LETTER TO THE EDITOR

To The Editor

Pyrroline-5-Carboxylate Reductase 2 Deficiency: A New Case and Review of the Literature

Keywords: Pyrroline-5-carboxylate reductase 2 deficiency, PYCR2, Microcephaly, Hypomyelination, Seizures, Global developmental delay

Pyrroline-5-carboxylate reductase 2 (EC 1.5.1.2) is involved in the endogenous proline synthesis from glutamate and pyrroline-5-carboxylate.[1,2] Its deficiency (MIM#616420) is caused by biallelic variants in *PYCR2*. Proline is an important amino acid for central nervous system and connective tissues.[2] Less than 30 patients have been reported in the literature.[3–6] The clinical features include global developmental delay, acquired microcephaly, movement disorder, seizures, and failure to thrive.[3–6]

We report a new patient with a known pathogenic homozygous *PYCR2* variant who presented with early infantile onset severe global developmental delay, acquired microcephaly, failure to thrive, and delayed myelination in brain magnetic resonance imaging (MRI). Additionally, we summarized all patients published in the literature for their phenotype and genotype in this case report.

This 2-year 2-month-old girl was born to healthy consanguineous Egyptian parents. The pregnancy was remarkable for maternal hypothyroidism and thyroid hormone treatment. She was delivered by an elective caesarian section at 37 weeks of gestation. Birth weight was at the 3rd percentile. Her apgars were 9 and 10 at 1 and 5 minutes, respectively. She was formula-fed due to lack of breast milk production. There was persistent vomiting and failure to thrive from the first few months of life. She was started on oral ranitidine at 4 months of age and vomiting was improved, but not failure to thrive. Developmental delay was noted from the first few months of age.

She had her first generalized tonic seizure lasting 1 minute at the age of 7 months. Her electroencephalography (EEG) showed intermittent diffuse 2–3 Hz delta slowing indicating cortical encephalopathy with no epileptogenic discharges at the age of 8 months. She underwent video EEG recording, which showed four brief myoclonic jerks during drowsiness and wakefulness with generalized 2.5–3 Hz spike- and polyspike-and-wave complexes. There was intermittent sharply contoured slow-wave activity over bilateral temporal head region during sleep. She was started on levetiracetam.

At the age of 18 months, she was attempting to reach objects, roll from prone to supine, and was babbling. She did not achieve unsupported sitting or acquired any words at the age of 26 months. Her weight, height, and head circumference were below the 3rd percentile. She had full eyebrows, upslanting palpebral fissures, long eyelashes, bulbous nasal tip, absent antihelix bilaterally and plagiocephaly. She had central hypotonia. Muscle stretch reflexes were +2 and symmetrical.

Chromosomal microarray, ammonia, lactate, acylcarnitine profile, plasma amino acids, total and free carnitine, total homocysteine, very long chain fatty acids, transferrin isoelectric focusing, urine organic acids, urine oligosaccharides and urine creatine, and guanidinoacetate were normal. Brain MRI showed delayed myelination and thin corpus callosum. Clinical whole-exome sequencing identified a known pathogenic homozygous variant c.796C>T (p.Arg266*)[4] (NM_013328.3) in *PYCR2* confirming the diagnosis of pyrroline-5-carboxylate reductase 2 deficiency. Both parents were heterozygous for the same variant.

