16-month-old boy presented with mild psycho-motor retardation, dysmorphism and seizures. He was born at term, 3250 gr. The parents were consanguineous. At first physical examination, his weight was 10 kg (17.1*p*; − 0.95 SD), height 78 cm (13.57 *p*; − 1.1 SD), and head circumference 47.3 cm (28.7*p*; − 0.56 SD). His neurological examination was normal. He started to walk at 27 months and spoke single words at 35 months. His brain MRI and auditory test were normal. Generalized epileptiform discharges were observed on his EEG._In the clinical course his autistic features and dysmorphic facial features became evident. The e

Pyrimidine Metabolism Disorders as a Rare Cause of Psycho-motor Retardation, Dysmorphism and Epilepsy

Defne Alikılıç[1], Deniz Sünnetçi-Akkoyunlu[2], Adnan Deniz[1], Merve Öztürk[1], Ömer Karaca[1], Mesut Güngör[1], Bülent Kara[1]

[1]Kocaeli University Medical Faculy, Department of Pediatrics, Division of Child Neurology, Kocaeli, Turkey

[2]Kocaeli University Medical Faculy, Department of Genetics, Kocaeli, Turkey

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OBJECTIVES

Pyrimidine nucleotides are important in function of the central nervous system. Metabolic changes in pyrimidine levels cause a variety of abnormal neurological activities. Enzyme deficiencies in the uracil and thymine pathways cause these metabolism disorders (Fıgure 1) ß-ureidopropionase deficiency is a very rare disease with autosomal recessive inheritance caused by mutation in the UPB1 gene. Cranial MRI abnormalities such as cerebral atrophy, brain stem hypoplasia, cortical dysplasia, corpus callosum hypoplasia, vermis hypoplasia, delay in myelination; seizures, cognitive retardation, dystonia and other neurological symptoms can be seen in patients. Dihidropyrimidinase is the second enzyme in pyrimidine metabolism. Mutations in the DPYS gene can lead to deficiency of this enzyme. Dihidropyrimidinase deficiency is also a very rare metabolic disorder with autosomal recessive inheritance. The most common clinical features are seizures, cognitive retardation and hypotonicity. We describe 2 patients with psycho-motor developmental delay, dysmorphic features and epilepsy diagnosed with pyrimidine metabolism disorder by detecting mutations in *UPB1* and *DPYS* with whole exome sequencing (WES) analysis.

MATERIALS & METHODS

The data of two cases diagnosed with beta-ureidopropionase deficiency and dihidropyrimidinase deficiency will be discussed.

CASE 1

A five-month-old boy presented with severe psycho-motor retardation, dysmorphism and epileptic spasms. He was born at term, 3,150 g. The parents were non-consanguineous. He had a familial history of a sibling who had seizures and dystonia and died at 13 months of age. His weight was 7 kg (6.18*p*;−1.54 SD), height 65 cm (3.59*p*; −1.8 SD) and head circumference 42 cm (2.87*p*;−1.9 SD)Neurological findings included axial hypotonia, spasticity in extremities, horizontal nystagmus with lateral gaze. He had dysmorphic facial features (eyebrows are scattered and thickened to the sides, long eyelashes, long and prominent philtrum, scattered eyebrows, flat nasal root). Brain MRI demonstrated diffuse cerebral atrophy and pontocerebellar hypoplasia. EEG examination revealed hypsarrhytmia. The patient was diagnosed as West syndrome. In his clinical course status dystonicus developed and managed with supportive care and dystonia spesific medications. Now, he is 2-year-old, and still has severe psycho-motor retardation, and partially controlled seizures with polytherapy. Routine diagnostic tests were uninformative. WES analysis showed pathogenic, compound heterozygous variants in *UPB1* (c.105-2A>G and c.917-1G>A).

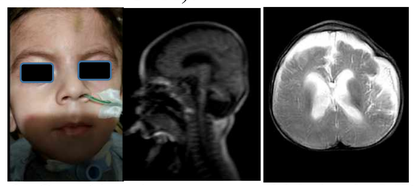

Figure 2. Case1's phenotype and his brain MRI images

CASE 2

16-month-old boy presented with mild psycho-motor retardation, dysmorphism and seizures. He was born at term, 3250 gr. The parents were consanguineous. At first physical examination, his weight was 10 kg (17.1*p*; − 0.95 SD), height 78 cm (13.57 *p*; − 1.1 SD), and head circumference 47.3 cm (28.7*p*; − 0.56 SD). His neurological examination was normal. He started to walk at 27 months and spoke single words at 35 months. His brain MRI and auditory test were normal. Generalized epileptiform discharges were observed on his EEG._In the clinical course his autistic features and dysmorphic facial features became evident. The etiology could not be identified with routine diagnostic tests. Now, he is 14-year-old, needs special education support, and seizures are partially controlled with monotherapy. WES analysis showed a likely-pathogenic, homozygous variant of *DPYS* (c.382G>A*)*. Both patients are diagnosed with pyrimidine metabolism disorder. The diagnosis was confirmed by urine pyrimidine metabolite analysis.

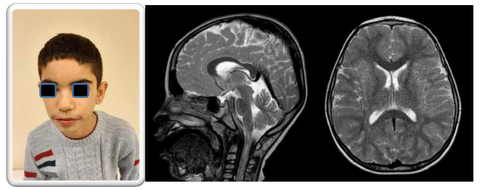

Figure 3. Case 2's phenotype and his brain MRI images

CONCLUSIONS

Psycho-motor retardation, dysmorphism and seizures are frequently observed in patients with inborn errors of metabolism disorders. Urine pyrimidine metabolites should be screened in patients with severe psycho-motor retardation and epilepsy if metabolic disorders screening tests were uninformative before performing more complicated diagnostic tests.

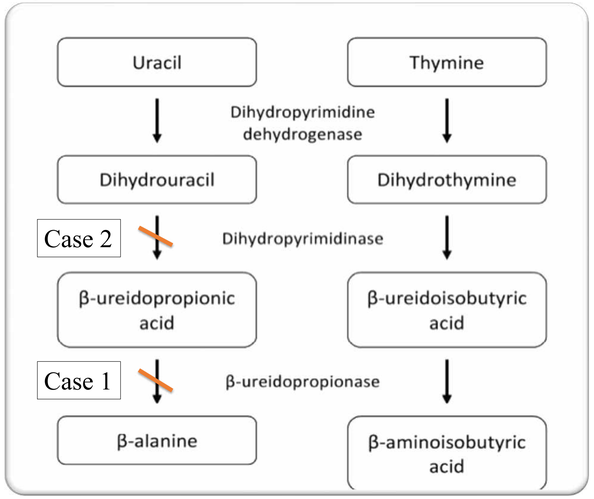

Figure 1. Metabolic pathway of pyrimidine

KEYWORDS

pyrimidine, status dystonicus, epilepsy, psycho-motor retardation