linezolid, beta-2 agonists, propofol, epinephrine, theophylline, ethanol, carbon monoxide, cyanides and cocaine. These substances must be used with caution in the treatment of MELAS patients.

Overall, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and reinforce the study's message. Organ transplantation in mitochondrial disorders requires phenotypic and genotypic assessment and a considered choice of lifelong immunosuppression.

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