Hepatic Encephalopathy Is Not Always due to Liver Cirrhosis

Miriam Eva Ecker a  Maria Paparoupa b  Bernd Sostmann c  Karin Weissenborn d  Frank Schuppert a

aDepartment of Gastroenterology, Endocrinology, Diabetology and General Medicine, Klinikum Kassel, Kassel, Germany; bDepartment of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; cGeneral Practitioner’s Private Practice, Melsungen, Germany; dDepartment of Neurology, Hannover Medical School, Hannover, Germany

Keywords
Hepatic encephalopathy · Liver cirrhosis · Hyperammonaemia · Liver failure · Ornithine transcarbamylase deficiency · Urea cycle enzymes

Abstract
Hepatic encephalopathy (HE) is a frequent and debilitating complication of liver disease and is oftentimes associated with hyperammonaemia. However, hyperammonaemia may occur in underlying conditions other than acute or chronic liver failure and clinical awareness is needed in order to be recognized and treated properly. A 24-year-old woman presented herself to our emergency department with acute confusion and altered mental state due to severe hyperammonaemia. The patient was diagnosed in the age of 14 with ornithine transcarbamylase (OTC) deficiency and was incompliant regarding her diet and suggested medication to treat this disorder. She was treated with sodium benzoate 250 mg/kg i.v., sodium phenylbutyrate/sodium phenylacetate 250 mg/kg i.v., L-arginine 250 mg/kg i.v., and received continuous hemofiltration. Under simultaneous medical treatment and haemodialysis, ammonia levels dropped to normal within 24 h and symptomatic encephalopathy ceased completely. OTC deficiency is rare in adults, and the majority of patients are diagnosed in childhood. It can lead to death if not diagnosed and treated properly. Our case underlines the importance of considering causes of HE other than liver cirrhosis.
Introduction

Hepatic encephalopathy (HE) is a frequent and debilitating complication of liver disease as 30–40% of all patients with liver cirrhosis will experience overt HE at one point in their lives [1]. Although the exact pathology is not yet completely understood, it is believed that increased portal-systemic shunting of gut-derived ammonia, accumulating in liver failure, plays a major role and exerts neurotoxic effects [2].

HE is considered manageable and potentially reversible in chronic liver failure with slower development of hyperammonaemia [1]. Conversely, in acute and fast-developing hyperammonaemia, damage to the brain can be extensive and may result in diffuse cerebral oedema, rising intracranial pressure, and eventually, brain stem injury [3]. Furthermore, the presence of HE in patients with acute liver failure – regardless of the cause – is associated with higher mortality and was shown to be an independent predictor of decreased patient survival [4].

The hepatic cause of encephalopathy is most commonly identified by the presence of liver cirrhosis, and the patient management will then lie in the hands of hepatologists. However, aetiologies other than cirrhosis or acute liver failure do exist, such as genetic defects of the urea cycle enzymes, leading to liver hyperammonaemia [5]. The absence of liver cirrhosis may prolong the time to diagnosis in these patients, as physicians need to identify other conditions than liver failure. In this report, we present the case of a 24-year-old woman, who was admitted to our emergency department because of HE without liver cirrhosis, highlighting the fact that many rare genomic diseases may overlap in symptoms with primary gastrointestinal (GI) disorders.

Case Presentation

A 24-year-old woman presented herself with acute confusion and altered mental state. She was oriented to person, but not to time and place. The physical examination showed no abnormalities; in particular, the abdomen was completely normal and no focal neurological signs were detected. Her accompanying partner reported that the patient suffers from ornithine transcarbamylase (OTC) deficiency and is incompliant regarding her diet and suggested medication to treat this disorder.

