Journal of Asian Scientific Research

journal homepage: http://aessweb.com/journal-detail.php?id=5003

FIVE CASES REPORT WITH MAPLE SYRUP DISEASE OVER A PERIOD OF 16 YEARS. METABOLIC SCREENING, DETECTION OF INBORN ERRORS OF METABOLISM AT THE HOSPITAL PARA EL NINO POBLANO, MEXICO

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ABSTRACT

The congenital inborn errors of metabolism (IEM) are detecTABLE diseases since 1908. Some of the most frequent IEM reported are fenilketonuria, galatosemy as albinism, cystinuria and porfiria and more rarely maple syrup urine disease reported in this study. It is caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC), leading to a buildup of the branched-chain amino acids (leucine, isoleucine, and valine) and their toxic by-products are detected in the blood and urine.

Case reported. 102 clinical cases with polymalformed muscle esqueletal and skull and dental dismorfies from this Hospital were already published Ma. De Lourdes Hurtado-Hernández et al, 2009, Figure I. Only 5 patients with maple syrup urine disease have been reported in a 16 years period of time Table 1, where the clinical evolution of one of the patients is reported in this study.

Conclusions. Actually, the IEM are defined as monogenic inherited diseases or mendelian, due to a metabolic error for a protein or enzyme absence. It might be incompatible with the patient life and sometimes if the patient lives it will modify its quality of life, especially in a severe metabolic disease as it is maple syrup urine disease.

Key Words: Inborn errors of metabolism, Protein, Enzyme and maple syrup

INTRODUCTION

Most of the inborn errors of metabolism (EIM) (Velázquez, 1998; Velásquez *et al.*, 2000; Manuel and Rodríguez, 2005), (Fernández *et al.*, 2000)are autosomal recessive diseases. The alteration in a gene produces an enzyme defect that leads to the features of each disease metabolic biochemical alterations. These inborn errors of metabolism is mainly manifested in childhood, since the first hours of life, such is the importance of the results of newborn screening and expanded (Wilcox and Cederb, 1996; Zschocke and Hoffmann, 1999; Velásquez *et al.*, 2000; Couce *et al.*, 2006).

Symptoms is variable; desnutricion (Terán *et al.*, 1998; Wendel *et al.*, 2006), seizures and mental or psychomotor retardation. (MSD) maple syrup disease is caused by alterations in three essential amino acids, which means body there them and need to buy them from feeding, Leucine, isoleucine and valine, which damages the central nervous system, l and most of the tissues in general. Table 2. The importance of these three essential amino acids alterations affects the different functions in humans (Cidras *et al.*, 1991; Jardim *et al.*, 1995; Fernández *et al.*, 1997; Nyhan *et al.*, 1998; Lin *et al.*, 2002), Valine, http://es.wikipedia.org/wiki/Leucina Figure 1 form part of the genetic code and is found in high concentration in the muscles, it is very important for its function and keep the body in good condition. Leucine, http://es.wikipedia.org/wiki/Leucina, Figure 2 is the most abundant amino acid of three amino acids branched chain (valine and isoleucine) and they are the only ones used during the exercise, in addition important part of the protein in muscle tissue. It is also part of the genetic code and is involved in the formation and repair of muscle tissue; it helps to regulate blood sugar levels. This amino acid is altered during aging, which causes a great imbalance in the production of proteins

Regarding to the http://es.wikipedia.org/wiki/Leucina Isoleucine, Figure 3, which structure is similar to the amino acids valine, Leucine and belongs to the Group of branched chain amino acids. It is very important in febrile states, trauma or stress. It is essential for human nutrition, since it regulates blood sugar levels, is involved in muscle repair and is needed for the formation of hemoglobin. After exercise help to repair the muscles, is involved in the production of blood and after their metabolism, can be converted into lipids or carbohydrates. Some EIM, as well as to endanger the life of patients, can alterate the skeletal muscle system, including the craniofacial development, it is important to take into account in the consultation of general pediatrics and pediatric dentistry.

MATERIALS AND METHODS

2 370 Metabolic studies in patients with different EIM were performed. five of them with maple syrup disease, including the 14 days aged patient in this study. The evaluation was conducted taking into account the national and international parameters. An expanded metabolic profile was conducted Figure 4, qualitative and quantitative study of blood and urine to detect amino acids alterations, organic acids and acilcarnitinas. The patients ages ranged were evaluated between newly born and 5 years of age.

