A Galloping Horse Deep into the Patient's Eyes

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PATIENT DESCRIPTION

A 49-year-old woman presented to the emergency department with a 3-day history of altered mental status. The patient's medical history was unremarkable, and she did not take medications. On examination, the patient's Glasgow Coma Scale was 8 (E8V2M4) and a slow rhythmic constriction and dilation of pupils were noticed [Figure 1]. The remainder of the examination was normal. Computed tomography scan of the brain and lumbar puncture were unremarkable. Laboratory tests were within a normal range (including lactate) apart from severe hyperammonemia (285 µmol/L, normal range 11 to 32 µmol/L). The patient was treated with hydration, ammonia chelators, arginine supplements, and hemodialysis with a rapid improvement in her mental status. A meticulous questioning revealed that three of her male babies had died a few days after birth without any diagnosed etiology. Consultation of an inherited metabolic disease specialist was requested, and the patient was diagnosed with ornithine transcarbamylase deficiency (OTCD), an X-linked disorder of the urea cycle. The patient was discharged in good clinical condition with supplemental arginine and sodium benzoate.

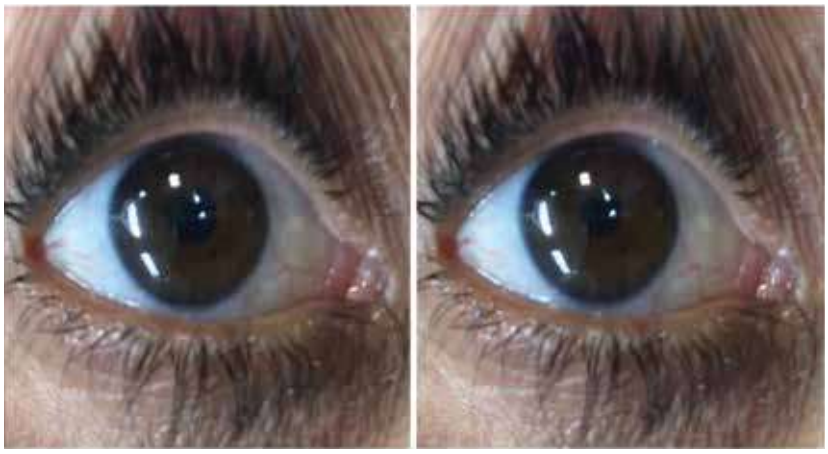
COMMENT

The term *hippus* is derived from a Greek word meaning horse and is defined as rhythmic pupillary oscillations with sufficiently large amplitude to be easily visible [1,2]. Mild pupillary oscillations may be a normal finding but marked hippus is a rare condition [1]. Although the pathophysiology of this phenomenon is not completely understood, it seems to be mediated by the Edinger-Westphal nucleus, the accessory parasympathetic cranial nerve nucleus of the oculomotor nerve and caused by continuous disequilibrium between the sympathetic activity (causing mydriasis) and the parasympathetic activity (causing miosis) in the central nervous system [2].

Hippus was previously described as a manifestation of nonconvulsive seizures and status epilepticus as well as in patients with alerted mental status due to hepatic encephalopathy, neurosyphilis, and amanita mushroom and aconitum poisoning [1-3]. Unrelated to the exact etiology, this phenomenon is an independent predictor of early mortality in the inpatient setting and may reflect metabolic encephalopathy or autonomic imbalance affecting the brain by different pathologic conditions [1].

OTCD is the most common urea cycle defect. The gene encoding the enzyme ornithine transcarbamylase is located on the X chromosome. Although it is mainly expressed in the liver and the intestine, the major complications of the disease are neurological. Affected males usually present with severe, occasionally fatal, hyperammonemic encephalopathy during the neonatal period, while heterozygote females may remain asymptomatic for many years. Adult patients usually present with fluctuating neurological symptoms, including headache, vomiting, lethargy, abnormal behavior, disorientation, confusion, ataxia, hypo-

Figure 1. Pupillary hippus is bilateral, synchronous, and rhythmic mydriasis **[A]** and miosis **[B]** in the absence of light variations or other external stimuli



tonia, and focal neurological signs such as hemiplegia. Up to 20% of patients may develop acute severe encephalopathy. The symptoms may develop spontaneously or be triggered by intercurrent infections, high protein intake, dietary changes, medications (i.e., sodium valproate), pregnancy, or other stress factors that precipitate protein catabolism. A low-protein diet with supplemental arginine and ammonia chelators such as sodium benzoate and phenylbutyrate are the cornerstone of the therapy. Dialysis or hemofiltration may be necessary in severe cases [4].

The exact trigger for the development of acute encephalopathy in our patient could not be determined despite careful investigation. We believe that uneventful dietary changes, intercurrent mild infection, and/or physiological stresses were responsible for the deterioration. To the best of our knowledge, this is the first description of hippus in a patient presenting with acute encephalopathy caused by adult-onset OTCD. The pathophysiology behind the association between this unique pupillary response and OTCD is unknown. Electroencephalography and magnetic resonance imaging (MRI) were not performed due to the rapid improvement in our patient's condition. Nevertheless, we can speculate that hippus in OTCD may be caused by impaired intracranial electrical activity caused by cerebellar atrophy and white matter lesions which are occasionally demonstrated in an MRI of patients with OTCD [5]. These processes may be responsible for the focal imbalance between sympathetic and parasympathetic tonus leading to rhythmic pupil movement.

CONCLUSIONS

Pupillary examination should be systematically performed in every patient with altered mental status or coma. In this context, pupillary hippus may be an important clinical clue to the correct diagnosis. In patients with unexplained hippus, measuring ammonia levels should be considered.

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The question is whether or not you choose to disturb the world around you, or if you choose to let it go on as if you had never arrived.
Ann Patchett (born 1963), American writer

You have to hold your audience in writing to the very end – much more than in talking, when people have to be polite and listen to you.
Brenda Ueland (1891–1985), journalist, editor, freelance writer, and teacher of writing

Capsule

Enterococci enhance *Clostridioides difficile* pathogenesis

Smith and associates showed that expansion of a group of antibiotic-resistant, opportunistic pathogens in the gut, the enterococci, enhances the fitness and pathogenesis of *Clostridioides difficile*. Through a parallel process of nutrient restriction and cross-feeding, enterococci shape the metabolic environment in the gut and reprogram *C. difficile* metabolism. Enterococci provide fermentable amino acids, including leucine and ornithine, which increase *C. difficile* fitness in the antibiotic-perturbed gut. Parallel depletion of arginine by enterococci through arginine catabolism provides a metabolic cue for *C. difficile* that facilitates increased virulence. The authors found evidence of microbial interaction between these two pathogenic organisms in multiple mouse models of infection and patients infected with *C. difficile*. These findings provide mechanistic insights into the role of pathogenic microbiota in the susceptibility to and the severity of *C. difficile* infection.

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