Innovative Journal of Medical and Health Science

IJMHS 10 (06), 955–956 (2020) ISSN (O) 2277:4939 | (P) 2589:9341

Ceftriaxone may not trigger seizures in *POLG1* carriers

Josef Finsterer, MD, PhD[⋆,†,1], Scorza Fulvio A, MD[2]

[1] *Krankenanstalt Rudolfstiftung, Messerli Institute, Austria*
[2] *Disciplina de Neurociência. Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM). São Paulo, Brasil.*

DOI: https://doi.org/10.15520/ijmhs.v10i03.288

Accepted 10/06/2020; Received 01/06/2020; Publish Online 17/06/2020

Reviewed By: Dr Daniel V.
Department: Medical

Key words: POLG1, mtDNA, seizures, ceftriaxone, side effects, myopathy

1 LETTER TO THE EDITOR

With interest we read the article by Gaudo et al. about a 4-year-old female with a mitochondrial disorder (MID) due to a compound heterozygous variant in *POLG1* for whom the authors claimed that Borreliosis or ceftriaxone had worsened the phenotype [1]. We have the following comments and concerns.

The main shortcoming of the study is that the diagnosis Borreliosis is questionable. For diagnosing acute Borreliosis not only IgM antibodies but also IgG antibodies against Borrelia burgdorferi need to be elevated in the serum. We also should know with which symptoms and signs Borreliosis manifested clinically, if Borrelia antibodies were also elevated in the cerebro-spinal fluid (CSF), if there was pleocytosis, and if neuroborreliosis was diagnosed. If Borreliosis was diagnosed erroneously, there was no indication for ceftriaxone.

Arguments against ceftriaxone as the trigger of seizures in the index patient are that so far no adverse reaction of ceftriaxone in *POLG1* mutation carries has been reported and that ceftriaxone is usually well-tolerated in MID patients [2], A further argument against a triggering effect of ceftriaxone is that beta-lactam antibiotics have an anticonvulsive effect [3].

Another shortcoming is that the description of the disease course at age 3y is unprecise. We should know if the increase of seizure frequency occurred before or after application of ceftriaxone, how often ceftriaxone was given intravenously, if there was fever which could have triggered seizures, and if the episode after the second application of ceftriaxone was a series of seizures or an epileptic state.

Another shortcoming is that the patient received valproic acid (VPA) although it is known that VPA is mitochondrion-toxic and hepatotoxic, particularly in carriers of *POLG1* variants and may even lead to acute, fatal liver cell necrosis [4]. In addition to VPA, phenobarbital (PB) and carbamazepine (CBZ) are potentially mitochondrion-toxic [5]. It is unclear if PB, CBZ and levetirazetam (LEV) replaced VPA or were given in addition to VPA. The authors should have tested not only the toxicity of ceftriaxone and lidocaine to fibroblasts, but also that of VPA.

The authors should explain why lidocaine was given intravenously in addition to ceftriaxone for Borreliosis. From some local anesthetics it is known that they may worsen MIDs [6].

A further shortcoming is that the parents or other family members were not tested for the presence or absence of either *POLG1* variant. If the mutation segregates with the phenotype, this would be an argument for the pathogenicity of the variants. Though the parents were described as healthy [1], they should be prospectively investigated for subclinical or mildly manifesting MID. Knowing the genetic status of the parents is a prerequisite for appropriate genetic counselling.

Unclear remains if tendon reflexes were reduced due to myopathy or neuropathy and if "increased tone" was classified as spasticity or rigor. Since the patient had hypomimia [1], an extra-pyramidal syndrome should be excluded. The term "right tetraparesis" is contradictory.

Overall, the study has a number of shortcomings which need to be addressed before drawing final conclusions. For the safety of MID patients, mitochondrion-toxic drugs should be avoided.

⋆ Corresponding author.
† Email: fifigs1@yahoo.de

REFERENCES

[1] Finsterer J, Haberler C, Schmiedel J. Deterioration of Kearns-Sayre Syndrome Following Articaine Administration for Local Anesthesia. Clinical Neuropharmacology.

2005;28(3):148–149. Available from: https://dx.doi.org/10.1097/01.wnf.0000165352.10841.21.
[2] Hynynen J, Komulainen T, Tukiainen E, Nordin A, Arola J, Kälviäinen R, et al. Acute liver failure after valproate exposure in patients withPOLG1mutations and the prognosis after liver transplantation. Liver Transplantation. 2014;20(11):1402–1412. Available from: https://dx.doi.org/10.1002/lt.23965.
[3] Finsterer J. Toxicity of Antiepileptic Drugs to Mitochondria. Handb Exp Pharmacol. 2017;240:473–488.
[4] Hussein AM, Ghalwash M, Magdy K, Abulseoud OA. Beta Lactams Antibiotic Ceftriaxone Modulates Seizures, Oxidative Stress and Connexin 43 Expression in Hippocampus of Pentylenetetrazole Kindled Rats. Journal of Epilepsy Research. 2016;6(1):8–15. Available from: https://dx.doi.org/10.14581/jer.16002.
[5] Gaudó P, Emperador S, Garrido-Pérez N, Ruiz-Pesini E, Yubero D, García-Cazorla A, et al. Infectious stress triggers a POLG-related mitochondrial disease. neurogenetics. 2020;21(1):19–27. Available from: https://dx.doi.org/10.1007/s10048-019-00593-2.
[6] Liu XQ, Shen SQ, Yang GC, Liu Q. Mitochondrial A3243G mutation causes mitochondrial encephalomyopathy in a Chinese patient: Case report. Medicine (Baltimore). 2019;98:15534–15534.

AUTHOR BIOGRAPHY

Josef Finsterer, MD, PhD Krankenanstalt Rudolfstiftung, Messerli Institute, Austria

Scorza Fulvio A, MD Disciplina de Neurociência. Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM). São Paulo, Brasil.