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4-Hydroxybutyric Aciduria as a Rare Presentation of Global Developmental Delay in Children: Case Report of Two Different Patients

Rahim Vakili[1], *Mehran Beiraghi Toosi[2], Asma Javid[3], Nahid Donyadideh[2], Farnoosh Ebrahimzadeh[4], Narges Hashemi[2], Somayeh Hashemian[1]

[1]Department of Pediatric Endocrinology, Emam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Department of Pediatric Neurology, Ghaem Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[3]Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[4]Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Succinic semialdehyde dehydrogenase (SSADH) deficiency or 4-Hydroxybutyric Aciduria is an autosomal recessive inherited disorder of amma-aminobutyric acid (GABA) degradation. It is characterized by developmental delay, infantile-onset hypotonia, cognitive impairment language deficit, and ataxia. Epilepsy, aggression, Hyperkinetic behavior, hallucinations, and sleep disturbances have been described in about half of the patients, more frequently in older individuals.

Its management is largely symptomatic, conducted at the treatment of seizures and neurobehavioral disorder. We present two girls with chief complaint of hypotonia and developmental delay how referred to department of Pediatrics (Ghaem hospital), Mashhad, Iran.

Key Words: Child, Developmental delay, 4-Hydroxybutyric Aciduria, Hypotonia.

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Corresponding Author:

Mehran Beiraghi Toosi (M.D), Department of Pediatric neurology. Ghaem hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

E-mail: beiragitoosimehran@gmail.com

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1- INTRODUCTION

Succinic semialdehyde dehydrogenase (SSADH) deficiency or 4-Hydroxybutyric Aciduria is an autosomal recessive inherited disorder of GABA degradation (1). GABA converts to succinate by combination of SSADH and GABA transaminase. The absence of SSADH leads to the transformation of GABA to γ-Hydroxybutyric acid (GHB) (2-4) . The incidence of this disorder is unknown. A study of 182 patients from 40 countries determine the incidence of SSADH deficiency, with the most number of patients noted from the USA (24%), Turkey (10%), China (7%), Saudi Arabia (6%), and Germany (5%) (5).

4-Hydroxybutyric Aciduria is characterized by developmental delay, infantile-onset hypotonia, cognitive impairment language deficit, and ataxia. Epilepsy, aggression, hyperkinetic behavior, hallucinations, and sleep disturbances have been described in about half of the patients, more frequently in older individuals. Basal ganglia signs including dystonia, choreoathetosis, and also myoclonus have been expressed in a minority of patients with earlier-onset and severe ones (6, 7).

SSADH deficiency is diagnosed by checking levels of organic acids in urine (increased concentrations of 4-hydroxybutyric acid (4-HBA) in urine (i.e., 4-hydroxybutyric aciduria), measurement the activity of the SSADH enzyme in white blood cells and molecular genetic testing (identification of biallelic pathogenic variants in aldehyde dehydrogenase 5 family member A1 [ALDH5A1]) (6, 8, 9). 4-Hydroxybutyric acid has been found in the urine of the all studied patients (10).The amounts excreted varied from 170 to340 mmol/mol creatinine. Concentration in urine have ranged from 2 fold to 5oo fold the normal level (11). Management is largely symptomatic, conducted at the treatment of seizures and neurobehavioral disorder (12, 13).

2- CASE REPORTS

2-1. Case.1

N.K, an Iranian girl born to consanguineous parents (cousin), presented at 4.5 years of age for evaluation of failure to thrive and hypotonia since the age of 4 months (**Figure.1**). She had one sibling who was an eight-year old healthy girl and had no developmental problems. Her mother had an uncomplicated pregnancy. She was a full term baby with birth weight of 2,700gr, birth length of 45cm, birth head circumference of 33cm and normal Apgar score. She admitted at hospital in the third day of life with chief complaint of poor feeding but no remarkable abnormal studies. She also had one hypoglycemic attack one year ago. Developmentally, at 54 months, she could not say any words but babbling, and had head drop until 12 months of age. She could seat without support at 18 months and walk alone in 30 months. Physical examination revealed a weight of 16 kilograms, head circumference of 48cm and length of 103cm.