RESULTS

Metabolic screening was conducted on 2 370 patients over a period of 16 years. A total of 102 patients had metabolic disturbances (4.3%) Table 1, grouped into four categories; 15 with mucopolysaccharides defects, 43 in carbohydrates and 2 mitochondrial diseases 42 had a disorder in amino acids, 5 with maple syrup, as well as the 24 patient presented in this study, which began with difficulty in their diet with secondary malnutrition where gastrostomy tube was performed Figure 5 to ensure their nutritional contribution, also respiratory problems were observed which

clinical evolution changed to serious deterioration of his neurological Figure 6, dehydration, and generalized infection in the dermis and organic septicemia Figures 7, 8.

DISCUSSION

Some patients were had a normal evolution, however some of them as in the case of two hiperlisinemia patients Table 1 were hospitalized in a coma to intensive therapy unit with poor prognosis. Patients with maple syrup disease manifested progressive deterioration, although nutrient management was changed entirely by the nutrition department. This deterioration is caused by a genetic abnormality in the metabolism of these three important essential amino acid; branched chain amino acids (Cidras *et al.*, 1991; Jardim *et al.*, 1995; Fernández *et al.*, 1997; Nyhan *et al.*, 1998; Lin *et al.*, 2002), http://es.wikipedia.org/wiki/Leucina leucine, isoleucine and valine. In its most severe form, this disease can damage the brain by septicemia as in the case of the patient with severe vascularization and discoloration problems at the dermis Figures 7,8, combined with periods of fever, malnutrition where gastrostomy was necessary Figure 5, for nutrient support. This series of functional and metabolic alterations are secondary to the deficiency of these essential amino acids, as mentioned earlier where valine, Figure 1 is part of the genetic code and found in high concentrations in the muscles considered important for its function and maintain in good condition the body.

Leucine Figure 2 is the most abundant amino acid of three amino acids branched chain (valine and isoleucine) and they are the only ones used during the exercise, in addition to constituting a third of the protein in muscle tissue. It is also part of the genetic code and is involved in the formation and repair of muscle tissue and It helps to regulate blood sugar levels. This amino acid is altered during aging, which causes a great imbalance in the production of proteins, fact that causes the loss of muscle mass. It has a beneficial effect on post-surgical patients. In addition to protecting the muscles, it acts as fuel in high training. With regard to Isoleucine, Figure 3, its structure is similar to the amino acids valine and leucine and belongs to the group of branched chain amino acids. It is very important in febrile states, trauma or stress. It is essential for human nutrition, since it regulates blood sugar levels, is involved in muscle repair and is needed for the formation of hemoglobin. After exercise help to repair the muscles, is involved in the clotting of blood and after their metabolism, can be converted into lipids or carbohydrates. It is one of the eight essential amino acids for the organism and it is part of the genetic code and an integral part of muscle tissue.

Early detection of the EIM (Velázquez, 1998; Fernández *et al.*, 2000; Velásquez *et al.*, 2000; Manuel and Rodríguez, 2005; Ma. De Lourdes Hurtado-Hernández. *et al.*, 2009), 1,2, 3, 4, 5 in pediatric patients is very important as well as the initial treatment as the five patients where their evolution had a fatal outcome FIGURE 7.8 which is relevant to take in consideration on the importance of newborn metabolic screening (Wilcox and Cederb, 1996; Wendel *et al.*, 1999; Zschocke and Hoffmann, 1999; Velásquez *et al.*, 2000; Couce *et al.*, 2006), 6,7,9 that should be a test in all newborn patients. This type of EIM is considered an emergency in pediatrics and

neonatology 8 to provide the patient with an early, appropriate treatment to ensure a better quality of life.

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FIGURES AND TABLES

Figure -1. Valine is part of the genetic code and found in high concentration in the muscles is very important for its function and keep the body in good condition. http://es.wikipedia.org/wiki/Valina.

Figure -2. Leucine is part of the genetic code and is involved in the formation and repair of muscle tissue; It helps to regulate blood sugar levels. This amino acid is altered during aging, which causes a great imbalance in the production of proteins, fact that causes the loss of muscle mass. http://es.wikipedia.org/wiki/Leucina.

Figure -3. Isoleucine is part of the genetic code and an integral part of muscle tissue, belongs to the Group of branched chain amino acids. It is very important in febrile States, trauma or stress. It is essential for human nutrition, since it regulates blood sugar levels, is involved in muscle repair and is needed for the formation of hemoglobin. http://es.wikipedia.org/wiki/Isoleucina.

