Letter to the Editor

Diagnosing MERRF requires clinical and genetic evidence

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Dear Editor,

we have received the letter commenting on our article entitled: *Pathology of skeletal muscle fibers and small blood vessels in* MERRF *syndrome: an ultrastructural study*. The cited title of the work, our research focused on a thorough, reliable and detailed ultrastructural analysis of the case of mitochondrial encephalomyopathy qualified by geneticists as the MERRF syndrome. Clinical and genetic data were not the purpose of our scientific deliberations, but served as a starting point for subcellular analysis of the pathology of skeletal muscles and small blood vessels of a patient with mitochondrial disease. This disease is considered to be difficult diagnostically. In connection with the above, we are in favor of carefully formulating far-reaching conclusions based on the results of ultrastructure. We believe that the occurrence of calcium deposits in the walls of small blood vessels in with data on the parathyroid hormone level of the patient does not authorize us, as the Author of the letter suggests, to treat these deposits as one of the manifestations of mitochondrial disease. Calcium depositions at the ultrastructural level show a specific morphology and in this form are recognized not only in mitochondrial diseases [1], but also for example in microangiopathies such as CADASIL [2] or in kidney diseases such as uremia [3].

Our studies were focused on the demonstration in the case report ultrastructural changes that corresponded to the detected mutation 8344A> G in the *MTTK* gene. Therefore, in our opinion, the presentation of the pedigree of the family members of the patient was not strictly necessary. The work did not concern the study of genetic variation and clinical variability of the population of people related to the patient who were suspected of mitochondrial disease. These data could be material for a separate specialist genetic or clinical work involving the cohort of the patient's family members. In addition, we considered it to be beyond the field of our study to include all clinical data of the patient, especially if the results of these tests were within the accepted norms, such as the level of lactate dehydrogenase. The estimated data indicate that the mutation 8344A> G in the *MTTK* gene is responsible for the occurrence of the MERRF syndrome in as many as 80% of the investigated cases [4]. In our case report, the reference of this mutation to the phenotype of the mitochondrial multiorgan disorder syndrome (MIMODS) instead of the phenotype of the MERRF syndrome raises our doubts. They result from the fact that the diagnostic algorithm for the mitochondrial multiorgan disorder syndrome (MIMODS) probably has not yet been determined.

There is also no commonly accepted binding definition of this syndrome (MIMODS) [5]. Apart from that, among the specific mitochondrial diseases (MIDs), which were recognized as manifested by MIMODS, there was no MERRF syndrome, but there were such diseases as, for example: Pearson syndrome, KSS, CPEO, ataxic neuropathy with dysarthria and ophthalmoparesis and MELAS [5]. According to the compendium MITOMAP [www.mitomap.org/MITOMAP], the molecular variant m.8344A> G in the *MTTK* gene is primarily associated with the MERRF syndrome, in addition to depressive mood disorder and leukoencephalopathy, but there is no reference to this molecular variant for MIMODS.

On the other hand, considering the fact that the 8344A> G mutation in the *MTTK* gene may exhibit very high phenotypic variability among members of one family and among members of different

families, and taking into account the overlap of the clinical spectrum of this mutation to other mitochondrial diseases [6] can not be exclude that variant m.8344A> G in the *MTTK* gene in certain clinical cases may manifest as a mitochondrial multiorgan disorder syndrome (MIMODS).

We would like to thank the Author of the letter for all the remarks and observations that contribute to the broadening of our knowledge about mitochondrial diseases.

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