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Acidemia Propionica: Diagnostic, Intervention and Therapeutic Answer in a Case of the Illness in Camaguey

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Abstract: Justification: The acidemia propionica (AP) is one of the most frequent organic acidemias constitutes inside the congenital errors of the metabolism (CEM). The organic acidemias originates of congenital enzymatic defects that affect the catabolism of the ramified amino acids (AACR) valina, leucina, and isoleucina. In the case of the AP, the molecular damage resides in the deficiency of the activity carboxilasa of the propionil-CoA: an enzyme mitocondrial biotina-clerk that catalyzes the propionil-CoA transformation in metilmanolil-CoA, metabolic step that makes possible the degradation of the AACR valina and isoleucina, as well as of the sulfurated metionina and treonina. The precocious diagnosis of the AP is important to prevent the mental delay and the affected boy's death. Objective: To present the case of preescolar with diagnostic of AP from the birth with favorable evolution, in spite of their multiple revenues with secondary states of extreme graveness to disproportionates. Clinical case: Patient of four years of age that began to present rejection to the foods, vomits and retard of the psychomotor development from the birth. The first revenues were motivated by dehydrations and severe metabolic acidosis, with neurological manifestations that took it to the coma in an opportunity. She was carried out the diagnosis of AP and doctors began the necessary and correct dietary treatment. Conclusions: Before a patient with neurological manifestations that could made a mistake with a sharp intoxication in the stage neonatal, accompanied by vomits, retard of the growth, metabolic acidosis of not very clear cause, it should be suspected the acidemia or aciduria propionica or any other of the CEM. Nutritional improvement was observed and of the psychomotor development after the introduction of a diet free of proteins and leaning with supplements of vitamins.

Keywords: Acidemia Propionica, Acidosis, Hiperamoniemia

1. Introduction

The organic acidemias constitutes a subdivision inside of the illnesses caused by congenital enzymatic defects that affect the catabolism of the ramified amino acids (AACR). [1, 2] Inside the organic acidemias the most frequent are the illness of the urine of maple syrup (of the English Mapple Syrup Urine Disease); [3] the acidemia isovalerica (AIV); [4] The 3-metil-crotonil-glicinuria (3-MCG); [5] the acidemia propionica (AP), [6,7] and the acidemia metilmaonica (AMM). [8, 9]

In the organic acidemias the accumulation takes place in the blood of the sour carboxilicos like consequence of the impossibility of the organism of having the skeleton carbonado of the AACR valina, leucina and isoleucina correctly. The catabolism and use of the amino acids treonina and metionina are also affected. The quantities accumulated in excess in the blood of these sour carboxilicos are excreted ulteriorly in the urine, what provides the base for the detection of the same ones by means of technical cromatograficas. [10, 11]

Table 1. *The organic acidemias. Critical steps in the cellular use of the sour carboxilicos, molecular deficiencies, and toxic effects.*

Condition	Step critical	Deficiency molecular	Toxic effects
Illness of the urine of maple syrup	Descarboxilacion oxidativa of the cetoacidos coming from those amino acids ramified valina, isoleucina and leucina	Deficiency in the activity of the complex of the deshidrogenasa of the cetoacidos of chain ramified	Concentrations risen in the blood of amino acids of ramified chain and alo-leucina
Acidemia isovalerica	Conversion of the isovaleril-CoA in 3-metil-crotonil-CoA	Deficiency of the enzyme mitocondrial deshidrogenasa of the isovaleril-CoA (IVD)	Accumulation in the blood of those derived of the isovaleril-CoA
3-metil-crotonil-glicinuria	Conversion of 3-metil-crotonoil-CoA in 3-metilglutaconil-CoA	Deficiency of the carboxilasa of the 3-metil-crotonil-CoA	Elevation in the blood of the concentration of 3-hidroxi-isovaleril-carnitina
Acidemia metilmalonica	Interconversion of the metilmalonil-CoA in succinil-CoA like previous step to the entrance of the sustrato in the cycle of Krebs	Deficiency of the enzyme mitocondrial mutasa of the metilmalonil-CoA (MMCM) Defects of the biosynthesis of the cofactor adenosilcobalamina (derived of the vitamin B12) of the MMCM	Accumulation in the blood of the sour metil-malonico
Acidemia propionica	Use of the proponil-Coa	Deficiency of the carboxilasa of the propionil-CoA	Elevation in the blood of those derived of the propionil-CoA: acid 3-hidroxi-propionico, 3-metil-citric acid, propionil-carnitina Accumulation in the blood of the fatty acids of odd chain