Figure -4. Metabolic screen done with gel electrophoresis in a patient with maple syrup that shows positive patterns for this disease.

Figure -5. Due to lack of swallowing the patient with malnutrition, gastrostomy was used as nutrient support.

Figure -6. The patient presented automatism respiratory problems where respirator was necessarily, in addition to serious deterioration of his neurological status with constant monitoring.

Figure -7. In its most severe form, this disease can damage the brain by septicemia development, as in the case of the patient with severe vascularization problems, dehydration and general infection with ectodermic changes.

Figure -8. The patient presented serious problems with his vascularization mainly at upper limbs and dermis changes with organic failure.

TABLE -1. Metabolic studies were performed in 2 370 patients (1994-2010) with a total of 102 patients with different alterations (4.3%). Five of them with maple syrup disease.

TABLE -2. Some of the EIM principal found at the Pediatric Hospital, clinical manifestations and biochemical alterations, including the maple syrup disease reported in this study

Table- 1.

Aminoácids	MPS	carbohydrates	mitochondrial
42	**15**	**43**	**2**
7 Cystinuria	8 Hurler	1 Glucogenosis	1 acetil COA tiolasa mitochondrial
8 fenilketonuria	2 Hunter	9 Galactosemia	1 respiratory chain mitochondrial
4 fanconi sx.	5 Morquio	33Glucosuria	
4 tirosinemia			
2 hiperlisinemia			
5 maple syrup.			
1 argininemia			
1 hiperalaninemia			
10 homocystinuria.			

Table- 2.

Disease	**Main symtoms**	**Biochemistry**
Alteratión		
Alterations of amino acids:		
Cistinuria	**Kidney stones. Increase in urinary excretion of cystine, lysine, arginine, and ornithine. Defienciente calcification bone and oral.**	**Decreased tubular reabsorption of amino acids cystine and dibasic (arginine, lysine, ornithine)**
Fenilketonuria	**Vomiting, mental retardation, hipopimentacion, crowding of teeth.**	**Fenilalanine Rivosiltransferasa enzime**
Fanconi syndrome	**Growth retardation. Bone and teeth deformations fever, dehydration, acidosis. In adults: glycosuria, aminoaciduria, hypokalemia, uremia and gingivorragia.**	**Change in the mechanism of renal transport of glucose, phosphate, amino acids, less marked for water and potassium**
Tirosinemia		
Hiperlisinemia	**Urinary elimination of acid p-hidroxifenilpiruvico**	
maple syrup	**Nerve damage, seizures, vomiting, coma and decay.**	**p-hidroxifenilpirúvico oxidasa Deficiency**
Hiperglicinemia	**Urine has an odor similar to the syrup of maple, vomiting, rejection of food a potentially deadly neurological damage.**	**Increase of the amino acid lysine.**
Homocistinuria	**A severe psychomotor mental impairment, drowsiness and seizures that accumulates in biological liquids especially in the**	**Branched-chain amino acids valine, Leucine and**

	CSF. Wear of teeth.	**isoleucine.**
	Mental retardation, dislocation of the lens, skeletal abnormalities, and tendency to thromboembolic events.	**Due to a congenital defect in the metabolism of glycine in the oxidation of glycine by a D-aminooxidasa deficiency causes the glioxalato.** **Deficiency of the above cistionina beta synthetase.**

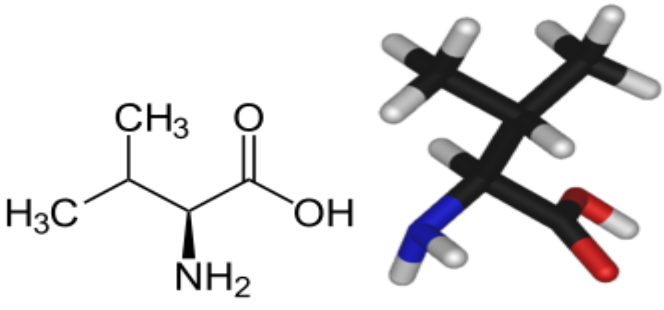


Figure- 1. Valine.

