East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online) |
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-1 | Issue-6 | Nov-Dec-2019 |

Letter to the Editor

Atypical Multisystem Mitochondrial Disorder Due To the Primary Lhon Mutations M.11778g>A and M.14484t>C

Josef Finsterer, MD, PhD*
Krankenanstalt Rudolfstiftung, Messrli Institute, Vienna, Austria

*Corresponding Author
Josef Finsterer, MD, PhD

Keywords: LHON, mtDNA, heteroplasmy, stroke-like episode, Leigh syndrome, myelitis, respiratory chain.

In a recent article, Berardo *et al*., reported about a 36yo Indian male with bilateral ptosis and right-sided visual impairment since childhood, visual loss of the left eye at age 25y, gait disturbance due to dystonia and ataxia, and dysarthria since age 33y, and painful weakness of the right upper and lower limb at age 34y (Berardo, A. *Et al*., 2019). Myelitis respectively myelopathy C2-3 and C7-T1 was diagnosed, which completely resolved upon steroids. At age 35y he experienced weakness and pain of the left upper limb being attributed to cervical and thoracic myelitis again and resolving again upon steroids (Berardo, A. *et al*., 2019). Genetic work-up revealed the mtDNA variants m.11778G>A (heteroplasmy 81% in fibroblasts) in *ND6* and m.14484T>C (homoplasmy) in *ND4*, which are usually associated with Leber's hereditary optic neuropathy (LHON) (Yu-Wai-Man, P., & Chinnery, P.F. 2000). We have the following comments and concerns.

Cerebral imaging in figure 1 resembles Leigh syndrome with bilaterally symmetric hyperintensities of the putamen (Finsterer, J. 2008). Leigh-like features have been previously reported in association with the variant m.11778G>A ((Fruhman, G. *et al*., 2011). Additionally, there was extensive bilaterally symmetric T2-hyperintensity of the anterior horns, resembling leukoencephalopathy with brain stem and spinal cord involvement, and lactate elevation (LBSL) (Lin, T. K. *et al*., 2019). Since some types of Leigh syndrome (e.g. *SLC19A3, TPK1*) favourably respond to thiamin (100mg/d) or biotin (20mg/d) (Savasta, S. *et al*., 2019), we should know if vitamin-B1 was tried and if it was effective in the index case. In case thiamin / biotin was ineffective, we should know if other antioxidants or cofactors were beneficial.

Since there was impaired visual acuity bilaterally we should know about the results of the ophthalmologic investigations (peripapillary teleangiectasias, retinal nerve fibre layer edema), optical coherence tomography (thickening of the temporal retinal nerve fiber layer), visually evoked potentials (reduced amplitude, delayed latency), and electroretinogram. Particularly we should know if there was optic atrophy, ocular myositis, or optic neuritis. Since the patient carried two primary LHON mutations it should be mentioned if funduscopy revealed typical features of presymptomatic or symptomatic LHON (Yu-Wai-Man, P., & Chinnery, P.F. 2000).

Since serum lactate and cerebro-spinal fluid (CSF) lactate were elevated and since there were morphological abnormalities on cerebral imaging we should know if magnetic resonance spectroscoyp (MRS) showed an increased lactate peak.

The authors describe complete resolution of the cord hyperintensities after the third application of steroids at age 35y. However, cervical MRI at age 38y revealed a "stable cervical cord abnormality C2-C5" (Berardo, A.*et al*., 2019). This discrepancy should be explained. We should know if clinical manifestations had recurred or if the cervical lesion at age 34y never resolved completely.

Quick Response Code

Journal homepage:
http://www.easpublisher.com/easms/

Article History
Received: 02.12.2019
Accepted: 15.12.2019
Published: 26.12.2019

We do not agree with the statement that the variant m.11778G>A has not been reported in association with dystonia. Dystonia was a prominent feature in 6 patients with LHON reported in 2007 (McFarland, R. *et al*., 2007). Also the variant m.14484T>C has been reported in association with LHON and dystonia (Kalinska-Bienias, A. *et al*., 2017).

Missing is a discussion about the nature of the spinal cord lesions. Particularly discussed should be if the spinal lesions represent stroke-like lesions, the morphological equivalent of a stroke-like episode, of the spinal cord rather than myelitis. Considering the spinal lesions as stroke-like lesions is crucial as therapy may be entirely different.

Overall, this interesting study has a number of shortcomings and inconsistencies which need to be addressed before final conclusion can be drawn.

REFERENCES

1. Berardo, A., Emmanuele, V., Vargas, W., Tanji, K., Naini, A., & Hirano, M. (2019). Leber hereditary optic neuropathy plus dystonia, and transverse myelitis due to double mutations in MT-ND4 and MT-ND6. Journal of neurology, 1-7.
2. Yu-Wai-Man, P., & Chinnery, P.F. (2000). Leber Hereditary Optic Neuropathy. [updated 2016 Jun 23]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from http://www.ncbi.nlm.nih.gov/books/NBK1174/
3. Finsterer, J. (2008). Leigh and Leigh-like syndrome in children and adults. Pediatric neurology, 39(4), 223-235.
4. Fruhman, G., Landsverk, M. L., Lotze, T. E., Hunter, J. V., Wangler, M. F., Adesina, A. M., ... & Scaglia, F. (2011). Atypical presentation of Leigh syndrome associated with a Leber hereditary optic neuropathy primary mitochondrial DNA mutation. Molecular genetics and metabolism, 103(2), 153-160.
5. Lin, T. K., Chang, Y. Y., Lin, H. Y., Liou, C. W., Wang, P. W., Chuang, J. H., ... & Peng, C. H. (2019). Mitochondrial dysfunctions in leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL). PloS one, 14(10).
6. Savasta, S., Bassanese, F., Buschini, C., Foiadelli, T., Trabatti, C., Efthymiou, S., ... & Marseglia, G. L. (2019). Biotin-Thiamine Responsive Encephalopathy: Report of an Egyptian Family with a Novel SLC19A3 Mutation and Review of the Literature. Journal of pediatric genetics, 8(02), 100-108.
7. McFarland, R., Chinnery, P. F., Blakely, E. L., Schaefer, A. M., Morris, A. A. M., Foster, S. M., ... & Taylor, R. W. (2007). Homoplasmy, heteroplasmy, and mitochondrial dystonia. Neurology, 69(9), 911-916.
8. Kalinska-Bienias, A., Pollak, A., Kowalewski, C., Lechowicz, U., Stawinski, P., Gergont, A., ... & Ploski, R. (2017). Coexistence of mutations in keratin 10 (KRT10) and the mitochondrial genome in a patient with ichthyosis with confetti and Leber's hereditary optic neuropathy. American Journal of Medical Genetics Part A, 173(11), 3093-3097.