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ORIGINAL ARTICLE

Selective Screening of Fatty Acids Oxidation Defects and Organic Acidemias by Liquid Chromatography/tandem Mass Spectrometry Acylcarnitine Analysis in Brazilian Patients

Carmen Regla Vargas,[a,b,c,d] Graziela Schmitt Ribas,[a] Janine Machado da Silva,[a,b] Angela Sitta,[a] Marion Deon,[a] Daniella de Moura Coelho,[a] and Moacir Wajner[a,c]

[a]*Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil*
[b]*Faculdade de Farmácia, UFRGS, Porto Alegre, RS, Brazil*
[c]*Programa de Pós-Graduação em Ciências Biológicas, Bioquímica, Faculdade de Farmácia, UFRGS, Porto Alegre, RS, Brazil*
[d]*Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, UFRGS, Porto Alegre, RS, Brazil*

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Background. Inborn errors of metabolism (IEM) are diseases which can lead to accumulation of toxic metabolites in the organism.

Aim of the study. To investigate, by selective screening, mitochondrial fatty acid oxidation defects (FAOD) and organic acidemias in Brazilian individuals with clinical suspicion of IEM.

Methods. A total of 7,268 individuals, from different regions of Brazil, had whole blood samples impregnated on filter paper which were submitted to the acylcarnitines analysis by liquid chromatography/tandem mass spectrometry (LC/MS/MS) at the Medical Genetics Service of Hospital de Clínicas de Porto Alegre, Brazil, during July 2008−July 2016.

Results. Our results showed that 68 patients (0.93%) were diagnosed with FAOD (19 cases) and organic acidemias (49 cases). The most prevalent FAOD was multiple acyl CoA dehydrogenase deficiency (MADD), whereas glutaric type I and 3-OH-3-methylglutaric acidemias were the most frequent disorders of organic acid metabolism. Neurologic symptoms and metabolic acidosis were the most common clinical and laboratory features, whereas the average age of the patients at diagnosis was 2.3 years.

Conclusions. Results demonstrated a high incidence of glutaric acidemia type I and 3-OH-3- methylglutaric acidemia in Brazil and an unexpectedly low incidence of FAOD, particularly medium-chain acyl-CoA dehydrogenase deficiency (MCADD). © 2018 IMSS. Published by Elsevier Inc.

Key Words: Fatty acids oxidation defects, Inborn errors of metabolism, Liquid chromatography coupled to tandem mass spectrometry, Organic acidemias.

Introduction

Inborn errors of metabolism (IEM) are genetic disorders generally caused by severe deficient function of enzymes or carrier proteins (1). Most of these diseases have autosomal recessive inheritance, although a few of them are X-linked. Thus, the probability of occurrence of an IEM increases with family history of consanguinity, hereditary diseases and neonatal death (2).

These pathologies are biochemically characterized by accumulation of specific metabolites or their by-products in tissues and biological fluids of the affected individuals that may cause toxic effects in the organism leading to severe metabolic crises that can result in permanent neurological damage, physical disability and even fatality (3). Although the IEM are considered rare, collectively they have a relative higher prevalence in the population,

Address reprint requests to: Carmen Regla Vargas, Dr. Serviço de Genética Médica, HCPA, Rua Ramiro Barcelos, 2350, CEP 90035-003, Porto Alegre, RS, Brazil; Phone: (+55) (51) 33598011; FAX: (+55) (51) 33598010; E-mail: crvargas@hcpa.edu.br

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corresponding to more than 600 metabolic diseases that affect 1:1,000 live newborns (4).

Fatty acid oxidation defects (FAOD) are a group of IEM in which the cells are unable to use fatty acids from diet and adipose tissue as an energy source. Overall, fatty acids are the main energy substrate for the body and more particularly to some organs such as the heart, skeletal muscle, liver and kidneys even at the fed state. In addition, fatty acids oxidation provide more energy in fasting states or during exercise, when most part of glucose reserves are consumed by glycolysis. In these IEM, the defects can occur at different steps of fatty acid metabolism, such as in the transport of fatty acids through the plasma membrane or the mitochondrial membrane, or also in the beta-oxidation pathways of long, medium or short chain fatty acids (5). Due to the deficient capacity of free fatty acids utilization as an energy source, these compounds and acyl-CoA intermediates accumulate in the body, reaching highly abnormal concentrations and leading to the formation of dicarboxylic and hydroxycarboxylic acids, as well as the conversion of acyl-CoA esters to their corresponding acylcarnitines and acylglycines (1).