We summarized clinical and neuroimaging features and genotype results of 24 patients including our current patient with pyrroline-5-carboxylate reductase 2 deficiency in Table 1. We listed demographics, birth history, detailed clinical features including dysmorphic features, skeletal and ophthalmological features of 25 patients with pyrroline-5-carboxylate reductase 2 deficiency in Supplemental Table 1.[3–6] Twelve *PYCR2* variants in 18 families were identified and 7 of them (58%) were missense and 5 of them (42%) were truncating. Eight patients had a homozygous known p.Arg266* variant in *PYCR2*. We grouped patients into two groups based on the type of variant (truncating variants in 12 patients and missense variants in 12 patients), to compare the frequency of seizures, hyperkinetic movements, and non-ambulation. In both groups, seizures (50%) and non-ambulation (92%) were reported at the same frequency. Whereas hyperkinetic movements seemed to be more common in patients with truncating variants (67%) compared to missense variants (50%). We also grouped patients into two groups including patients with the p.Arg266* variant (8 patients) and patients without the p.Arg266* variant (16 patients). In both groups, seizures (50% in both groups) and non-ambulation (87.5% of the patients with the p.Arg266* variant and 94% of the patients without the p.Arg266* variant) were reported at the similar frequencies. Whereas, hyperkinetic movements seemed to be more common in patients with the p.Arg266* variant (75%) compared to patients without the p.Arg266* variant (50%). Phenotype was variable in a sibling pair with the homozygous p.Val193Met variant: older sibling had seizures at the age of 15 years and was nonambulatory, whereas younger sibling did not present with seizures and was walking with a walker at the age of 12 years. The *PYCR2* p.Arg266* variant has been reported in the five nonrelated Egyptian families and a Moroccan family.[4,5] This variant could be a founder variant in the north African population.

None of the reported patients have had a biochemical derangement to provide a diagnostic clue to guide molecular genetic confirmation of pyrroline-5-carboxylate reductase 2 deficiency. This inherited metabolic disease is restricted to central nervous system. Cerebrospinal fluid metabolomic analysis might identify a potential biomarker to increase our understanding and might help us to search for treatment targets. It is not certain, if the disease onset is prenatal and if proline supplementation during pregnancy or in the neonatal period would provide any benefit in patients.

Pyrroline-5-carboxylate reductase 2 deficiency is classified as hypomyelinating leukodystrophy-10 (OMIM#616420) by Nakayama et al.[3] Delayed myelination, demyelination, cerebral atrophy, thin corpus callosum, and cerebellar atrophy in brain MRI were also reported in patients.[4–6] Hypomyelination and delayed myelination have a similar appearance on a single MRI. The diagnosis of hypomyelination requires another MRI at least

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Table 1. Clinical features, neuroimaging, and genotype of 24 patients with pyrroline-5-carboxylate reductase 2 deficiency are listed

Patients/age (years)	Clinical features	Brain MRI features	Molecular genetic result
1[a]/11.5[3]	GDD, nonambulatory, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Hypomyelination, thin corpus callosum, thin brain stem	Hmz c.355C>T (p.Arg119Cys) in *PYCR2*
2[a]/10.3[3]	GDD, nonambulatory, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Hypomyelination, thin corpus callosum, thin brain stem	Hmz c.355C>T (p.Arg119Cys) in *PYCR2*
3[b]/9.4[3]	GDD, nonambulatory, dysmorphic features, microcephaly, FTT, muscle wasting	Hypomyelination, thin corpus callosum, thin brain stem	Hmz c.751C>T (p.Arg251Cys) in *PYCR2*
4[b]/7.6[3]	GDD, nonambulatory, dysmorphic features, microcephaly, FTT, muscle wasting	Hypomyelination, thin corpus callosum, thin brain stem	Hmz c.751C>T (p.Arg251Cys) in *PYCR2*
5[c]/6[5]	GDD, seizures, nonambulatory, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Demyelination, thin corpus callosum	Hmz c.28C>T (p.Glu10*) in *PYCR2*
6[c]/2.1[5]	GDD, seizures, nonambulatory, dysmorphic features, microcephaly, FTT, spasticity	Delayed myelination, thin corpus callosum	Hmz c.28C>T (p.Glu10*) in *PYCR2*
7/2.4[5]	GDD, nonambulatory, dysmorphic features, microcephaly, FTT	Delayed myelination, agenesis of corpus callosum	Hmz c.796C>T[h] (p.Arg266*) in *PYCR2*
8[d]/16.8[5]	GDD, seizures, nonambulatory, dysmorphic features, microcephaly, FTT, spasticity	Cerebral atrophy	Hmz c.577G>A (p.Val193Met) in *PYCR2*
9[d]/12.7[5]	GDD, FTT, microcephaly, spasticity	NA	Hmz c.577G>A (p.Val193Met) in *PYCR2*
10[e]/5 died[4]	GDD, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Temporal atrophy	Hmz c.796G>A[h] (p.Arg266*) in *PYCR2*
11[e]/NA[4]	GDD, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, spasticity	Frontotemporal atrophy, thin corpus callosum	Hmz c.796G>A (p.Arg266*)[h] in *PYCR2*
12/4 died[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, FTT, muscle wasting, microcephaly, spasticity	Cerebral atrophy, demyelination	Hmz c.796G>A (p.Arg266*)[h] in *PYCR2*
13/NA[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	NA	Hmz c.694A>C (p.Cys232Gly) in *PYCR2*
14/NA[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Cerebral atrophy, thin corpus callosum	Hmz c.595G>A (p.Arg199Trp) in *PYCR2*
15/3 died[4]	GDD, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Frontotemporal atrophy, thin corpus callosum	Hmz c.796G>A (p.Arg266*)[h] in *PYCR2*
16/5 died[4]	GDD, seizures, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	Cortical changes, thin corpus callosum	Hmz c.796G>A (p.Arg266*)[h] in *PYCR2*
17[f]/6 died[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Cerebral atrophy, thin corpus callosum	Hmz c.773T>C (p.Val184Ala) in *PYCR2*
18[f]/NA[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Cerebral atrophy, thin corpus callosum	Hmz c.773T>C (p.Val184Ala) in *PYCR2*
19[g]/NA[4]	GDD, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	Cerebral atrophy, cerebellar atrophy	Hmz c.139-3C>G (p. ?) in *PYCR2*
20[g]/NA[4]	GDD, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	Cerebral atrophy, cerebellar atrophy	Hmz c.139-3C>G (p.?) in *PYCR2*
21/NA[4]	GDD, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	Cerebral atrophy, white matter changes	Hmz c.394C>T (p.Gly159Arg) in *PYCR2*

