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Ornithine transcarbamylase (OTC) deficiency based on a hemizygous p.R277W mutation causing life threatening hyperammonemic crisis during treatment for Hodgkin's lymphoma

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Dear Editor,

We report on a rare case of ornithine transcarbamylase (OTC) deficiency as origin for life threatening hyperammonemia in a young adult male patient with Hodgkin's lymphoma.

Clinical case report

The reported patient was diagnosed with mediastinal Hodgkin's lymphoma (Ann Arbor stage IA) at the age of 23 years in November 2008. He underwent initial remission induction with chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) and involved field irradiation. In April 2009, early relapse (stage IIA) caused upper airway obstruction. Immediate treatment with intravenous prednisolone (continued with methylprednisolone p.o.) and irradiation was initiated. Four weeks later the patient presented with reduced vigilance finally progressing to coma. Blood testing revealed markedly elevated plasma ammonia levels ($>400 \mu\text{mol/l}$, reference range [RR] $16\text{--}48 \mu\text{mol/l}$; Fig. 1); bilirubin and aminotransferases were marginally elevated. Electroencephalography displayed a moderately severe general alteration suggestive of metabolic encephalopathy. Cranial magnetic resonance imaging (MRI) showed slight cerebral edema and bilateral subcortical FLAIR hyperintensities in the precentral region with patchy distribution. Cerebrospinal fluid analysis, liver MRI and histology, drug and medication screening as well as microbiological investigations were negative. Corticosteroids were discontinued and the patient recovered completely without extensive anti-hyperammonemic therapy. In June 2009, chemotherapeutic treatment of relapse was initiated with dexamethasone, cytarabine and cisplatin (DHAP), and switched to the Dexa-BEAM regimen (dexamethasone,

carmustine, etoposide, cytarabine, melphalan) due to refractory disease. Twelve days after the onset of DEXA-BEAM the patient again presented with nausea, vomiting, and progressive loss of vigilance. He was transferred to the intensive care unit for transient mechanical ventilation. Blood testing revealed severe hyperammonemia (Fig. 1), reduced citrulline (13 $\mu\text{mol/l}$, RR 19–55 $\mu\text{mol/l}$) and slightly elevated alanine levels (622 $\mu\text{mol/l}$, RR 241–597 $\mu\text{mol/l}$) pointing to a possible block of ureagenesis at the level of or proximal to OTC. Other plasma amino acids (including arginine and glutamine) and urinary orotic acid were in the reference range. Blood glucose, lactate, carnitine, acylcarnitines and urinary organic acids were normal. Accordingly, severe hepatic failure, organoacidurias and disorders of fatty acid oxidation appeared unlikely. Molecular analysis revealed a point mutation in the OTC gene leading to an exchange of arginine by tryptophan at position 277 (p.R277W mutation). Encephalopathy resolved within two days and further chemotherapy was continued without dexamethasone. In November 2009 the patient received autologous peripheral blood stem cell transplantation after a single dose of prednisolone (100 mg i.v.). Treatment was well tolerated and hyperammonemic encephalopathy did not re-occur. In January 2010, however, the patient died from infectious complications.

Catalyzing the carbamylation of citrulline, mitochondrial OTC is crucially involved in ureagenesis and ammonia elimination. Currently, more than 300 mutations compromising enzyme activity are known [1]. OTC deficiency is an X-linked disorder [2] that represents the most frequent inherited urea cycle defect. Hemizygous males with complete OTC deficiency display severe hyperammonemia within the first week(s) of life. Although males and heterozygous females with subtotal defects

frequently present later, adult-onset OTC deficiency is rare [3-5] and found mostly in females with unfavorable lyonization.

Several environmental factors have been implicated as potential triggers of late-onset OTC deficiency. These include valproate [6], gastrointestinal bleeding [7], parenteral nutrition [8] and possibly corticosteroids [5,9]. In the present case hyperammonemic encephalopathy and steroid administration showed correlation, and, in addition, a corticosteroid-dose dependence of the clinical manifestations was evident (Fig. 1). Notably, chemotherapy without corticosteroids did provoke neither hyperammonemia nor encephalopathy. This suggests that both episodes of hyperammonemic encephalopathy resulted from a steroid-induced excessive protein catabolism on the background of a pre-existent reduction in the capacity of ammonia clearance. The latter was found to result from a specific mutation in the ornithine transcarbamylase (*OTC*) gene (p.R277W) previously shown to be associated with late disease onset [10]. Further genetic testing revealed the same mutation in the patient's mother and his thirteen-year-old brother both of whom were asymptomatic.

In conclusion, the reported case illustrates that late-onset OTC deficiency should be considered in hyperammonemic patients treated with steroids. Genotyping is essential for diagnosis, as our patient did not show elevated orotic acid commonly assumed to be central for the diagnosis of OTC deficiency.

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Figure legend

Fig. 1 Correlation of hyperammonemia and encephalopathy with corticosteroid administration. **A**, Cumulative cortisol-equivalent dose. Vertical dotted lines point to onsets and offsets of corticosteroid administration. Cortisol equivalent doses were calculated assuming: 30 mg cortisol i.v. = 7.5 mg prednisolone i.v. = 6 mg methylprednisolone p.o. = 1 mg dexamethasone i.v./p.o. **B**, Time course of plasma ammonia in relation to episodes of encephalopathy (vertical grey bars). Reference range is indicated by horizontal dashed lines. Note that high cumulative doses of corticosteroids (>7 g cortisol equivalent) apparently triggered hyperammonemic encephalopathy, whereas lower doses did not