The AP is caused by the deficiency of the activity carboxilasa of the propionil-CoA: an enzyme mitocondrial biotina-clerk that is necessary for the metabolism of the propionil-CoA. The AP is inherited then with character autosomico recesivo. [6, 7] The boy should receive from each progenitor an anomalous copy of the codificant gene of the enzyme so that it presents the illness. The enzyme is composed of two parts and those that, in turn, they are coded by the corresponding genes PCCA and PCCB. The damage genomic moves then to the damage proteomico, and with it, to the faulty expression of the structure and the functionality of the enzyme.

The AP has as main characteristic a serious metabolic acidosis with values of the sanguine pH under 7.25 and (HCO_3) seric bicarbonate (HCO_3) under 15 mmol.L [1, 12] The metabolic acidosis in the AP accompanies besides cetonemia, cetonuria, and hiperamoniemia of intensity variable. [12] The basal glicemia and the seric acid lactic they are usually inside normal values or, on the contrary, high. The affected patients of AP can exhibit pancitopenia.

The AP shows an incidence of 1 in each 50,000 cases. In the United States a case of the illness is presented on the contrary by each 35,000 births. [13], in the Arabia Saudita you a sick person can count for each 3,000 births. [14]

The premiere of the AP can happen in the stage neonatal, or in more ages. Although the AP can show of agreement with different clinical patterns, the presentation neonatal is one in the most habitual ways. The symptoms of the AP neonatal are presented from the first week of life extrauterin and they understand anorexia and rejection to the foods, vomits and dehydration, loss of corporal weight, and decrease of the muscular tone and convulse. All these symptoms can culminate in a sharp coma. The neurological damages can cause delay of the psychomotor development that would be increased and it would be deepened if the AP is not detected on time, and not mitigate. The AP can also cause renal dysfunction and heart disease. [15]

The treatment of the AP is adjusted to the clinical square of presentation and the predominant symptoms. In the sharp cases she should recover the liquid balance, to correct the metabolic acidosis and the dysfunctions of the internal means, stop the convulsions and to overcome the coma. In occasions they can be necessary the renal dialysis and the exsanguineo transfusion for the removal of the toxic quantities of the sour accumulated carboxilicos.

Achieved the sick person's hemodynamic and metabolic stability, you need to the design, implementation and conduction of the corresponding program of alimentary intervention, nutrimental and metabolic. Such a program will be in charge of the satisfaction of the daily requirements of energy to sustain the growth and development, the election of the sources of nutritious proteins, and the contribution of the strictly necessary quantities of essential amino acids (the AACR among them) for already not overloading the mechanisms affected of degradation and disposition of the same ones.

In Cuba the AP is a not very frequent illness. The case that is presented in this text is the unique case of the AP in Camaguey city.

2. Presentation of Case

The case is about a four years old girl, of mixed blood, who coming from a rural community so-called Cespedes of the county Camaguey, without perinatal antecedents to highlight. The girl´s mother was a 17 years old adolescent in the moment of the girl´s birth. The conditions socioeconomic relatives were not very favorable for the birth and the girl's upbringing.

The girl was assisted to the 10 days of born due to a sharp square of incompatible vomits, severe dehydration, drowsiness, taking of the conscience, convulsions, and quick evolution toward the coma. To these symptoms they were added the widespread muscular weakness. The graveness of the clinical square forced to the hospitalization in the Unit of Pediatric Intensive Cares and the mechanical ventilation

through endotracheal intubation. During the hospital stay the presence of serious and persistent metabolic acidosis was verified given by a pH under 7.28, HCO_3 <9 mmol.L, and a breach anionic (of the English anion gap) uper 16: an indicator this of the serious deterioration happened in the ions HCO_3 that doesn't compensate the sum of the ions Na+ and K+. In addition, she was very high cipher of ammonium (more than 150 µmol.L). That values can provoke deterioration of the neurological square.

The concurrent symptoms and the graveness of the same ones, in a girl of so short age, they made think to the multidisciplinary team of attention of a congenital error of the metabolism (CEM) to type organic acidemia. The AP was confirmed by means of the identification of organic acids in the patient's urine.