Initial routine blood chemistry parameters were all within normal ranges, except of serum-level ammonia, which was severely increased to 235 μmol/L (reference value: 18–72 μmol/L). Abdominal sonography revealed no signs of pathology. The diagnosis of HE due to OTC deficiency was made, and medical treatment with sodium benzoate 250 mg/kg i.v., sodium phenylbutyrate/sodium phenylacetate 250 mg/kg i.v., L-arginine 250 mg/kg i.v., and parenteral glucose to ameliorate the catabolic state was promptly initiated. This therapeutic scheme was received from the patient’s practitioner, with whom she counsels quarterly.

After commencing emergency medical treatment, the patient was transferred to the intensive care unit in order to receive continuous hemofiltration, which was supposed to remove ammonia and is widely implemented in crises of OTC deficiency [2, 5]. Haemodialysis is considered to be first-line treatment in refractory cases of hyperammonaemia [5]. Under simultaneous medical treatment and haemodialysis, ammonia levels dropped to normal levels within 24 h and symptomatic encephalopathy ceased completely.

At that time, it was possible to obtain a more detailed history from the patient and to access her medical records. From the age of 11 years on, she experienced multiple episodes of what was thought to be encephalitis of unknown origin and periods of reduced awareness, but an explicit diagnosis had not been made yet. Her first diagnosis of OTC deficiency was
made at the age of 14, when she initially presented herself with impaired awareness, focal seizures, hyperammonaemia, and raised urine levels of orotate. This prompted molecular genetic testing for urea cycle disorders (UCDs), and a heterozygous deletion of exons 3–10 in the OTC gene was detected – a mutation, which was previously not described in the literature (Fig. 1). The role of OTC in the urea cycle is depicted in Figure 2. Furthermore, she suffers a minor intellectual disability. Since her first manifestation of OTC deficiency, the patient has experienced multiple hyperammonaemic crises with encephalopathy and impaired consciousness. On the fourth day as an inpatient, she left the hospital against medical advice. At the time of discharge, she was advised to take her usual medication consisting of 2.5 mg sodium benzoate capsules three times daily and sodium phenylbutyrate 500 mg daily (8 capsules á 62.5 mg three times daily) and to follow a low-protein diet (35% of normal requirements).

Discussion

In adults, liver cirrhosis is the most common cause of HE. Our case demonstrates that other rare underlying conditions may also exist in adults and need to be considered particularly in the absence of obvious signs of liver disease. In enzyme deficiencies, such as OTC, only subtle histopathological changes are observed, instead of the extensive histopathological findings in cases of liver cirrhosis [6]. Whereas 10–20% of patients present with HE at the time of their first diagnosis with liver cirrhosis [7], patients with late-onset UCD enzyme deficiencies almost exclusively present with symptoms of HE [5].

The most common cause of hyperammonaemia due to enzyme deficiencies within the urea cycle is the deficiency of OTC, like in our patient [8]. UCDs occur in 1:40,000 to 1:50,000 patients [9]. The prevalence of OTC deficiency is estimated to be between 1:14,000 and 1:80,000 [8, 10]. Approximately one-third of all patients with OTC deficiency present within the first 4 weeks of life, more than 60% between the age of 1st and 6th year, and the remaining small percentage later in life. Of those being diagnosed during the neonatal period, 71% are male [11].

Fortunately, in our case a third-party medical history could be obtained and this allowed us to initiate prompt and targeted treatment. Oftentimes, those patients remain undiagnosed for a long time. Many of them may primarily present themselves to the Department of Neurology. That is the reason that neurologists should be aware of this condition as well. Patients with encephalopathy grade III or IV, according to the West Haven Criteria [1, 12], need immediate care, but those with less severe symptoms can be evaluated using psychometric tests, such as the Number Connection Test (NCT). Figure 3 shows an example of an NCT. These tests are able to detect minimal or beginning HE and thus become lifesaving for the patient. Even though they are not helpful to differentiate among the different causes of HE, they can be helpful.
to discern subtle cognitive dysfunction which may precede overt HE [13]. A constellation of hyperammonaemia, encephalopathy, and absence of chronic or acute liver disease may indicate UCDs or enzyme deficiencies.

