Assessment of serum levels of zinc and copper in a sample of Egyptian children with phenylketonuria.

Prof. Randa Abdel Raouf
Professor of pediatrics Ain Shams university
Prof. Laila Effet
Professor of molecular genetics
National researchg center
Prof. Maha Saber
Professor of child health
National researchg center
Dr. Yasmin Ziada

Abstract:

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder in which phenylalanine (Phe) cannot be converted into tyrosine, leading to the accumulation of toxic metabolites. In the absence of treatment, the clinical manifestations of PKU include mental retardation, behavioral and dermatological problems. Consequently, the dietary regimen of PKU depends mainly on a protein restricted diet together with phenylalanine free milk formula, such type of diet may decrease the bioavailability of many nutrients. Some studies reported low serum level of zinc and copper in phenylketonuric children and adolescents. Objectives: This study aimed to assess serum levels of zinc and copper in a group of Egyptian children with phenylketonuria, and to determine the effects of diet on blood phenylalanine levels, IQ and neurological functions of this group.

Methods:

This study was carried on thirty one children suffering from phenylketonuria and it was conducted in the pediatric clinic of the National Research Center in the period from August 2009 to February 2010. (19 males and 12 females). Their age ranged from 3 to 18 years with a mean age of 11±4.5. Full history taking, thorough clinical examination, assessment of serum levels of zinc and copper, plasma phe and IQ assessment were done for all studied patients.

Results:

Different degrees of mental retardation were reported in 50% of them. Non compliant children had significant higher phenylalanine (p. value 0.002) and lower IQ (p. value <0.001) than compliant children. There was significant negative correlation between IQ and age of start of diet therapy, age of sitting, standing, walking, mother recognition and speaking. Significant negative correlation was found between phenylalanine and weight, height and darkness of hair color, while there was significant positive correlation between phe

and Cu. Cu and IQ were significantly higher in children who received early diet therapy. (p. value 0.023, 0.017 respectively).

Conclusion:

The current study assessed serum levels of zinc and copper and determined the effect of diet compliance on the mentality and physical growth in a sample of 31 Egyptian children with PKU. Zinc and copper levels were within the normal ranges, and these may be due to milk formula supplemented with these elements. Keywords: phenylketonuria, Zinc, Copper.

Introduction:

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterized by a deficiency in the enzyme phenylalanine hydroxylase (PAH). This enzyme is necessary to metabolize the amino acid phenylalanine to the amino acid Tyrosin. When PAH is deficient, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which is detected in the urine (Scriver et al, 1998).

If Left untreated, this condition can cause problems with brain development, leading to progressive mental retardation and seizures. However, (PKU) is one of the few genetic diseases that can be controlled by diet. A diet low in phenylalanine and high in tyrosine can be a very effective treatment (Burgard et al, 1997).

Untreated children are normal at birth, but fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, EEG abnormalities, seizures, and severe learning disability are major clinical problems later in life. A "musty" odor of skin, hair, sweat and urine (due to phenylacetate accumulation); and a tendency to hypopigmentation and eczema are also observed, in contrast, affected children who are diagnosed early enough and treated by eating a special diet low in phenylalanine are less likely to develop neurological problems or mental retardation (Beblo et al, 2007).

Dietary therapy is the predominant treatment for phenylketonuria (PKU). To maintain the level of phenylalanine within a narrow range (Since phenylalanine is necessary for the synthesis of many proteins, it is required but its levels must be strictly controlled), the recommended diet is a low protein diet that excludes animal products (because of their phenylalanine content) and includes controlled amounts of cereal, fruit, and vegetables, in addition to protein supplementation with phenylalanine-free metabolic formulas (Mira et al, 2000).

Trace elements are essential in the daily diet because they have various important functions. Protein and carbohydrate malnutrition can develop due to deficiencies in micronutrients like vitamins and in trace elements like Zinc and Copper which are involved in multiple biological processes as constituents of enzyme systems including superoxide dismutase, oxidoreductase, and glutathione peroxidase. Blood levels of zinc and copper have been monitored in several experimental nutrition studies and are widely used to determine the presence of the deficiency states or toxicity (Cunninngham, 2005).

Zinc is an essential mineral found in almost every cell and approximately 100 enzymes contain this element for biochemical reactions in the body and its deficiency occurs due to inadequate intake, decreased absorption or when there is increased loss of it from the body, or when the body's requirement for it increases (Anug et al, 2006).

Copper can affect different target organs such as bone marrow, the central and peripheral nervous systems and the cardiovascular system.

