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PHENYLKETONURIA A CASE STUDY

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Abstract : Classical type of phenylketonuria (PKU) is characterized by complete or near complete deficiency of phenylalanine hydroxylase. Classical PKU is associated with less than 2 activity of normal phenylalanine hydroxylase. The infants are normal at birth, if the disease is unrecognized and untreated, mental retardation may develop gradually and may not be evident for few months. Symptoms of PKU can range from mild to severe. The most severe form of this disorder is known as classic PKU. An infant with classic PKU may appear normal for the first few months of his or her life. If the child is not treated for PKU during this time, he or she will begin to develop symptoms such as intellectual disabilities or mental retardation, seizures tremors or jerky hand and leg movements, hyperactivity. stunted growth, eczema, distinct odor in breath, skin that is often described as mousy odour, lighter skin, hair, and eye color than their family members. . A mousy odour in the child's breath, skin caused by too much phenylalanine in the body. Fair skin and blue eyes are present because phenylalanine cannot be transformed into melanin, the pigment responsible for hair and skin tone. Abnormally small head (microcephaly) can also be present. A less severe form of this disorder is called variant PKU or non-PKU hyperphenylalaninemia (having too much phenylalanine.) Children with this form of the disorder may have only mild symptoms, but they will need to follow a special diet to prevent mental retardation. In rare cases in which the disorder was not diagnosed at birth and treatment was not started quickly, symptoms of PKU can cause irreversible brain damage and mental retardation within the first few months of life, behavioural problems and seizures in older children Once a specific diet and other necessary treatments are started, symptoms diminish. People with PKU who properly manage their diet dont show any symptoms.

Keyword : Phenylketonuria, Phenylalanine, Phenylalanine hydroxylase, mental retardation , Tetrahydrobiopterin.

CASE HISTORY

A 5 years old male child was detected to have a phenylketonuria classical type at the age of five years. The child was born to parents of consanguineous marriage and presented to our pediatric OPD with history of diarrhea and vomiting for 2 days. Child is a mentally retarded child, had 6 episodes of seizures. The first episode started at 9 month of age and now on anticonvulscent therapy. Child delivered normally with a birth weight of 3kg and cried immediately after birth. Child was only on breast feed for first nine months of life. Light colored hair was noticed at the age of 4 months. Color of the hair was golden brown. Child had delayed mile stones.

ON EXAMINATION:

Height - 94cms
Weight - 14 kg.
Head Circumference - 56.5 CMS.
Color of the skin - fair
Color of the hair - listic golden
Iris color - light brown
Hyperpigmentation - Nil
Child - dehydrated .
heart rate - 114 per minute.
blood pressure - 70/50 mmhg
Mousy odour - Present all over his body.
CVS - Normal
RS - Normal
CNS - Hyptonia present.

Child was treated for his AGE with moderate dehydration. Provisional diagnosis of Phenyl Ketonuria was made and the following investigations were done.

INVESTIGATIONS

· Urine Reducing Sugars - Absent.
· Urine Ferric Chloride Test

Patient advised to have an overnight fast and at morning 7 a.m. urine samples were collected and the test performed immediately. 3 - 5 drops of the reagent (Ferric Chloride 10%) was added to 5ml of urine. There was an appearance of blue green colour immediately. The colour fades within 2 minutes. This suggest the presence of phenyl pyruvate in urine.

· Blood Sugar - 70mg/dl
· Total Protein - 5gram/dl
· Serum Albumin - 2.5gram/dl
· Serum Phenylalanine - 29 mg/dl done on 11/02/2015

DISCUSSION

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterized by a deficiency in the enzyme phenylalanine hydroxylase. When this -enzyme is eficient, phenylalanine accumulates and is converted to phenyl pyruvate, which is also known as phenylketone, which is detectable in the urine1 The clinical symptoms suggestive of probable preliminary diagnosis of PKU. are delayed milestones

of growth, vomiting since birth, blonde hair and eyebrows, jaundice and organomegaly, rickets, diarrhea, pneumonia, convulsions and skeletal deformities2. Untreated PKU can lead to intellectual disability, seizures, and other serious medical problems. The disease may present clinically with seizures, albinism (excessively fair hair and skin), and a "mousy odor" to the baby's sweat (due to phenylacetate, a carboxylic acid produced by the oxidation of phenylketone3). The mainstream treatment for classic PKU patients is a strict PHE-restricted diet supplemented by a medical formula containing amino acids and other nutrients. Patients who are diagnosed early and maintain a strict diet can have a normal life span with normal mental development4. However, recent research suggests that neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology are slightly suboptimal if diet is not supplemented with amino acids5. In addition, PKU diets include all the nutrients normally required for good health and normal growth, such as carbohydrates, fats, vitamins, and minerals. High protein foods like meat, fish, chicken, eggs, nuts, beans, milk, and other dairy products are banned from PKU diets. Small amounts of moderate protein foods (such as grains and potatoes) and low protein foods (some fruits and vegetables, low protein breads and pastas) are allowed. Sugar-free foods, such as diet soda, which contain the artificial sweetener aspartame, are also prohibited foods for PKU patients. That is because aspartame contains the amino acid phenylalanine. Ideally, school-age children with PKU should be taught to a sume responsibility for managing their diet, recording food intake, and for performing simple blood tests to monitor their phenylalanine levels. Blood tests should be done in the early morning when phenylalanine levels are highest. Infants and young children require more frequent blood tests than older children and adults. The amount of natural foods allowed in a diet could be adjusted to ensure that the level of phenylalanine in the blood is kept within a safe range—two to 6 mg/dL before 12 years of age and 2- 15 mg/dL for PKU patients over 12 years old.6 It was recently suggested that PKU may resemble amyloid diseases, such as Alzheimer's disease and Parkinson's disease, due to the formation of toxic amyloidlike assemblies of phenylalanine5.

