CASE REPORT

BIOTIN METABOLISM DEFECT - A CASE REPORT

Ananth N Rao, Rajesh B Iyer*, Kavitha J, Minakshi Koch and Suresh Kumar V

Metabolism Laboratory and *Department of Neurology, Narayana Hrudayalaya, Bangalore, India.

ABSTRACT

Defects in biotin metabolism are mainly associated with either the enzyme Biotinidase or Holocarboxylase synthetase. Defects in either enzymes deplete biotin utilization by the cells. Holocarboxylase synthetase deficiency is an inherited disorder in which the body is unable to use the vitamin biotin effectively. This condition is inherited in an autosomal recessive pattern. We present a case of a 9 year old girl with atypical symptomatology as a case holocarboxylase synthetase deficiency, who demonstrated an increased excretion of propionic and methyl malonic acids, with her biotinidase activity being normal. She demonstrated remarkable improvement on biotin supplementation.

KEY WORDS

Biotin Metabolism, Holocarboxylase, Inherited disorder, Autosomal recessive.

INTRODUCTION

Holocarboxylase synthetase (HLCS) deficiency is an inherited disorder in which the body is unable to use the vitamin biotin effectively. This disorder is classified as a multiple carboxylase deficiency, a group of disorders characterized by impaired activity of certain enzymes that depend on biotin. This condition is inherited in an autosomal recessive pattern. The exact incidence of this condition is unknown, but it is estimated to affect 1 in 87,000 people (1). The HLCS gene provides instructions for making an enzyme called holocarboxylase synthetase. This enzyme is important for the effective use of biotin, a B vitamin found in foods such as liver, egg yolks, and milk. Holocarboxylase synthetase attaches biotin to certain enzymes that are essential for the normal production and breakdown of proteins, fats and carbohydrates in the body. Mutations in the HLCS gene reduce the enzyme's ability to attach biotin to these enzymes, preventing them from processing nutrients properly and disrupting many cellular functions. These defects lead to the serious medical problems

associated with holocarboxylase synthetase deficiency (2).

The signs and symptoms of holocarboxylase synthetase deficiency typically appear within the first few months of life, but the age of onset varies. Affected infants often have difficulty feeding, breathing problems, a skin rash, hair loss (alopecia) and a lack of energy (lethargy). Immediate treatment and lifelong management with biotin supplements may prevent many of these complications. If left untreated, the disorder can lead to delayed development, seizures and coma. These medical problems may be life-threatening in some cases (3).

CASE

A nine years old girl presented with history of developmental delay, cognitive impairment and behavioral problems. The child was born of second degree consanguineous parentage. Birth was at term by a normal vaginal delivery. The antenatal period was uneventful. The child cried immediately after birth and the neonatal period was uneventful. Subsequently there was delay in development. The child achieved head control after 6 months was able to turn by one year and stand by 3 years. At presentation at nine years of age she could speak only eight words without sentence formation, was ambulant, could indicate only some of her needs and was dependant for most activities of daily living. She had poor comprehension and was mostly irritable when awake. Behavioral problems consisted

Address for Correspondence :

Dr. Ananth N Rao,
Consultant & Head,
Metabolism Laboratory,
Narayana Hrudayalaya, Bangalore 560099
E-mail: ananthnrao@yahoo.co.in

of frequent crying spells and motor events. The motor events were noted since three years of age and were characterized by bizarre eye movements, posturing of limbs followed by hypotonia of limbs lasting about 1-2 minutes. She would often fall if not supported. She would cry after each such event and go to sleep. These occurred at variable frequency from 3 per month to several per day. She had been on antiepileptic medications since about 4 years of age without any benefit.

On examination, she appeared mentally challenged, did not comprehend commands and was irritable. There was alopecia. No definite lateralizing neurological deficits could be detected. MRI brain was normal. Video EEG was done to characterize her events. No intricate epileptic form discharges were seen. Events recorded did not have any electrographic correlate suggesting non epileptic events.

The blood and the urine sample of the subject were tested for inborn errors of metabolism which involves the amino acids, organic acids, carbohydrates, ketones were measured quantitatively. We have used High Performance Liquid Chromatography (HPLC, Shimadzu LC 20AD) with a Diode array detector (SPD M20A) for quantitations of aminoacids & organic acids. Aminoacids were quantitated using the

Phenylisothiocyanate method (PICOTAG) from Waters Corporation. Organic acids were quantitated on the HPLC using a C-18 (150x4.6mm, particle size 5µm) column; mobile phase of 6mM orthophosphoric acid (pH 2.6). Flow rate was set of 1.0 ml/minute and detection was at 210nm (5). Urine organic acid studies revealed the significantly elevated levels of methyl malonic and propionic acid. The presence of methyl malonic and propionic acid were confirmed by co-elution with standard methyl malonic and Propionic acid (Fig 1). The elevated levels of the above mentioned organic acids suggesting the biotinidase deficiency. The enzyme assay for the biotinidase (6) was performed for the confirmation, but the results indicated normal biotinidase activity. Hence, we concluded on holocarboxylase deficiency.

Antiepileptic medications were tapered off. She was started on multivitamins in addition to 10mg of Biotin per day. She gradually improved. The crying spells and motor events abated after 1 month. She started picking up language. After 6 months she was able to name herself, obey simple commands and had started writing alphabets. The 2 years old younger sibling was also subjected to metabolic screening, which was normal.

DISCUSSION

This child presented with developmental delay, cognitive impairment, behavioral problems and motor events. The constellation of symptoms usually point towards a metabolic disorder, particularly if there is a consanguineous parentage. The nature of the child's events was uncertain, though she had been on antiepileptic medications without any benefit. Video EEG was useful to confirm that these were not epileptic in origin. The movements could have been due to psychogenic causes although dystonia was a differential. Metabolic evaluation clinched the diagnosis. Biotin supplementation has resulted in remarkable improvement. No mutation studies were possible at our centre. Parents were unwilling to conceive another child. The follow-up improvement in the child holds promise to many such affected children, who may go undiagnosed if not screened for an inborn error of metabolism. Any case with presentation of seizures, spasms, delayed milestones and abnormal behavior should be screened for this class of disorders.

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Figure 1: Analysis: HPLC for Organic acids with Acetic acid as Internal Standard

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