

POLG1 phenotypes may worsen rather from valproic acid and lidocaine than borreliosis or ceftriaxone

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1 LETTER TO THE EDITOR

With interest we read the article by Gaudio et al. about a 3yo female with generalised epilepsy due to the compound heterozygous variants c.2591A>G and c.3649G>C in *POLG1* [1]. The authors concluded that a concomitant *Borrelia burgdorferi* infection and the administration of ceftriaxone triggered the occurrence of clinical manifestations of the *POLG1* variants and that the antibiotic worsened the phenotype [1]. The study has several shortcomings.

The first shortcoming is that the diagnosis of borreliosis remains questionable. A recent insect bite and elevated IgM-antibodies not necessarily justify diagnosing borreliosis. We should know if it was a tick-bite, if also IgG-antibodies were elevated, and the results of the immunoblot and the PCR. Since the patient presented with central nervous system (CNS) manifestations, neuroborreliosis needs to be excluded, by presentation of appropriate cerebrospinal fluid (CSF) findings.

A second shortcoming is that the notion that borreliosis triggered the clinical manifestations is not comprehensible. Epilepsy had developed >1y prior to the infection and is most likely the initial manifestation of the underlying mitochondrial disorder (MID).

A third shortcoming is that the authors did not consider factors other than the infection and the antibiotic responsible for the clinical deterioration. It is conceivable that the patient's condition deteriorated from lidocaine, since it is well established that local anesthetics may worsen the clinical manifestations of MID patients [2]. Worsening of the phenotype could be also due to VPA. Mitochondrion-toxicity of VPA is well documented [3]. Also phenobarbital (PB) and carbamazepine (CBZ) are potentially mitochondrion-toxic [3]. In *POLG1* carriers it is generally

advisable not to apply VPA because of fatal liver toxicity [4]. We should know if VPA was chosen without knowing the genetic diagnosis.

A strong argument against ceftriaxone is that worsening of an MID phenotype has not been previously reported under this antibiotic. However, in rare cases cephalosporins may trigger seizures, like under penicillin [5].

We do not agree that seizures were well controlled. An argument for this statement is that VPA was replaced by a combination of three other AEDs (PB, CBZ, LEV) [1]. Why?

There are a number of inconsistencies. In the abstract the index patient is 3y old in the case description 4y. Which figure is correct? It is unclear why the patient received lidocaine. We should know what the authors mean with the contradictive expression “generalised focal crisis” [1]. It should be specified if the authors mean focal and generalised seizures or other focal or generalised neurological deficits. It should be specified what the authors mean with hypertension (arterial, pulmonary, muscle, portal, cerebral?) Was hypo/areflexia due to myopathy or neuropathy?

Overall, this interesting case has a number of shortcomings which need to be solved before drawing final conclusions(?). How do the authors explain the discrepancy between hypo/areflexia and distally elevated muscle tone? We agree that environmental factors may trigger clinical manifestations of a MID or may worsen already existing abnormalities. However, before accusing Borreliosis or ceftriaxone as the culprit, the causal relation has to be unequivocally demonstrated and other possibilities need to be excluded.

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