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NOTE

5-Aminolevulinic acid can ameliorate language dysfunction of patients with ATR-X syndrome

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ATR-X syndrome (OMIM #301040) is one of the X-linked intellectual disability syndromes caused by mutations in the *ATRX* gene, characterized by male patients, severe intellectual disability, characteristic central hypotonic facies, α-thalassemia (HbH), skeletal, genital, and digestive abnormalities, and autistic behavior.[1] Based on these clinical features, the expression of many genes, including the α-globin gene, should to be disturbed in ATR-X patients. The ATRX protein targets tandem repeats, forming guanine-quadruplex (G4) structures, and regulates nearby genes.[2] We have recently reported that 5-aminolevulinic acid (5-ALA), can be a potential therapeutic strategy to target G-quadruplexes as it improved cognitive function in ATR-X model mice.[3]

This is the first case report of a boy with ATR-X syndrome, whose language ability has been improving since taking 5-ALA. The case is a 5-year-6-month-old boy, who was diagnosed as ATR-X syndrome with a nonsense variant in *ATRX* gene; NM_000489.5(*ATRX*): c.7192C>T, p.Gln2398*. His cousin is also diagnosed as ATR-X syndrome with the same *ATRX* mutation. He was born without asphyxia at 37 weeks gestational age (weight: 3172 g, height: 51 cm, head circumference: 42.5 cm). His motor development was delayed and he started walking without support at 31 months. He has characteristic clinical features of ATR-X syndromes, including severe intellectual disability, failure to thrive, central hypotonic facies, recurrent vomiting, constipation, cryptorchidism, and undescended testis. His brain magnetic resonance imaging shows hypoplasia of the corpus callosum.

At the age of 3 years and 4 months, he could not speak any meaningful words. His father started to give him 5-ALA orally once

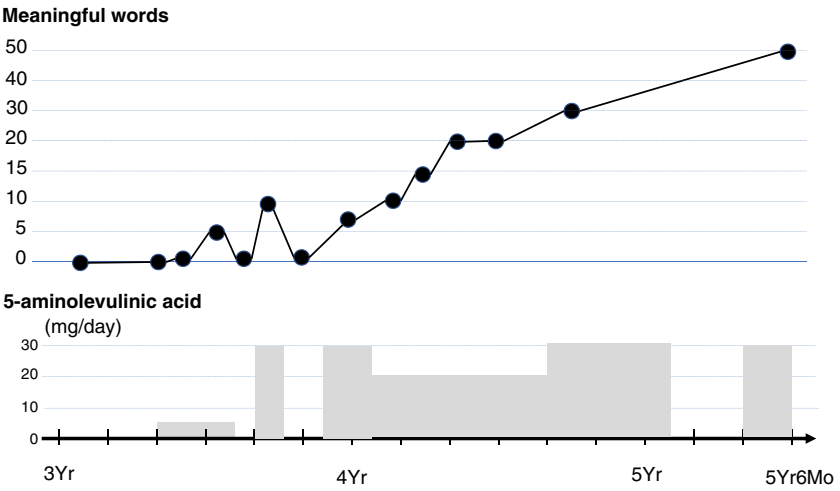

FIGURE 1 Language ability has been developing since taking 5-ALA; the top schema indicates the number of meaningful words that the patient could speak, and the bottom indicates the dose of 5-ALA that the patient took daily

daily at 5 mg as a nutritional supplement, which is available commercially in Japan (Figure 1). In a week, he started talking more babbling. And at the second month, he started speaking several meaningful words, including "Ocha (tea in English)," "Ka-san (Mom)," and "Ji-chan (Grandpa)." After stopping 5-ALA for a month transiently, he seemed to lose the aforementioned words he had acquired. However, after restarting 5-ALA at 30 mg daily, he recovered his language ability and acquired more new words, including "Tentei (teacher)," "Ko-ki (airplane)," "Ju-su (juice)," and "Gyu-gyu (milk)." His language ability has been developing for 2 years since he started taking 5-ALA. He is 12 kg in weight, and he takes 5-ALA daily at 30 mg orally and can speak more than 50 words and two-word phrases at the age of 5 years and 6 months. 5-ALA seems to attenuate his aggressiveness and improve his appetite. No side-effects have been observed to date.

It is distinctive that our patient can speak meaningful words after taking 5-ALA, because almost all ATR-X patients have severe intellectual disability and can never acquire any meaningful words. Actually, some patients can speak a few words, who have a few specific variants in *ATRX*, including p.R37*, p.Thr1621Met, or p.Ala1622Val.[1,4,5] The patient's 10-year-old male cousin with ATR-X syndrome presents with severe intellectual disability and cannot speak any meaningful words. This observation does not suggest that his nonsense variant of *ATRX* causes a mild enough phenotype to acquire language ability.

This report suggests that 5-ALA can be effective for some ATR-X syndrome patients. Clinical trials are required to confirm that 5-ALA is a good treatment for cognitive and/or language dysfunction in ATR-X patients.

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DISCLOSURE OF INTEREST

This study was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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