INTRODUCTION

Urea Cycle Disorders (UCD) are Inborn Errors of Metabolism (EIM) related to ammonia detoxification process in the human body. Through a cyclic and enzymatically controlled mechanism that occurs in the liver, the urea cycle transforms ammonia into urea (non-toxic), and a safe excretion occurs in the body (Summar et al., 2018). The impairment of this metabolic route causes an intoxication due to the accumulation of ammonia (hyperammonemia) and other intermediate metabolites of the cycle, characterizing an UCD. High levels of ammonia are neurotoxic and capable of exerting deleterious effects on the central nervous system (Brusilow et al., 2001; Herman et al., 2018). Ornithine transcarbamylase deficiency (OTCD), one of the most prevalent UCD’s, is a X-linked genetic disorder caused by a total or partial lack of ornithine transcarbamylase (OTC) activity, one of the enzymes involved in the cycle. The dysfunction makes it impossible to convert the complex carbamoyl phosphate and ornithine to citrulline, resulting in an increase in plasmatic glutamine and alanine and a decrease of citrulline. OTCD often presents as neonatal encephalopathy and can result in severe neurological disability or death (Burgard et al., 2016; Haberle et al., 2019). The phenotype presented by male patients usually is most aggressive, although heterozygous women can present both the classic and asymptomatic form. Therapy consists in removing the extra nitrogen from the body, dietary restriction with low protein intake and amino acids supplementation (Bartholomew et al., 1987; Rocha et al., 2020).
OBJECTIVE

• In this study, we describe and analyze the biochemical and clinical profile of OTCD patients diagnosed at Hospital de Clínicas de Porto Alegre (HCPA-POA/ Brazil), a referral hospital in Brazil, in order to better elucidate these profiles.

MATERIALS AND METHODS

• The blood amino acid analysis was performed by high performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) when UCD was suspected. Medical records of OTCD patients were analyzed to find the biochemical profile parameters and clinical picture in diagnosis.

• This study was approved by the Ethics in Research Committee of Hospital de Clínicas de Porto Alegre (2020-0562).

RESULTS

• 8 individuals with mean age of 9.8 months-old (SD±8.5) were diagnosed with OTCD among 30 UCD patients.

• OTCD patients demonstrated elevated levels of blood ammonia and orotic acid in the urine (table 1).

Table 1. Biochemical markers of patients with OTCD.

<table>
<thead>
<tr>
<th>Laboratorial finding</th>
<th>Level (mean ± SD)</th>
<th>Reference range</th>
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<tbody>
<tr>
<td>Blood ammonia (µmol/L)</td>
<td>724 ± 457</td>
<td>≤ 80 (µmol/L)</td>
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<tr>
<td></td>
<td>(n = 4)</td>
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<tr>
<td>Orotic acid (µm/mg de creatinine)</td>
<td>158,2 ± 141</td>
<td>≤ 14 (µm/mg de creatinine)</td>
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<td>(n = 5)</td>
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</table>
RESULTS

• Amino acid profile (figure 1) showed a decrease in citrulline blood levels in all of the patients (100%). Six of them demonstrated an increase in plasmatic alanine (75%) and 5 in glutamine (63%).

• Hyperammonemia, high excretion of orotic acid in the urine, metabolic acidosis and hypoglycemia were the most frequent laboratorial findings (table 2).

• Clinical symptoms were highly severe, being the majority neurological abnormalities and developmental delays, such as coma and altered consciousness (table 2).

Table 2. Principal signs and symptoms presented by OTCD patients in diagnosis.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Hyperammonemia</td>
<td>8 (100%)</td>
<td>Vomit</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Orotic aciduria</td>
<td>5 (62,5%)</td>
<td>Coma</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>3 (37,5%)</td>
<td>Altered consciousness</td>
<td>3 (37,5%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2 (25%)</td>
<td>Hypoactivity</td>
<td>3 (37,5%)</td>
</tr>
<tr>
<td>Altered hepatic function</td>
<td>1 (12,5%)</td>
<td>Convulsions</td>
<td>3 (37,5%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>1 (12,5%)</td>
<td>Ataxy</td>
<td>1 (12,5%)</td>
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</table>

• Medical records demonstrated that one patient (12,5%) has died due to the severe outcomes of OTCD.
DISCUSSION AND CONCLUSION

• Differently of other UCD, ornithine transcarbamylase deficiency has its gene located on the X chromosome and usually manifests a very severe neonatal condition in males. In the other hand, female carriers phenotypes is quite variable and women can range from asymptomatic form to severe (Scaglia et al., 2002).

• The group of individuals diagnosed with OTCD in HCPA-POA manifested the classical neonatal form with severe signs and symptoms, which contributes to poor outcomes if the hyperammonemia is not diagnosed and treated quickly. Furthermore, one patient (12%) has died due to the complications of OTCD, corroborating with the severity of the disease (Brassier et al., 2015).

• It is essential to investigate and monitor ammonia levels when an UCD is suspected and, in OTCD cases, the observation of decreased levels of citrulline is also a key point to reach the right diagnosis (Haberle et al., 2019). Orotic acid is also a valuable biomarker to be evaluated in OTCD, since other UCD with similar symptoms demonstrate normal levels and, therefore, it can be used to differential diagnosis (Salerno et al., 2002; Held et al., 2014).

• With this analysis we highlight the importance of urgency in identification and correct diagnosis of OTCD, in order to increase the chances of survival and minimize neurological and psychomotor damage in affected patients.

ACKNOWLEDGMENTS

• We would like to thank all participants of the study and financial support by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundo de Incentivo à Pesquisa e Eventos (FIFE/HCPA).

REFERENCES