Fig. 2. Overview of the role of OTC in the urea cycle. Top: normal urea cycle. In the mitochondria of hepatocytes, bicarbonate (HCO₃⁻) and toxic ammonium (NH₄⁺) are catalysed by the ATP-dependent and rate-limiting enzyme CPS into carbamoyl phosphate. Together with ornithine, it is converted by OTC into citrulline, which enters the urea cycle. The end product is water-soluble, non-toxic urea. Bottom: OTC deficiency. In the case of OTC deficiency, carbamoyl-P and eventually ammonium accumulate, as CPS is overwhelmed. Accumulating carbamoyl-P is synthesized to orotate and uracil. Orotate is mainly excreted via the kidneys. Characteristic lab parameters of OTC deficiency are decreased blood levels of citrulline, increased ammonium, and increased urinary orotate [5]. CPS, carbamoyl phosphate synthetase; OTC, ornithine transcarbamylase; ASS, argininosuccinate synthetase; ALS, argininosuccinate lyase; ARG, arginase.
The OTC deficiency follows an X-linked recessive inheritance pattern, but some cases of de novo mutations in germ cells have been also observed. The onset and severity of OTC deficiency are highly variable, ranging from severe hyperammonaemia in neonates, to late diagnoses during adulthood or asymptomatic individuals. By now, more than 341 mutations within the gene encoding OTC have been identified [8]. The distribution of different classes of mutations is displayed in Table 1.

Notably, mutations affecting amino acid residues close to the active site of the enzyme are linked to a more severe and early onset phenotype [8]. Particularly, in female patients as in our case, atypical and late-onset presentations of OTC deficiency are common due to the inheritance pattern [10]. 20% of heterozygote females are estimated to experience symptoms, and 80% will remain asymptomatic. Symptoms are mainly caused by the effects of ammonia on the brain and may range from lethargy, psychomotor retardation, vomiting, and neurological deficits to coma and cerebral oedema. The large deletion mutation of 8 exons in the OTC gene made the symptomatic phenotype more likely in our case. Only 4% of patients with OTC deficiency have an underlying large deletion mutation [8].

In individuals with a less severe form of OTC deficiency, the major trigger for a hyperammonaemic crisis is the presence of a catabolic state, which is an increase in protein breakdown occurring either in periods of insufficient caloric intake [14] or in periods of excessively high protein intake. Atkin’s diet (high in protein and fat, and low in carbohydrates) has been identified as a trigger for hyperammonaemic crisis in a previously asymptomatic 47-year-old

---

**Table 1.** Distribution of different classes of mutations

| Mutation                        | Percentage |
|---------------------------------|------------|
| Single-base substitutions       | 84%        |
| Small deletions or insertions   | 12%        |
| Large deletions                 | 4%         |

Distribution of groups of mutations in the OTC gene, adapted from Yamaguchi et al. [8].
male with OTC deficiency [15]. Dietary management should consist of protein intake, which meets the cellular requirements but is low enough to prevent hyperammonaemia. Interestingly, several case reports of late-onset OTC deficiency describe instances of patients experiencing protein intolerance and they subsequently avoid high protein content [5]. This phenomenon has not been observed here.

The treatment of OTC deficiency depends on disease severity: in cases with early onset and severe manifestations, a liver transplant is required, whereas in a late-onset or less severe disease course an appropriate diet and proper medication may suffice as adequate therapy. Early detection and treatment of hyperammonaemia in OTC deficiency are of great importance, and debilitating neurological sequelae should be prevented by early intervention and brain imaging.

In the acute setting of our patient's hospital admission, imaging of the brain was not performed as the cause and diagnosis were clear and most importantly, her symptoms ceased quickly after initiation of the treatment. The fast clinical improvement confirmed the absence of increased intracranial pressure due to cerebral oedema. The patient's last brain MRI was performed 9 years previously, when she suffered another hyperammonaemic coma, and it did not reveal any suspect lesions or pathology. The minor intellectual disability could be a consequence of the multiple hyperammonaemic crises since her childhood. Several case reports show a wide range of different neuropsychological effects of hyperammonaemia in OTC deficiency, ranging from mild intellectual disability over mental delay up to attention deficit hyperactivity disorder or impulsivity in adulthood [5].