The low ingestion of proteins with a high biologic value and the predominance of vegetable-origin foods containing fibers, phytates, oxalates,

and tannins in the diet decrease the bioavailability of many nutrients (Acosta et al, 1996).

Some studies reported low serum level of zinc and copper in phenylketonuric children and adolescents (Anderson et al, 2002).

Subject And Methods

This study was carried on thirty one children suffering from phenylketonuria the study was done in out-patient clinic of pediatrics in the National Research Center.

The children were of both sexes, their ages range between 3-18 years. Oral consent was taken from the parents of patients.

Inclusion Criteria:

1. Children With PKU.
2. Age 3- 18 years.
3. Both males and females.

Exclusion Criteria:

1. Cases associated with other genetic or metabolic disorders.
2. Cases who refuse to participate.
3. All patients were subjected to the following;
   a. Complete medical history taking, family history, age of diagnosis and progress of the disease.
   b. Dietary history including age of start of diet therapy and compliance.
   c. Full clinical examination, laying stress on Neurological examination.
   d. IQ assessment by using Stanford Binet intelligence scale (fourth edition).

Anthropometric Measurement:

- Weight: It was measured using beam balance on a firm flat surface; the balance was checked and adjusted regularly. All children were weighed bare footed with light clothes. The weight was recorded to the nearest 0.1 Kg.
- Height: It was measured using a vertical measuring board. The child stood bare footed on a flat platform, with feet parallel and with heels, buttocks, shoulders and back of head touching the upright surface. The head was held comfortably erect; with the lower border of the orbit on the same horizontal plane with the external ear (Frankfort plane). The arms were hanging at the sides in natural manner. The headpiece of the measuring board was gently lowered, crushing the hair and making contact with the top of the head. Height was recorded to the nearest 0.5 centimeter.

Laboratory Investigation:

The patients were subjected to determination of serum level of copper and zinc using Atomic Absorptiometer Zeiss, Model, PMQ 3, where copper and zinc were estimated together in the same dilution but at different wave lengths (324.8 nm for copper, and 427.7 nm for Zinc).

Plasma phenylalanine levels were measured by enzymatic colorimetric method (Eliza) in a dry blood spot.

Results:

The study was conducted in the out-patient clinic of pediatrics in the National Research Center.

The study was comprised of 31 children suffering from phenylketonuria (19 males and 12 female). Their ages ranged from 3 to 18 years with a mean age of 11.

Full history taking, thorough clinical examination, assessment of serum levels of zinc and copper, plasma phe assessment and IQ assessment were done for all studied patients.

The overall consanguinity rate recorded in the current study was 90.3% with a prevalence of family history of (PKU) of 64.5%.

Different degrees of mental retardation were reported in 50% of (PKU) cases enrolled in the current study. The IQ of the studied sample ranged between 30 and 90 with mean value of 68, SD (16).

The median of the values of phe was 12, with IQR (4- 15). The mean value of zinc concentration in the studied groups was 105.9 microgram with SD (29.9), While the mean value of copper was 88.8, with SD (20.4).

In the current study serum levels of zinc and copper were within normal ranges in nearly all of the studied patients.

Non compliant children had significant higher phenylalanine and lower IQ than compliant children.

There were significant negative correlation between IQ and ages of start of diet therapy, ages of sitting, standing, walking, mother recognition and speaking.

Significant negative correlations were found between phenylalanine and weight, height and darkness of hair color, while there was significant positive correlation with Cu.

Cu and IQ were significantly higher in children who received early diet therapy.

Conclusion:

In conclusion, the current study assessed serum levels of zinc and copper in a sample of 31 Egyptian children with (PKU). These levels were within the normal ranges, and these may be due to milk formula supplemented with these elements that ingested by the patients.

Discussion:

This study was carried out to assess serum levels of zinc and copper in a sample of Egyptian children with (PKU).

In the current study male to female ratio of the studied sample of PKU was 1.6 (19m: 12f) that goes with the foregoing fact about PKU AS one of the AR disorders. In comparison, Abdel-Fattah et al (1993) reported a male to female ratio of 1.06 among 68 mentally retarded children with miscellaneous metabolic causes of AR pattern of inheritance.

In this study, the age at time of diagnosis of PKU has been defined and the dietary therapy was considerably late for most of the enrolled cases as 10 cases has been diagnosed at or less than six months (32%), those started diet therapy within 2 years was 16 cases (51%).

The median of the values of weight of the cases in the study was 33, with IQR (23-55), and that of weight percentile (median 50 and IQR (22-75)).

The mean value of height was 136.3±21.3. The median of the values of height percentile was 20, with IQR (5-40).