No organomegaly were noticed. Neurological examination results show mild hypotonia (low muscle tone), and decreased deep tendon reflexes. No ataxia was detected. She didn't have any history of seizure. The patient's plasma showed normal Ammoniac (67 µmol/L), and lactate (12 mg/dl). Tandem mass spectrometry (MS/MS), high-performance liquid chromatography (HPLC) for serum amino acids and Urine sugar thin-layer chromatography (TLC) were normal. The concentration of Glycosaminoglycans (GAGs) or mucopolysaccharides in urine was 15.1 mg/mmol creat (normal range 5.2 to 10.6). The organic acids in her urine showed an elevated 4-Hydroxybutyric Acid (450 mmol/mol creatinine, normally

not detected). Electromyography (EMG) and nerve conduction velocity (NCV) tests, Auditory Brainstem Response (ABR) test and brain computed tomography scan were normal. Brain Magnetic Resonance Imaging (MRI) shows unspecified personality in white matter of right parietal lobe (**Figure.2**). Also, Electroencephalogram (EEG) showed unspecific changes.

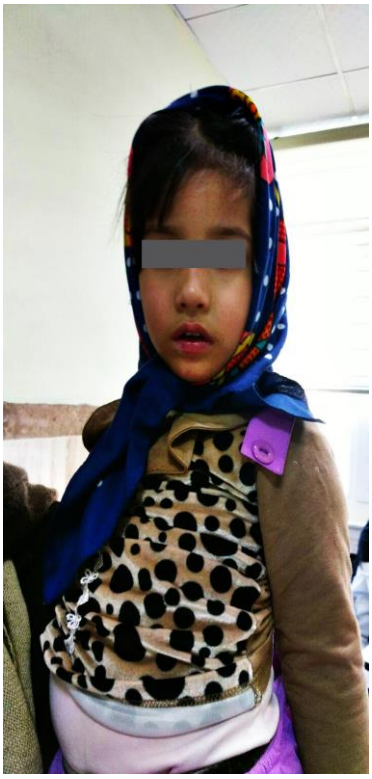

Fig.1: A 4.5-year-old with 4-Hydroxybutric Aciduria.

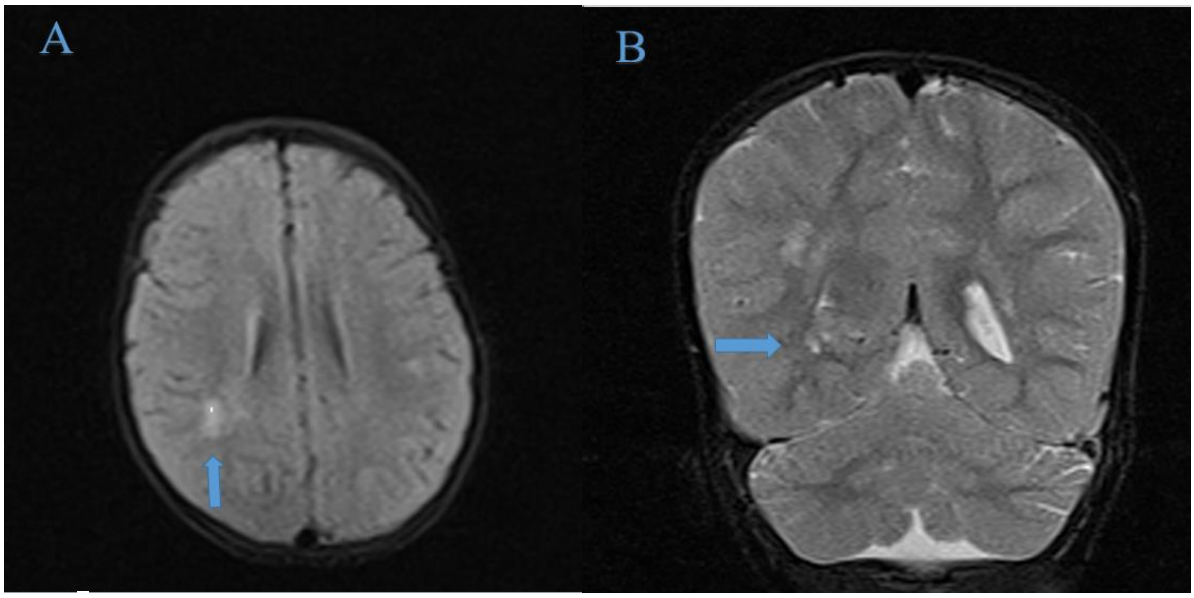

Fig.2: Brain Magnetic Resonance Imaging: unspecified hypersignal in white matter of right parietal lobe. (A) Axial view, Fluid Attenuated Inversion Recovery (flair) sequence (B) coronal view, T2 - weighted sequence.