In the current manuscript, we present a case of a rare genomic disease, which could be confusing for practitioners not specialized in this field, because of its overlap with clinical symptoms reflecting more common GI disorders. In the era of individualized medicine, rare genomic diseases, affecting directly or indirectly the GI system, gain an increasingly important role in the differential diagnosis of otherwise common diseases. Physicians need to be aware that rare genomic diseases do occur and attention should be focused on diagnosing and treating such entities.

**Conclusion**

Our case report of a 24-year-old female patient with OTC deficiency underpins the relevance and importance of considering causes of HE other than liver cirrhosis. OTC deficiency is rare in adults, and the majority of patients are diagnosed in childhood; nonetheless, it can lead to death due to its complications if not diagnosed and treated properly. Further, this case shows that with early recognition, intervention, and management, permanent damage can be prevented in case of late OTC deficiency.

**Statement of Ethics**

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Conflict of Interest Statement**

The authors have disclosed that they have no significant relationship with or financial interest in any commercial companies pertaining to this article.
Funding Sources

No funding was received.

Author Contributions

Miriam Eva Ecker and Maria Paparoupa collected all needed data and wrote the manuscript. Bernd Sostmann, Karin Weissenborn, and Frank Schuppert treated the patient throughout time. Karin Weissenborn and Frank Schuppert reviewed the manuscript and provided consultation regarding intellectual argumentation. All authors have read and approved the submitted version of the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715–35.
2 Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525–34.
3 Wijdicks EF. Hepatic encephalopathy. *N Engl J Med*. 2016;375(17):1660–70.
4 Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhear M, Auzinger G, et al. Lessons from look-back in acute liver failure? A single centre experience of 3,300 patients. *J Hepatol*. 2013;59(1):74–80.
5 Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J Inherit Metab Dis*. 2019;42(6):1192–230.
6 Yaplito-Lee J, Chow CW, Boneh A. Histopathological findings in livers of patients with urea cycle disorders. *Mol Genet Metab*. 2013;108(3):161–5.
7 Elsaid MI, Rustgi VK. Epidemiology of hepatic encephalopathy. *Clin Liver Dis*. 2020;24(2):157–74.
8 Yamaguchi S, Brailley LL, Morizono H, Bale AE, Tuchman M. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. *Hum Mutat*. 2006;27(7):626–32.
9 Walker V. Ammonia toxicity and its prevention in inherited defects of the urea cycle. *Diabetes Obes Metab*. 2009;11(9):823–35.
10 Summar ML, Dobbelaeere D, Brusilow S, Lee B. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. *Acta Paediatr*. 2008;97(10):1420–5.
11 Kido J, Nakamura K, Matsubashi H, Ohura T, Takayanagi M, Matsuo M, et al. Long-term outcome and intervention of urea cycle disorders in Japan. *J Inherit Metab Dis*. 2012;35(5):777–85.
12 Weissenborn K, Rücker K, Hecker H, Manns MP. The number connection tests A and B: interindividual variability and use for the assessment of early hepatic encephalopathy. *J Hepatol*. 1998;28(4):646–53.
13 Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic principles. *Drugs*. 2019;79(Suppl 1):5–9.
14 Laemmle A, Gallagher RC, Keogh A, Stricker T, Gutschi M, Nuoffer JM, et al. Frequency and pathophysiology of acute liver failure in ornithine transcarbamylase deficiency (OTCD). *PLoS One*. 2016;11(4):e0153358.
15 Ben-Ari Z, Dalal A, Morry A, Pitlik S, Zinger P, Cohen J, et al. Adult-onset ornithine transcarbamylase (OTC) deficiency unmasked by the Atkins’ diet. *J Hepatol*. 2010;52(2):292–5.