PREVENTION

PKU was the first disorder to be tested for through widespread newborn screening. Robert Guthrie introduced the newborn screening test for PKU in the early 1960s6. With the knowledge that PKU could be detected before symptoms were evident, and treatment initiated, screening should be done in the newborn If a child is not screened during the routine newborn screening test (typically performed 2-7 days after birth, using samples drawn by neonatal heel prick), In most cases, a repeat test should be done at approximately two weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed7. A biosensor was developed for the detection of L-phenylalanine (Phe) and demonstrated for use in the diagnosis of phenylketonuria (PKU). It consists of L-phenylalanine dehydrogenase (L-PheDH) immobilized on a membrane an ultraviolet light-emitting diode excitation system, and a photomultiplier tube. The L-PheDH was immobilized on a teflon membrane modified with 2-methacryloyloxyethyl phosphorylcholine and placed at the distal and of an optical fiber. The concentration of Phe was determined by immersing the sensor into a sample solution that also contained NAD+ and measurement of the fluorescence of the NADH produced by enzymatic reaction. The fluorescence intensities of thebiosensor are linearly related to the L-Phe concentrations in the range from 10 mol L1 to 10 mmol L1. The sensor also operated in the kinetic mode by differential determination of the slope of the signal within 2 min. The analyticalrange of the sensor is adequate for application in the genotypic diagnosis of PKU (diagnostic value >600 mol L1). High sensitivity, good cost-benefit ratio, and low power consumption are typical features of this biosensing system that can can be applied to routine screening of newborn8,9. A new method for quantifying specific amino acids in small volumes of plasma and whole blood has been developed. Based on isotopedilution tandem mass spectrometry, the method takes only a few minutes to perform and requires minimal sample preparation. The accurate assay of both phenylalanine and tyrosine in dried blood spots used for neonatal screening for phenylketonuria successfully differentiated infants who had been classified as normal, affected, and falsely positive by current fluorometric methods. Because the massspectrometric method recognizes aminoacidemias and is capable of automation, it represents a useful development toward a broad-spectrum neonatal screening method10. In contrast, affected children who are detected and treated are less likely to develop neurological problems or have seizures and intellectual disability. While prescribing the diet the foodstuffs which are low in phenylalanine and high in calories should be selected. This diet should provide all nutrients in required quantities and should also provide satiety. Very low phenylalanine contained foods can be used in liberal amount11

TREATMENT

General treatment

The oral administration of tetrahydrobiopterin or BH4 (a cofactor for the oxidation of phenylalanine) can reduce blood levels of this amino acid in certain patients12. Dietary supplementation with large neutral amino acids(LNAAs), with or without the traditional PKU diet is another treatment strategy13. The LNAAs (e.g. leucine, tyrosine, tryptophan, methionine, histidine, isovaline, valine, threonine) compete with phenylalanine for specific carrier proteins that transport LNAAs across the intestinal mucosa into the blood and across the blood brain barrier14 Another interesting treatment strategy for PKU patients is casein glycomacropeptide (CGMP), which is a milk peptide naturally free of Phenyl alanine in its pure form. CGMP can substitute the main part of the free amino acids in the PKU diet and provides several beneficial nutritional effects compared to free amino acids. The fact that CGMP is a peptide ensures that the absorption rate of its amino acids is prolonged compared to free amino acids and thereby results in improved protein retention and increased satiety, compared to free amino acids. Another important benefit of CGMP is that the taste is palatables and this may help ensure improved compliance to the PKU diet15. Furthermore, CGMP contains a high amount of the phenyl alanine lowering LNAAs, which maintains the plasma phenyl alanine levels in the target range16. Other therapies are currently under investigation, including gene therapy and enzyme substitution therapy with phenylalanine ammonia lyase (PAL)17.

In the past, PKU-affected people were allowed to go off diet and today, most physicians recommend PKU patients must manage their Phenyl alanine levels throughout life and sufferers often bear children who will be carriers of the recessive gene, and may themselves live past the age of sixty18,19.

Treatment for the above mentioned child

The above mentioned child was put on low phenyl alanine diet (35mg/kg/day) formulated from locally available foods. Clinical and biomedical response monitored with the aid of urinary Ferric Chloride test and serum Phenyl Alanine levels. Serving list for vegetables, fruits, bread, cereals and lentils were prepared according to their phenyl alanine content of 15mg or30mg in the diet. This list of exchange allowed for some variety in the diet. High protein food such as meat, soya and milk were avoided as far as possible. On the other hand, sugars, jam and ghee were freely allowed. The importance of

dietary control was stressed to the parents and instructed to record the food consumed in a day. The diet was modified according to serum Phenyl Alanine levels at weekly intervals. Vitamins were supplemented and infections promptly treated. On follow up after 2 months and 9 months the parents reported an improvement in his behavior. He related better to his parents. His weight gain was satisfactory, but precise response to therapy could not be judged by IQ. On this diet he showed mild clinical and biochemical improvement.

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