Overcome the sharp moment, doctors proceeded to the evaluation of the nutritional state and the estimate of the requirements of nutriments, energy and nitrogen of proteins. The nutritional requirements (included energy) they were employees in the design of the outlines of complementary feeding and artificial nursing. The dear quantities of energy and nitrogen of proteins were the necessary ones to assure the prospective rates of growth and the girl's development.

The dear quantities of proteins kept in mind the content in valina, isoleucina and treonina of the sources of nutritious proteins. It is remembered that these amino acids are essential, and therefore, they should be contributed with the regular diet to prevent deficit states | lacking of the same ones. Nevertheless, the quantities that are contributed of such amino acids will be those that can be used efficiently by the organism without it is it in the toxic accumulation of the products of the metabolism of the same ones. Some examples of foods that AACR contains are the cheese and the curd, the white meats (birds and fish) and the red meats, the leguminous ones (as the lentils and the bean of soya), and eggs. [6]

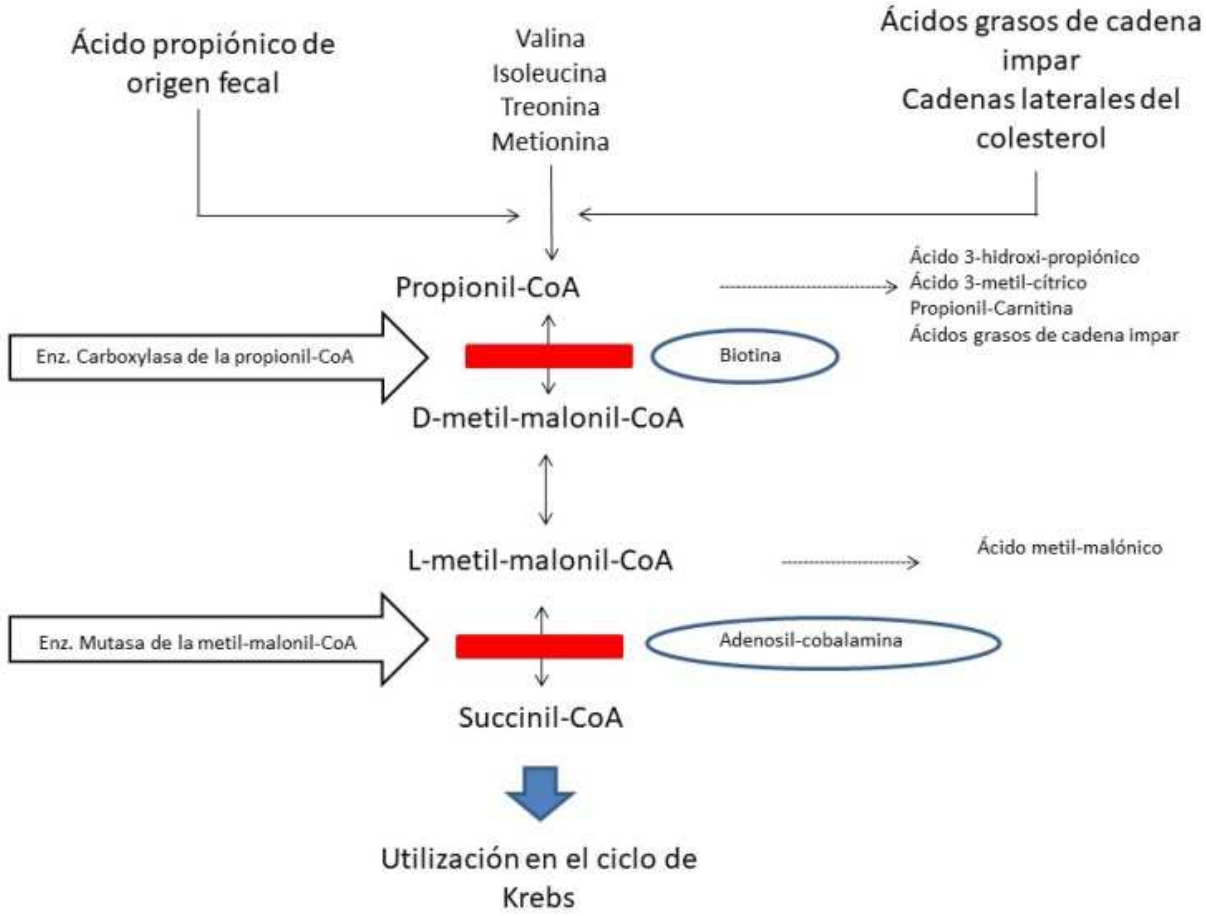

Figure 1. *Metabolic routes of use of the amino acids of ramified chain.*

Table 2. *Energy requirements, proteins and chain amino acids ramified according to the fellow's age.*

