This issue's letters

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Possible new clinical sign of hyperammonemia

Saleh Alqahtani and colleagues have provided a welcome reminder that hyperammonemia is a common side effect of valproate therapy.[1] However, I am not convinced that hyperammonemia is a benign asymptomatic condition. I wonder whether the sedation that is often seen as a side effect of valproate therapy is in fact a symptom of low-grade encephalopathy.

In the past year, 2 of my patients with bipolar disorder who were taking valproate complained of foul-smelling urine. Both described the odour as strong, and when I smelled their urine myself I was unable to come up with a better descriptor. Blood ammonia levels were elevated in both patients. Both patients noted that the smell disappeared when they were switched to a different medication (oxcarbazepine), and they felt that their mental clarity improved as well.

If strong-smelling urine is indeed a sign of valproate-related hyperammonemia, it is simple enough to ask patients who take valproate whether they are experiencing this side effect. If they are, and if their blood ammonia level is elevated, the need for valproate therapy should be reassessed.

The authors' recommendations for managing valproate-related hyperammonemic encephalopathy are prudent, but I wonder if they missed half the picture. Does valproate therapy unmask underlying conditions such as urea-cycle disorders or fatty-acid-oxidation disorders? Did the authors look for these conditions in their patient? If not, why not? More importantly, how should family physicians begin investigating these possibilities? What tests should the physician in the trenches order to screen for these conditions once suspicions are raised?

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REFERENCE

1. Alqahtani S, Federico P, Myers RP. A case of valproate-induced hyperammonemic encephalopathy: look beyond the liver. *CMAJ* 2007;177:568-9.

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[The authors respond:]

We thank Harold Pupko for raising several relevant points concerning our article.[1] Valproate-induced hyperammonemic encephalopathy is a well-described phenomenon, but its precise incidence is unknown. Mild asymptomatic elevations in ammonia concentrations have been described in 16%–52% of patients receiving valproate therapy.[2] As suggested by Pupko, valproate therapy may unmask congenital enzymatic disorders, particularly in children.[3,4]

In virtually all of the reported cases of valproate-induced hyperammonemic encephalopathy, the patients had symptoms attributable to an underlying metabolic disorder that predated the onset of the condition. We did not search for an underlying metabolic disorder in our patient because she was previously asymptomatic and because there was nothing in her medical history to prompt such a search (e.g., a family history of metabolic disorders or other unexplained childhood disorders or deaths).

Currently there are no specific guidelines for screening patients for valproate-induced hyperammonemia (asymptomatic or symptomatic). We believe that the factors that should be considered include symptoms attributable to hyperammonemia (i.e., encephalopathy) or an underlying metabolic disorder, the magnitude of the increase in ammonia concentration, patient age and a family history of metabolic disorders or early childhood deaths. Screening blood tests could include a complete blood count with white blood cell differential count; tests for electrolytes, creatinine, urea, glucose and lactate; a quantitative amino acid screen and an acyl carnitine profile. A urine organic acid screen could also be considered. These tests would help to identify most of the alternative causes of hyperammonemic encephalopathy listed in Box 1 of our report.[1]

We do not systematically ask patients receiving valproate therapy about strong-smelling urine. The patient we described in our article did not report this symptom nor have our other patients taking valproate. To our knowledge there are no published reports of this symptom in this patient population. Future studies should investigate the utility of this symptom as a noninvasive clue to the diagnosis of valproate-induced hyperammonemia.

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