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Table 1. *(Continued)*

Patients/age (years)	Clinical features	Brain MRI features	Molecular genetic result
22/NA[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	Cerebral atrophy, thin corpus callosum	Hmz c.595G>A (p.Arg199Trp) in *PYCR2*
23/NA[4]	GDD, seizures, nonambulatory, hyperkinetic movements, dysmorphic features, microcephaly, FTT, muscle wasting	Cerebral atrophy, thin corpus callosum	Hmz c.796G>A (p.Arg266*)[h] in *PYCR2*
24/2.2 (current patient)	GDD, seizures, nonambulatory, dysmorphic features, microcephaly, FTT, muscle wasting, spasticity	Delayed myelination	Hmz c.796C>T (p.Arg266*)[h] in *PYCR2*

FTT = failure to thrive; GDD = global developmental delay; Hmz = homozygous; MRI = magnetic resonance imaging; NA = not available.
[a,b,c,d,e,f,g]Sibling pairs.
[h]Arginine at 266 is encoded by three bases CGA (NM__013328.3). Some patients are reported with c.796C>T, which is the first base change and some patients are reported with c.796G>A, which is the second base change. According to current NM__013328.3, c.796G>A should have been c.797G>A. Both base pair changes affect arginine at 266 and results in stop codon. As c.796G>A is reported in the literature, we did not correct this in the table.

6 months apart from the first MRI to see if myelin content has been increasing. An increase in the myelin content is called delayed myelination. No change in the myelin content between two MRIs is called hypomyelination.[7] After the first report by Nakayama, none of the patients had hypomyelination in brain MRI. To the best of our knowledge, none of the patients had two MRIs to differentiate delayed myelination from hypomyelination.

Pyrroline-5-carboxylate reductase 2 deficiency is a rare inherited metabolic disorder affecting central nervous system. Hyperkinetic movements seem to be more common in patients with truncating variants and the p.Arg266* variant in *PYCR2*. Identification of more patients might expand the phenotypic spectrum of pyrroline-5-carboxylate reductase 2 deficiency.

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Statement of Authorship

Dr. Afroze drafted the manuscript, reviewed the literature, and approved the final version of the manuscript.

Dr. Mercimek-Andrews supervised and mentored Dr. Afroze for data analysis and completeness of manuscript.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary Material

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