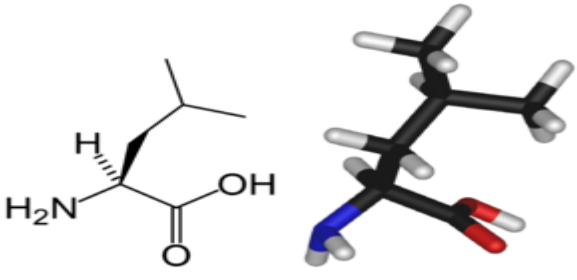


Figure- 2. Leucine.

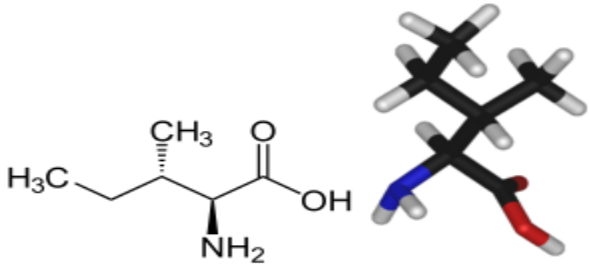


Figure- 3. Isoleucine.

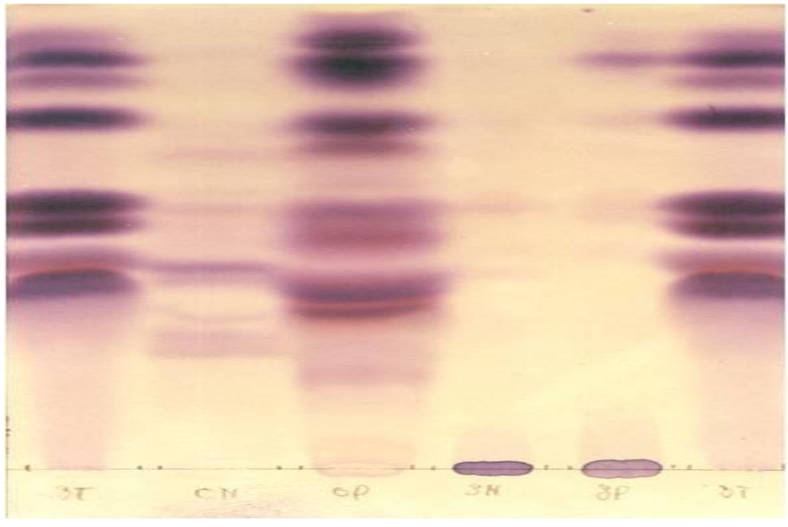
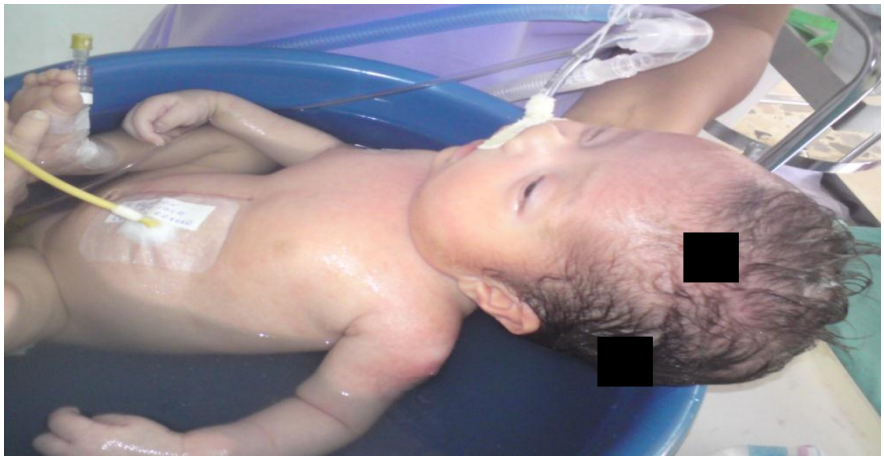


Figure - 4.



