Is pyridoxine effective in the treatment of hyperphosphatasia with mental retardation syndrome type 4: Single center experience

Şeyda Beşen[1], İlknur Erol[1], Özlem Sangün[2] , Leman Tekin Orgun[1], Atıl Bişgin[3]

[1]Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Application and Research Center, Department of Pediatric Neurology, Adana,Turkey

[2]Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Application and Research Center, Department of Pediatric Endocrinology, Adana,Turkey

[3]Cukurova University AGENTEM (Adana Genetic Diseases Diagnosis and Treatment Center) and Medical Genetics Department of Medical Faculty, Adana,Turkey

ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION

Hyperphosphatasia mental retardation syndrome (HPMRS) is a rare, autosomal recessive disease which is caused by homozygous or compounds heterozygous mutations of six genes (PIGV, PIGY, PIGO, PGAP2, PIGW and PGAP3) which involved in phosphatidylinositol biosynthesis.

Glycosyl phosphatidylinositol (GPI) is a glycolipid that anchors nearly 250 proteins to the cell surface. It has a very important role in neuronal and embryonic development. Alkaline phosphatase (AP) is one of the GPI anchoring enzymes. So defects of GPI synthesis cause the elevation of alkaline phosphatase. **Alkaline phosphatase is also a key enzyme for dephosphorylation of circulating pyridoxal-5'-phosphate to pyridoxal, the primary vitamin B6 derivative which crosses the blood-brain barrier.** Depending on the mutated gene, HPMRS is divided into six subtypes as HPMRS types 1-6. All subtypes have common clinical features: dysmorphic facial findings, severe to profound mental motor retardation (MMR), hypotonia and persistent alkaline phosphatase(ALP) elevation. There are nearly 30 HPMRS type 4 cases in the literature and only two of which are Turkish.

OBJECTIVES

Herein the largest series from Turkey diagnosed with PGAP3-associated HPMRS type 4 whose epileptic seizures responded to pyridoxine are reported.

MATERIALS & METHODS

Results of all four HPMRS type 4 cases, two of which were siblings, had significant dysmorphic features, mental retardation, epilepsy, elevated alkaline phosphatase levels and hypotonia. The age of patients ranged from 10 months to 12 years and 6 months, all cases had epilepsy and one had drug-resistant epilepsy, who has applied a vagal nerve stimulator (VNS) in another territory center. **The AP levels of the patients range from 922 U/L to 2258 U/L. In addition to the antiepileptic drug treatment, all cases were started with pyridoxine, considering the pathophysiological mechanisms after the underlying genetic diagnosis. Seizure control was achieved in all cases**.

DISCUSSION

Glycosylphosphatidylinositol anchored protein (GPI-AP) consists of glycosylphosphatidylinositol (GPI) anchor and a certain protein. At least 250 different human proteins are anchored via GPI anchor. There are nearly 30 genes involved in the biosynthesis of GPI-AP. Mutations of some genes in this pathway cause glycosylphosphatidylinositol deficiencies (IGDs). **Major symptoms of IGDs are mental retardation, epilepsy, facial anomalies, and persistent AP elevation that vary in severity depending upon the degree of defect and/or position in the pathway of the affected gene.** Seizures, which may become intractable, are one of the most common symptoms among the IGD patients.

Most GPI-anchored proteins such as AP are affected by disturbances in IGDs. Alkaline phosphatas is a well-characterized enzyme activity that is easily and frequently measured in clinical medicine. It can be a useful biomarker for IGDs**. It is also esential for dephosphorylation of circulating pyridoxal-5'-phosphate (PLP) to pyridoxal (PL), the primary vitamin B6 derivative which crosses the blood-brain barrier. Pyridoxal is converted to PLP intracellularly and functions as a cofactor for glutamate decarboxylase, the enzyme that synthesizes an inhibitory neurotransmitter, g-aminobutyric acid (GABA). In IGDs, there may be reduced neuronal AP expression, which may in turn lead to intracellular PLP and GABA deficiency**. **As a result, the lack of PLP dephosphorylation on the neuronal surface may cause the intractable seizures observed in patients with IGDs**.

All the subjects in our study had epilepsy and one had drug-resistant epilepsy, who applied VNS. Pyridoxine is another form of vitamin B6 that can penetrate cell membranes without the need for phosphatase**. A few studies have shown that high-dose pyridoxine treatment is effective for seizures in patients with IGDs. So in addition to the antiepileptic drug treatment, all cases were started with pyridoxine**. All of the patients became seizure-free in a month time İncluding the patient with VNS. We also observed improvement in interictal EEG's of the patients. Among the patients with a confirmed causative gene, some of the previous studies showed the effectiveness of pyridoxine treatment for PIGV, PIGO, and PIGS, deficiencies. All of our patients had PGAP3 mutation and responded to the administration of pyridoxine**. There is only one case report, a Croatian boy with PGAP3 mutation, who was administered a high dose of pyridoxine and responded to the treatment, properly. Therefore, patients in this study are the widest PGAP3 mutation group which a pyridoxine response has been demonstrated in the literature.**

CONCLUSION

Identifying the underlying genetic mutations and mechanisms will open new horizons in the control of diseases with specific targeted therapies, as in our cases. In this study, pyridoxine response in epilepsy of HPMRS type 4 cases was shown for the second time in the literature.