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LETTER TO EDITOR

Reply to the "Letter to the Editor" from Dr. J Finsterer and colleagues

Yuichiro Hisatomi[1] · Kei Murayama[2] · Akira Ohtake[3] · Yasushi Okazaki[4,5]

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Firstly, we thank Drs. Finsterer and Scorza for their interest and detailed comments to our recent paper describing the first patient diagnosed with *PTCD3* mutations. We appreciate the opportunity to clarify the comments and concerns from Drs. Finsterer and Scorza in their "Letter to the Editor."

We diagnosed our patient with *PTCD3* deficiency as having Leigh syndrome [1] but not Leigh-like syndrome based on the Rahman's stringent criteria [2], which was also used in our previous publication [3]. Namely, our patient had (a) progressive neurological disease with motor and intellectual developmental delay; (b) signs and symptoms of brainstem and/or basal ganglia disease; (c) raised lactate levels in blood and/or cerebrospinal fluid (CSF); and (d) characteristic features of Leigh syndrome on neuroradioimaging (symmetrical hyperintense lesions on T2-weighted magnetic resonance imaging).

One of the main neurological symptoms in our patient was myoclonus with abnormal EEG, which showed focal spikes in her right temporal area during the initial stage of disease, and generalized spikes in the later stage. Therefore, we diagnosed her with myoclonic epilepsy of basal ganglia origin and prescribed her clonazepam at 13 months of age, and clobazam was added later on. She had nystagmus as another sign of basal ganglia involvement. At first, she had high CSF lactate level (3.21 mM, L/P is 29.2) in spite of normal blood lactate (1.30 mM, L/P is 19.7). Then, her blood lactate level gradually increased to 5.50 mM. We also prescribed her a mitochondrial drug cocktail which consists of vitamin B_1, vitamin C, biotin, vitamin E, coenzyme Q10 and L-carnitine [4], and sodium pyruvate [5]. Ketogenic diet was not used. She had microcephaly, depressed nasal bridge, and blepharophimosis but had no other major anomalous signs. Her endocrine functions were all within normal range and she showed no signs of pancreatitis. Although the shape of her head looks asymmetric in Fig. 1 [1], we think this asymmetry was not caused by her disease itself but was due to the distortion resulted from her continuous recumbency since birth. Her elder sister does not carry the mutant allele, as shown in Fig. 2 [1].

For these reasons above, we diagnosed our patient with *PTCD3* deficiency as having Leigh syndrome [1] according to the Rahman's stringent criteria [2], not Leigh-like syndrome. We hope that our clarifications addressed the comments and concerns raised by Drs. Finsterer and Scorza and, together with our original article, would benefit future diagnosis and improve the understanding of mitochondrial diseases.

✉ Yasushi Okazaki
ya-okazaki@juntendo.ac.jp

[1] Department of Pediatrics, Kumamoto City Hospital, Higashi-ku, Kumamoto 862-8505, Japan

[2] Department of Metabolism, Chiba Children's Hospital, Midori, Chiba 266-0007, Japan

[3] Department of Pediatrics, Saitama Medical University, Moroyama, Saitama 350-0495, Japan

[4] Diagnostics and Therapeutics of Intractable Diseases, Intractable Disease Research Center, Graduate School of Medicine, Juntendo University, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan

[5] Laboratory for Comprehensive Genomic Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Kanagawa 230-0045, Japan

References

1. Borna NN, Kishita Y, Kohda M, Lim SC, Shimura M, Wu Y, Mogushi K, Yatsuka Y, Harashima H, Hisatomi Y, Fushimi T, Ichimoto K, Murayama K, Ohtake A, Okazaki Y (2019) Mitochondrial ribosomal protein PTCD3 mutations cause oxidative phosphorylation defects with Leigh syndrome. Neurogenetics. https://doi.org/10.1007/s10048-018-0561-9
2. Rahman S, Blok RB, Dahl HH, Danks DM, Kirby DM, Chow CW, Christodoulou J, Thorburn DR (1996) Leigh syndrome: clinical features and biochemical and DNA abnormalities. Ann Neurol 39:343–351
3. Ogawa E, Shimura M, Fushimi T, Tajika M, Ichimoto K, Matsunaga A, Tsuruoka T, Ishige M, Fuchigami T, Yamazaki T, Mori M, Kohda

M, Kishita Y, Okazaki Y, Takahashi S, Ohtake A, Murayama K (2017) Clinical validity of biochemical and molecular analysis in diagnosing Leigh syndrome: a study of 106 Japanese patients. J Inherit Metab Dis 40(5):685–693

4. Omata T, Fujii K, Takanashi J, Murayama K, Takayanagi M, Muta K, Kodama K, Iida Y, Watanabe Y, Shimojo N (2016) Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy with onset of febrile convulsive status epileptics. J Neurol Sci 360:57–60
5. Komaki H, Nishigaki Y, Fuku N, Hosoya H, Murayama K, Ohtake A, Goto YI, Wakamoto H, Koga Y, Tanaka M (2010) Pyruvate therapy for Leigh syndrome due to cytochrome c oxidase deficiency. Biochim Biophys Acta 1800(3):313–315