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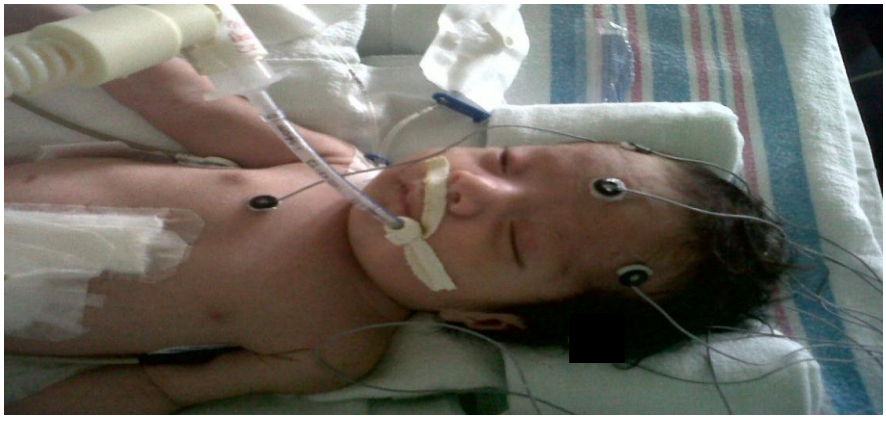

Figure- 6

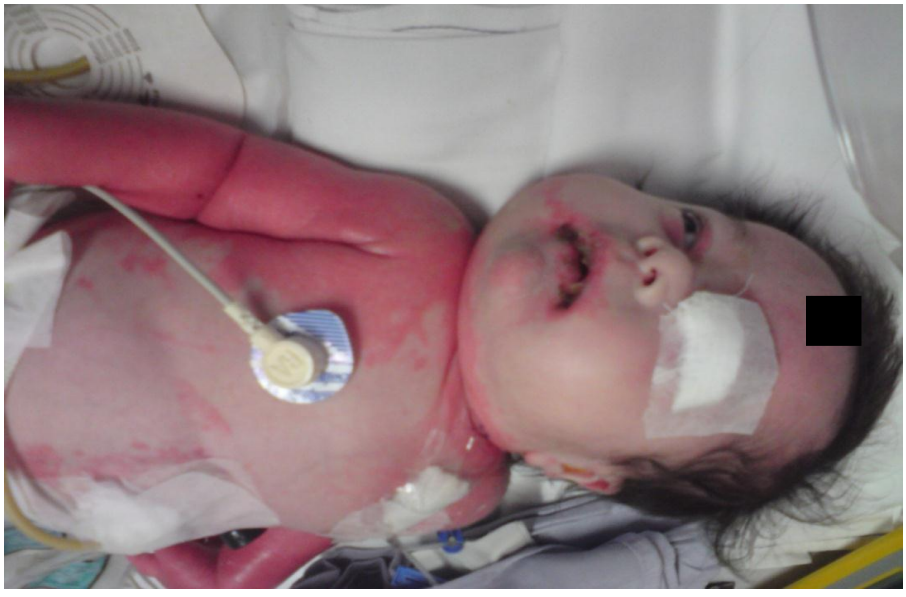

Figure- 7.

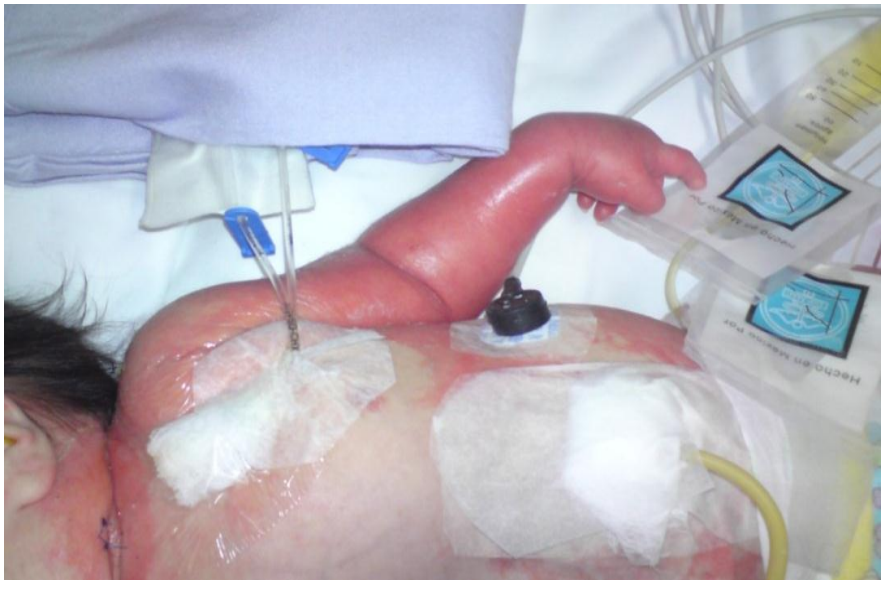

Figure- 8.