In the current study, different degrees of mental retardation were reported in 50% of pku cases. The IQ of the studied sample ranged between 30 and 90 with mean value of 68 ±16.

The late diagnosis and implementation of dietary therapy for cases enrolled in the current study (diagnosis more than 6 months in 74% of cases) as well as the high prevalence of irregular dietary therapy (50% of studied cases) are expected to be associated with the previously mentioned prevalence of MR and the recorded reduction of IQ as it is universally accepted that loss of IQ can be minimized by implementation of dietary prophylaxis as early as possible in the neonatal period. (Smith et al, 1990).

There were significant negative correlation between IQ and ages of start of diet therapy, ages of sitting, standing, walking, mother recognition and speaking. 5 cases (16%) were started diet therapy early and have average IQ, and these results matched with other researches that demonstrated that if diagnosis is made and treatment is started in the first few weeks of life, normal brain development is not disturbed (Dennison B., 2005).

In our study non compliant children had significant higher phenylalanine and lower IQ than compliant children. Gassió et al found similar results

as Good metabolic control of PKU seems necessary to prevent cognitive function impairments, especially during the first 6 years of life.

There were significant positive correlation between Cu, weight percentile and phenylalanine. These results differ from Dobbelaere et al study as they found no correlation between plasma cu and growth parameter in their patients with (PKU). (Dobbelaere et al, 2003).

In the current study significant negative correlation were found between phenylalanine and weight, height and darkness of hair color, while there was significant positive correlation with Cu.

Cu and IQ were significantly higher in children who received early diet therapy.

In conclusion, the current study assessed serum levels of zinc and copper in a sample of 31 Egyptian children with (PKU). These levels were within the normal ranges, and these may be due to milk formula supplemented with these elements that ingested by the patients. Non compliant children had significant higher phenylalanine (pvalue0.002) and lower IQ (p. value <0.001) than compliant children. There were significant negative correlations between IQ and age of start of diet therapy, age of sitting, standing, walking, mother recognition and speaking. Significant negative correlation was found between phenylalanine and weight, height and darkness of hair color, while there was significant positive correlation between Phe and Cu. Cu and IQ were significantly higher in children who received early diet therapy.

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الملخص

تقييم مستوى الزنك والنحاس فى عينة من الاطفال المصريين مصابين بمرض الفينيل كيتونوريا

ان هدف هذه الدراسة هو تقييم مستوى الزنك والنحاس فى عينة من الاطفال المصريين المصابين بمرض فينيل كيتونوريا.

وقد اجريت الدراسة فى العيادة الخارجية للاطفال بالمركز القومى للبحوث. وكان عدد الاطفال موضع الدراسة ٣١ طفلا منهم ١٩و ١٢ من الاناث وتراوحت اعمارهم من ثلاث سنوات وحتى ثمانية عشر سنة وكان المتوسط العمرى ١١ سنة.

وشملت الخطوات الاجرائية للبحث:

١. اخذ التاريخ المرضى والفحص الاكلينيكى الشامل.
٢. قياس مستوى الزنك والنحاس فى الدم.
٣. قياس مستوى الفينيل الانين فى الدم.
٤. قياس نسبة الذكاء.

النتائج:

١. كانت نسب الزنك والنحاس فى المعدل الطبيعى لجميع الحالات.
٢. ٥٠% من الحالات كانوا يعانون من التخلف العقلى بدرجات متفاوتة وتراوحت نسب الذكاء لجميع الحالا ت المدرجة فى الدراسة بين ٣٠ و٩٠ بمتوسط ٦٤.
٣. كان متوسط نسبة الفينيل الانين ١٢، متوسط نسبة الزنك ١٠٥، متوسط نسبة النحاس ٨٨.
٤. وعند مقارنة الاطفال الذين اتبعوا النظام الغذائى لعلاج المرض والذى يتميز بقلة البروتينات الحيوانية بصورة منتظمة بالاطفال الذين الذين اتبعوه بصورة غير منتظمة تبين تمتع الاطفال من المجموعة الاولى بنسبة ذكاء اعلى وبنسبة فينيل الانين اقل.
٥. هناك علاقة عكسية بين نسبة الذكاء وعمر الاطفال عند بداية اتباعهم النظام الغذائى

الخلاصة:

١. نسبة الزنك والنحاس فى الدم كانت فى المعدل الطبيعى للاطفال موضع الدراسة.
٢. كلما كان اتباع النظام الغذائى لعلاج المرض مبكرا كلما زادت نسبة الذكاء وقلت نسبة التخلف العقلى.

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