2-2. Case.2

K.K. presented at 4 years of age for evaluation of developmental delay and hypotonia (**Figure.3**). She was the first child of consanguineous parents from Iran. She was a 32 weeks' preterm baby with birth weight of 1,560gr, birth length of 41cm and birth head circumference of 32cm. At birth she was admitted at neonatal intensive care unit (NICU) for 17 days, and discharged without any complication. At 12 months, the infant had a probable seizure and her motor development was retard. At examination in 4 years old, her weight was 13.5kg, height was 100 cm, and head circumference was 47 cm. She had autistic spectrum disorder and had bilateral ptosis, oculomotor apraxia, increased deep tendon reflexes, mild dystonia and stereotypy. No organomegaly was detected. The patient's plasma showed normal Ammonia (89 µmol/L) and lactate (11.5 mg/dl). Tandem mass spectrometry (MS/MS), high-performance liquid chromatography (HPLC) for serum aminoacids and Urine sugar thin-layer chromatography (TLC) were normal. The organic acids in her urine showed an elevated Lactic acid (487 mmol/mcl creatinine, normal<158mmol/mcl creatinine), an elevated 3-Hydroxybutyric acid (83.9 mmol/mcl creatinine, normal < 5.8 mmol/mcl creatinine), and an elevated 4-Hydroxybutanoic Acid (41.9 mmol/mol creatinine, normally not detected). MRI was normal. She had mildly abnormal electroencephalogram (EEG).

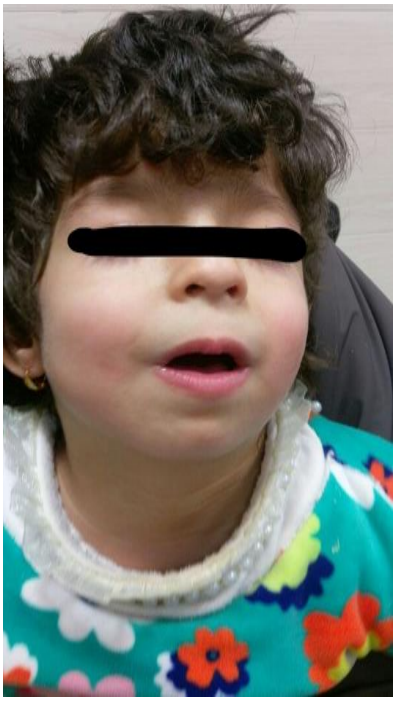

Fig.3: The index patient with 4-Hydroxybutyric Aciduria.

3- DISCUSSION

In this case report, we described two patients with 4-Hydroxybutyric Aciduria who initially presented with developmental delay and hypotonia. They had nonspecific clinical features witch could astound the correct diagnosis. Patients with 4-Hydroxybutyric Aciduria do not manifest the regular concomitant of an inborn error of metabolism. There was no hyperammonemia, metabolic acidosis, growth retardation, episodic vomiting or lethargy that often seen in other inborn

error of metabolism. Although urine mucopolysaccharides (MPS) in urine was elevated in the first girl, because it does not match with clinical signs the diagnosis was ruled out. So it is important to match the clinical and para clinical findings to get the true diagnosis and keep in mind that we must check levels of organic acids in urine in any child with hypotonia and developmental delay without any reason.

4- CONCLUSION

Our suggestion would be exact, quantitative, organic acid analysis be ordered for any patient presenting with hypotonia and motor, mental or language delay of unknown cause. We think that expansion the use of organic acid analysis will lead to increase the diagnosis of SSADH deficiency, which will afford a more definite representation of the disease frequency. As additional patients are diagnosed, we should have a better perceptive of both the metabolic and clinical profile of SSADH deficiency.

5- CONFLICT OF INTEREST: None.

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