Age	Energy	Proteins	Amino acids, mg.kg^{-1}.24 hour^{-1}		
	kcal.kg^{-1}.24 hour^{-1}	g.kg^{-1}.24 hour^{-1}	Valina	Isoleucina	Treonina
15 – 30 days	105.0	2.2	93	70	87
12 months	101.0	1.5	93	70	87
2 years	100.0	1.2	38	31	37
3 years	95.0	1.1	38	31	37
4 years	90.0	1.1	38	31	37

The outlines of complementary feeding and artificial nursing were supplemented with the prescription of L-carnitina, biotin and vitamin B12 in supplementary quantities The L-carnitina it favors the use mitochondrial of the acids fatty poliinsaturados of long chain. On the other hand, the biotin acts as co-enzyme of the activity carboxilasa of the propionil-CoA facilitating the carboxilacion reactions and transcarboxilacion of the sour propionic, as well as the metabolism of the leucina. Lastly, the vitamin B12 participates in the metilacion reactions and activation of the folic acid, contributing this way to a better use of the sour derived tricarboxilicos of the metabolism of the AACR.

Fact the diagnosis of the AP, compensated the hemodynamic and metabolic, reduced square the hiperamoniemia, and implemented the program of alimentary intervention, nutrimental and metabolic, doctors decided the girl's expenditure, and the ambulatory pursuit to regulate.

In the following 4 years they registered the girl's several hospital revenues amid squares with disproportionate of the metabolic illness due to breathing infections and/or alimentary transgressions. The last of them happened in November of the 2018. Be for excessive revenues of nutritious sources of AACR, the appearance of vomits, diarrheas and sharp dehydration; or the subsequent changes to a sharp inflammatory answer after the microbial infection, the certain thing is that she settles a serious metabolic acidosis that bears the normal hydration, the purification extrarrenal of the toxic quantities of organic acids, the rehabilitation of the internal means, and the antibiotics use (in this case the metronidazol) to limit the production of sour propionic for the present bacteria in the thick intestine. The graveness of the metabolic acidosis (and the therapeutic answer) it is evaluated of the values of ammonium, pH and bicarbonate.

Table 3. *Content of amino acids of ramified chain of agreement with the group of foods. It is not sought that the list is exhaustive.*

Group of foods	Amino acids of ramified chain (mg/100 g of total proteins)		
	Valina	Leucina	Isoleucina
Milk and milky	690	640	600 – 700
Meats	700 – 800	1,000	600 – 700
Fish	611	810	478
Eggs	742	880	664
Leguminous	582	843	543
Cereals	510	810	380
Viandas and tubers	467	603	377
Fruits	370	440	290
Vegetables	410	460	350
Oil, fatty and shortenings	670	830	580

During the reanimation and the girl's rehabilitation is interrupted the contribution of proteins, and the control of the state of the ammonium. The nutritional performance is limited to the contribution of the quantities of energy to reduce the hyper catabolism of proteins. Once the seric ammonium descends below the 100 µmol.L, doctors introduced the slow nutritious proteins and progressively until reaching the nutritional goals preset in the intervention program. She also recovers the supplementation with L-carnitina, biotin and vitamin B12 for a better use of the contributed amino acids.

At times of the last medical interview she was proven that the girl showed an appropriate external aspect for the age, and she developed the activities that were he own as playing, to run, and intercommunicate with other people. The anthropometric evaluation returned the following results: stature for the age: percentile 3; weigh for the age: Percentile 25; and Weigh for the stature: percentiles 25 - 50. The language is the affected and that was motivate for which stays under the attention of the Department of Language and Infant Rehabilitation of the county.

