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ORIGINAL ARTICLE

Maple syrup urine disease in Brazil: a panorama of the last two decades☆,☆☆

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KEYWORDS
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Abstract
Objective: To characterize a sample of Brazilian patients with maple syrup urine disease (MSUD) diagnosed between 1992 and 2011.
Methods: In this retrospective study, patients were identified through a national reference laboratory for the diagnosis of MSUD and through contact with other medical genetics services across Brazil. Data were collected by means of a chart review.
Results: Eighty-three patients from 75 families were enrolled in the study (median age, 3 years; interquartile range [IQR], 0.57–7). Median age at onset of symptoms was 10 days (IQR 5–30), whereas median age at diagnosis was 60 days (IQR 29–240, p = 0.001). Only three (3.6%) patients were diagnosed before the onset of clinical manifestations. A comparison between patients with

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☆☆ Study conducted at Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.
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(n = 12) and without (n = 71) an early diagnosis shows that early diagnosis is associated with the presence of positive family history and decreased prevalence of clinical manifestations at the time of diagnosis, but not with a better outcome. Overall, 98.8% of patients have some psychomotor or neurodevelopmental delay.
Conclusion: In Brazil, patients with MSUD are usually diagnosed late and exhibit neurological involvement and poor survival even with early diagnosis. We suggest that specific public policies for diagnosis and treatment of MSUD should be developed and implemented in the country.

PALAVRAS-CHAVE
Doença da urina de xarope de bordo;
DXB;
Erros inatos do metabolismo;
Diagnóstico

Doença da urina de xarope de bordo no Brasil: um panorama das últimas duas décadas

Resumo
Objetivo: Caracterizar uma amostra de pacientes brasileiros com a doença da urina de xarope de bordo (DXB) diagnosticados entre 1992 e 2011.
Métodos: Neste estudo retrospectivo, os pacientes foram identificados por meio de um laboratório de referência nacional para o diagnóstico de DXB e por meio do contato com outros serviços de genética médica no Brasil. Os dados foram coletados por meio de uma revisão de prontuários.
Resultados: 83 pacientes de 75 famílias foram incluídos no estudo (idade média: 3 anos; intervalo interquartil (IQR): 0,57-7). A idade média no surgimento dos sintomas era de 10 dias (IQR: 5-30), ao passo que a idade média no diagnóstico era de 60 dias (IQR: 29-240; p = 0,001). Somente três (3,6%) pacientes foram diagnosticados antes do surgimento de manifestações clínicas. Uma comparação entre pacientes com (n = 12) e sem (n = 71) um diagnóstico precoce mostra que o diagnóstico precoce está associado à presença de histórico familiar positivo e à redução na prevalência de manifestações clínicas no momento do diagnóstico, porém sem melhor resultado. Em geral, 98,8% dos pacientes têm algum atraso no desenvolvimento psicomotor ou neurológico.
Conclusão: No Brasil, os pacientes com DXB normalmente recebem um diagnóstico tardio e exibem um envolvimento neurológico e baixa sobrevivência, mesmo com um diagnóstico precoce. Sugerimos que políticas públicas específicas para o diagnóstico e tratamento da DXB sejam desenvolvidas e implementadas no país.

Introduction

Maple syrup urine disease (MSUD) is an autosomal recessive genetic disorder caused by deficient activity of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC). Deficiency of this enzyme complex leads to high levels of the branched-chain amino acids (BCAA) leucine, valine, and isoleucine. Leucine and its keto analog 2-oxoisocaproic acid are particularly toxic to the central nervous system (CNS). Although the incidence of MSUD worldwide is usually estimated as being 1:185,000 newborns (NB),[1] data retrieved from newborn screening suggest this rate can be higher; in Germany, for instance, the incidence is estimated at 1:133,000 NB,[2] and in some Mennonite and Pennsylvania Dutch communities in the United States, it may be as high as 1 in 200 live births.[3]

Neonatal screening by tandem mass spectrometry (MS/MS), also known as expanded newborn screening, enables diagnosis of MSUD while the patient is still asymptomatic, as well as early treatment onset—two essential factors in improving the clinical course.[3] Before the introduction of expanded newborn screening, the severe form (classical MSUD) was believed to account for 75-80% of cases,[4] but recent data suggest the milder forms of MSUD can account for up to 50% of diagnosed cases.[5] In the classical form, symptoms first occur between the 4th and 7th day of life, and often include respiratory changes, encephalopathy, a characteristic odor, seizures, and coma.[6] In the acute phase, prompt, aggressive treatment to reduce leucine levels is required, which should consist of a high-rate glucose infusion to stimulate insulin secretion and suppress protein catabolism. If this fails, invasive interventions such as peritoneal dialysis, hemodiafiltration or hemodialysis may be required. During the maintenance phase, treatment usually consists of dietary BCAA restriction and supplementation with thiamine and a BCAA-free formula,[6–8] although liver transplantation is a good alternative.[9–11]

The Brazilian Public Newborn Screening Program was implemented in 2001 and does not include screening for MSUD. The BCAA-free formula, a high-cost product, is not provided by the public Brazilian Unified Health System (Sistema Único de Saúde, SUS). Furthermore, the laboratory tests required for diagnosis of this condition are also not provided through the SUS, and are only available at a few select university centers or private medical laboratories. Regarding liver transplantation, there is no coordinated countrywide