Correspondence on "Aminoacyl-tRNA synthetase deficiencies in search of common themes" by Fuchs et al.

Diseases related to aminoacyl-tRNA synthetase deficiencies are one of our interests. Fuchs et al. published their work "Aminoacyl-tRNA synthetase deficiencies in search of common themes" in 2018[1] and recently published a correction that corrected the published variations on the *QARS* gene, which we are also interested in.[2] As we know, aminoacyl transfer RNA (tRNA) synthetases (ARSs) are a group of enzymes that are essential for accurate protein production. So, it was not surprising that the authors shared their focus on the protein production and proteinosis in certain organs, which provided many clues that might explain the mechanism of these ARS related diseases.

In Fuchs's work,[1] there were five patients carrying compound heterozygous pathogenic variations in *IARS*, *LARS*, *KARS*, and *QARS* respectively. *QARS* was the one we paid the most attention to because we had three patients who all carried compound *QARS* pathogenic variations. In Fuchs's work, the albumin level was normal in P5 (*QARS* variations). But in our three patients, serum albumin levels were mildly declined or normal, and the total serum protein levels were obviously lower than normal (Fig. 1: Supplement material). We checked the amino acid sequences of albumin (GI: 178344) and found only 20 glutamines in a total of 609 amino acids (3.28%).[3] It seemed that total protein production might be slightly affected while albumin production might not.

In patients with compound *QARS* variations, the most affected system was the central nervous system (CNS). Is the CNS being affected by excessive misinterpreted protein or insufficient production? Where and how? It was a pity that Fuchs's work did not involve protein level in cerebrospinal fluid (CSF) or brain tissue. As a supplement, in one of our patients, the CSF was tested (age: 45 days old). The albumin in CSF was 0.655 g/L compared with serum albumin level 34 g/L, and total protein level in CSF was 0.821 g/L compared with serum total protein level 49.7 g/L; the globulin in CSF was 0.0359 g/L compared with serum globulin level 2.86 g/L (she was a full-term infant). It seemed that the protein level and albumin were not affected in CSF.

Most of these patients had seizures within the first week of life and their epilepsy was pharmacoresistant.[4,5] Brain magnetic resonance image can be normal at birth and atrophy later in life.[4,5] Only five reported patients had no seizures and they all carried homozygous missense variants located in the catalytic domain.[4,5] For another two patients who also had compound variants within the catalytic domain but who had severe epilepsy, all had at least one truncated variant. In Zhang's research,[6] the *QARS*$^{-/-}$ zebrafish, which displayed small eyes and brain at 3 dpf, showed no differences in the number of mitotic cells and apoptotic cells in these tissues at 2 dpf but significantly more apoptotic cells at 6 dpf compared with wild-type zebrafish.

QARS was one of the three ARSs (KARS, GARS, QARS) located in both cytosol and mitochondria.[1,6] In many neurons, messenger RNAs (mRNAs) were found in synapses and proteins were produced and assembled in synapses. In many prokaryotes that lacked QARS, Gln-tRNA (Gln) could be formed by transamidation of the misacylated Glu-tRNA (Gln).[7] We suspected that QARS might be important in synapses or neurons but could be compensated by misacylated Glu-tRNA(Gln) or other ARSs in other tissues or in different parts of the cell. In the BrainSpan atlas,[8] *QARS* was highly expressed as early as the 8th week of pregnancy within the human brain and gradually declined after birth, finally reaching a very low level in the adult brain. Is it possible that lack of QARS results in excessive glutamine by catalytic function? The excessive glutamine that cannot be incorporated into peptide chains could be turned into glutamic acid under glutaminase, which could also lead to accumulation of excitatory glutamic acid in a certain position.

We suspected that epilepsy of QARS deficiency syndrome might be due to excessive glutamine/glutamic acid in the local microenvironment, especially at synapses, and the disease might be a natural model providing proof for the excitation/inhibition imbalance hypothesis in epileptogenesis (Fig 2: Supplement material). One of our patients was diagnosed before birth. It seemed that his treatment well fit the suspicion that early onset of epilepsy in QARS deficiency syndrome results from an imbalance of the excitation/inhibition system. Large dose of pyridoxine, which could help transfer glutamine to GABA, could relieve the seizures to a limited degree but the effect could decline over time. He later tried a small dose of memantine (6–10 mg/m^2/d) at three months that decreased the frequency of seizures by nearly 50%, which was the best performance of all antiepilepsy drugs (AEDs) that he tried. Supplement of oral glutamine could obviously aggravate the seizures, by stopped taking oral glutamine, the frequency of seizures could return to the previous level. The effect of memantine on seizures could decrease over time especially after age 10 months, when QARS expression gradually decreased. The other two patients were well controlled by

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clonazepam and clobazam, respectively, after they tried many AEDs at increasingly older ages. Based on what we observed in our patients, we have made the bold suggestion that QARS deficiency might serve as a good model to understand the unbalancing excitation/inhibition mechanism in developmental epilepsy.

SUPPLEMENTARY INFORMATION

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DISCLOSURE

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Yan-Wen Shen, MD, PhD[1] *and Li-Ping Zou, MD, PhD*[1,2,3]

[1]Department of Pediatrics, The First Medical Center of PLA General Hospital, China Medical School of Chinese PLA, Beijing, China; [2]Beijing Institute for Brain Disorders, Center for Brain Disorders Research, Capital Medical University, Beijing, China; [3]Southern Medical University, Guangzhou, China. Correspondence: Li-Ping Zou (zouliping21@hotmail.com)

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