The symptoms manifested by these defects are mainly due to the failure of the metabolism in maintaining a normal energy supply, although toxicity of the accumulating metabolites are growing in importance (5). They include hypoketotic hypoglycemia, lethargy that can lead to coma, seizures, muscle weakness, manifested generally in the neonatal period and after exercise. Cardiac and hepatic alterations also frequently occur. The central nervous system is often affected due to the severity of the hypoglycemia episodes or hyperammonemia, which can arise under fasting, stress and physical exercise conditions (6).

Organic acidemias (OA) are intermediary IEM that affect the metabolism of amino acids, carbohydrates and lipids. Due to the deficient activity of enzymes or carrier proteins involved in the catabolism of these substrates, specific organic acids accumulate in the organism, causing alterations in several systems, mostly the central nervous system (2,7). More than 65 different types of organic acidemias are so far known. Together, they have an incidence of 1:2,000 live births, but it may reach a higher figure according to the population group studied (8). Due to its acidic properties, the accumulation of organic acids in biological fluids provokes crises of metabolic acidosis, which are a striking feature of this class of IEM (2).These patients may present with any of the following clinical features: elevated anion gap, hyperammonemia, hypoglycemia, ketosis, hypotonia, seizures, physical and psychomotor developmental delay, lethargy to coma and ataxia, reflecting permanent damage of the CNS (1).

As part of the treatment, patients follow a protein-restricted diet, which is, sometimes, supplemented with L-carnitine or vitamins, in order to control the concentrations of the organic acids in the body and, consequently, to prevent the metabolic crises (3). Despite the dietary restriction, infections and stressful catabolic situations can also trigger a scenario of metabolic decompensation, making these diseases very difficult to treat. These conditions of metabolic disequilibrium are characterized as medical emergencies and require immediate specialized support in large hospitals since they represent a life-threatening risk (1). The diagnosis of organic acidemias is made through the identification of the specific accumulated organic acids in biological fluids of the patients, being the urine the material of choice for the investigation, since the excretion of these specific metabolites is highly increased in the presence of these diseases (9). The analysis of organic acids is performed, in most laboratories, by gas chromatography coupled to mass spectrometry (GC/MS), which allows the identification of characteristic patterns of organic acids highly suggestive of the disease (9).

In both organic acidemias and fatty acid oxidation defects, acyl-CoA esters accumulate in the mitochondria (1). In these disorders, carnitine plays a key role, removing the potentially toxic acylCoA esters through the formation of acylcarnitineesters and thereafter releasing coenzyme A and restoring mitochondrial homeostasis (10). So, screening and diagnosis of these diseases can be done through the evaluation of the acylcarnitines profile by liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) in dried blood spots samples (11), or by demonstration of an altered profile in the urinary excretion of dicarboxylic acids by GC/MS at the time of the metabolic crisis. In addition to the analysis of metabolites in fluids such as blood and urine, the molecular diagnosis for both FAOD and organic acidemias can also be performed in order to identify the mutation involved in the disease (1).

Actually the National Program of Newborn Screening in Brazil is performed for phenylketonuria, congenital hypothyroidism, cystic fibrosis, hemoglobinopathies, biotinidase deficiency and congenital adrenal hyperplasia diseases, not including, therefore, the FAOD and OA in the investigation. This makes it difficult the knowledge about the incidence of these diseases in the population. So, the objective of this work was to help to establish the relative prevalence of FAOD and OA by LC/MS/MS in high-risk Brazilian patients referred to the Medical Genetics Service of Hospital de Clínicas de Porto Alegre, Brazil, which is a regional and national center for the diagnosis of IEM.

Materials and Methods

Samples

Diagnosis of fatty acids oxidation defects and organic acidemias was performed through the analysis of acylcarnitines at the Medical Genetics Service of Hospital de Clínicas de

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