3. Discussion

In this rehearsal the case has been presented from an organic acidemia to type AP in a newly born one. In spite of the serious complications suffered in the lapsed time, it was achieved the girl's survival, and the continuity of the rates characteristic of growth and development extrauterin. In the last completed nutritional evaluation when the girl arrived to the alone 4 years of age you/he/she was of highlighting a value of the size for the age corresponding with the percentile 3 of the reference charts, what would point toward an increased risk of "stunting" (or what is the same thing, detention of the lineal growth), and that you/he/she should alert to the basic team of work for the required interventions.

Two clinical forms of the PA have been described. One of them is the form of presentation neonatal of the illness, and that one manifests excessively in the first days of life extrauterin in a newly born one seemingly healthy. The symptomatic cohort is varied at the same time that dramatic, and in her the lethargy prevails (that usually progresses until the coma), the muscular weakness, and the serious metabolic acidosis with a breach high anionic.

Such it seems that this form neonatal behaves a high mortality. For when one has a possible diagnostic certainty, it can be too much late for the boy who usually develops a sharp breathing inadequacy that leads to the intubation and the mechanical ventilation.

The case developed in this text is adjusted the PA of premiere neonatal, but it is probable that the girl proving still shows activity (although it is residual) of the enzyme

carboxilasa of the propionil-CoA like to respond favorably to the implemented therapy, and with it, the girl's survival.

As it is described in the specialized texts, and as the work team it has checked with this clinical case, the AP is an illness that usually evolves for crisis. Such crisis can be unchained by high breathing infections, or alimentary transgressions. When a crisis happens, it is required of immediate hospitalization and intensive treatment to avoid the first boy's death, and to assure the best quality of life during the periods inter crisis, later. The intensive treatment heads to the correction of the metabolic acidosis that he/she appears and it progresses (and that it is usually serious) even by means of heroic measures as the purification extrarrenal and the exsanguineo-transfusion.

The restriction of the dietary proteins would be necessary also to control the azotemia and the hiperamoniemia. Once the values of ammonium diminish below 100 mol.L and the acid-basic balance has been achieved, the nutritious proteins you slow begin and progressively until reaching the goals nutrimental foreseen in the maintenance regimen. A better use of the proteins contributed with the diet is possible (and feasible) by means of the supplementation with L-carnitina, biotin and vitamin B12. The carnitina is involved in the entrance of the fatty acids of long chain for the ulterior degradation inside the route of the - oxidation of the fatty acids at level of the main mitochondrial. The biotin is the co-enzyme that accompanies to the activity carboxilasa of the propionil-CoA, and an increased contribution of the same one would cooperate to an activity enzymatic superior, and with it a better disposition of the AACR. On the other hand, the vitamin B12 is the co-enzyme of the activity mutasa of the metil-malonil-CoA that one of the key steps of the oxidation of the AACR catalyzes. This way, he/she would move the speed of the metabolic route in the sense of to favor the catabolism of the AACR and to prevent in consequence the toxic products originated as consequence of the overload of the route.

The antibiotics use like the metronizadol could be necessary also to limit the production of sour propionic (and other fatty acids of short chain) for the intestinal bacteria, and this way, to contain the presence in the blood of those derived toxics of the metabolism of the AACR.

Nevertheless, the made medical and nutritional measures, the AP doesn't pass without leaving prints. The girl whose case has been pointed out in this exhibition, today it still suffers of dysfunctions of the language that are being assisted by means of intensive language intervention. New investigations should be made to demonstrate the nature of such dysfunctions of the language, and if these are due to acquired dysfunctions during the process of learning of the speech, or on the contrary, they represent structural damages of the area of Brocal: the center articulator of the speech.

The AP is inherited with a patron recessive autosomico. The occurrence of this case in the county of Camaguey outlines the certain possibility of the existence of payees of faulty copies of the genes codificantes of the enzyme carboxilasa of the propionil-CoA inside the population seated in the region, and with it, the appearance of new cases of the AP. They would be justified the community genetic studies that are necessary then to establish the frequency and the distribution of these genes, and with it to trace a map of risk of the AP and for extension other organic acidemias.

4. Conclusions

Before a newly born one, or a nursling, with manifestations of sharp intoxication, convulse, taking of the conscience with quick evolution toward the coma, serious metabolic acidosis with an increased AG, and retard of the psychomotor development, the AP should be one from the first diagnostic considerations to make. The early diagnosis, and the alimentary intervention, nutrimental and metabolic opportune, they can be decisive in the insurance of the boy's survival, and the evolution free of complications and/or sequels.

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