Letter to the Editor

Diagnosing MERRF requires clinical and genetic evidence

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The interesting case about a patients with myoclonic epilepsy with ragged-red fibers (MERRF) syndrome due to the variant m.8344A>G with a heteroplasmy rate of 95% reported by Felczak *et al*. expands the phenotypic spectrum of MERRF syndrome. The authors reported a pituitary adenoma, calcium deposits in arterial walls, and an intra-cerebral lipoma in the corpus callosum in their patient. Shortcomings of the study are that the diagnostic criteria for MERRF were not accomplished, that the patient should be rather diagnosed as a mitochondrial, multiorgan disorder syndrome (MIMODS), that no pedigree and heteroplasmy rates in first degree relative were provided, that hormone levels were not provided despite obvious endocrinological involvement, and that no serum or cerebrospinal fluid (CSF) lactate levels were reported.

Key words: mtDNA, mitochondrial, MERRF, m.8344A>G, multisystem, MIMODS.

With interest we read the article by Felczak *et al.* about the clinical and ultrastructural muscle biopsy findings in a 30 years old female with putative MERRF syndrome due to the variant m.8344A>G with a heteroplasmy rate of 95% in muscle [1]. We have the following comments and concerns.

We do not agree that the described patient had MERRF. Diagnosing MERRF not only relies on the detection of a pathogenic mtDNA mutation associated with MERRF [2], but also on the presence of the canonical phenotypic features of the syndrome, myocloni, generalised seizures, ataxia, and ragged-red fiber myopathy [3]. However, none of these four features was described in the index patient. Thus, the patient should rather be diagnosed with mitochondrial multiorgan disorder syndrome (MIMODS) due to the m.8344A>G variant than with MERRF [4]. Organs affected in the index patient were the brain, muscle, ears, and the endocrine system.

Since some relatives were obviously clinically affected (gait disturbance, dysarthria, myoclonic epilepsy) and even carried the m.8344A>G variant, we should be informed about the relation between these relatives and the index case, preferentially by presentation of a pedigree. This is crucial as there was obviously broad phenotypic heterogeneity. Thus, we should be informed about the heteroplasmy rates of the variant in clinically affected relatives and discussion of alternative explanations than heteroplasmy rates as the cause of the phenotypic heterogeneity.

The patient was diagnosed with hypoprolactinemia and a microadenoma of the pituitary gland [1]. Were all endocrine abnormalities, such as hypothyroidism, short stature, hypogonadism, and hypocorticism attributable to the adenoma or was there additionally pituitary insufficiency? In particular we should be informed about the serum levels of sexual hormones, cortisol, aldosterone, parathormone, and calcitonin. Pituitary insufficiency is quite likely as the patient had short stature, menstrual disorder, adrenal insufficiency, and hypothyroidism which are not attributable to a microadenoma.

The authors found calcium deposits in the walls of arterioles. Thus, we should know if function and

morphology of the parathyroid glands were normal and if parathormon and calcitonin levels were normal or abnormal. This is crucial as hypo- or hyper-parathyroidisms can be a manifestation of a mitochondrial disorder (MID) [5].

Interestingly, cerebral CT (CCT) revealed a lipoma of the corpus callosum [1] but cerebral MRI was normal. This discrepancy should be addressed. Usually, lipomas are more accurately seen on MRI than on CCT. Since lipomas most frequently occur subcutaneously in a mono-local or multi-local distribution in MERRF, the CCT diagnosis is highly questionable since the MRI does not show the lesion.

Missing in the report are the serum and CSF values of lactate. MERRF is frequently associated with lactic acidosis, which may strongly influence the clinical presentation if elevated. Serum lactate may be also helpful for diagnosed purposes in the form of the lactate stress test [6]. Thus we should be informed about lactate levels, MR-spectroscopy findings, and the results of the lactate stress test.

Overall, this interesting study shows that the m.8344A>G variant may not only manifest as MERRF and that MIDs in general can manifest with pituitary adenomas. The study has a number of shortcomings and inconsistencies as indicated above, which need to be resolved to make the results more reliable.

The author declares no conflict of interest.

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