Hyperammonaemic encephalopathy after initiation of valproate therapy in unrecognised ornithine transcarbamylase deficiency

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Abstract
Ornithine transcarbamylase deficiency is an X linked disorder and the most common inherited cause of hyperammonaemia. Fluctuating concentrations of ammonia, glutamine, and other excitotoxic amino acids result in a chronic or episodically recurring encephalopathy. A heterozygous female patient first presented with protein intolerance, attacks of vomiting, and signs of mental retardation in early childhood. At the age of 16 complex partial seizures occurred which were treated with sodium valproate. Seven days after initiation of valproate therapy, she developed severe hyperammonaemic encephalopathy with deep somnolence. The maximum concentration of ammonia was 480 µmol/l. After withdrawal of valproate, three cycles of plasma dialysis, and initiation of a specific therapy for the inborn metabolic disease, ammonia concentrations fell to normal values. The patient remitted, returning to her pre-morbid state. Valproate can cause high concentrations of ammonia in serum in patients with normal urea cycle enzymes and may worsen a pre-existing hyperammonaemia caused by an enzymatic defect of the urea cycle. Sufficient diagnostic tests for the detection of metabolic disorders must be performed before prescribing valproate for patients with a history of encephalopathy.

Keywords: ammonia in blood; valproic acid therapy; ornithine transcarbamylase deficiency

Deficiency of the mitochondrial urea cycle enzyme ornithine transcarbamylase (synonym ornithine carbamoyltransferase, OTC) is an X linked disorder causing hyperammonaemia.1 Most male patients develop severe hyperammonaemia with seizures and coma in the neonatal period; a few patients are asymptomatic until juvenile or adult age.2,3 Heterozygous females show a widespread variation in onset and severity of symptoms. Episodic vomiting, protein intolerance, mental retardation, psychiatric manifestations such as bizarre behaviour, irritability and aggression, ataxia, focal and generalised tonic-clonic seizures, and disturbances of consciousness are typical symptoms of the chronic and episodically exacerbating encephalopathy in OTC deficiency.4,5 Diagnosis is often delayed because symptoms are non-specific and inherited diseases are rarely considered in young adults. Influences such as high protein intake, infection, or postpartum state can provoke exacerbations of hyperammonaemia.

We report a heterozygous patient with complex partial seizures and undiagnosed heterozygosity for OTC deficiency who, after initiation of valproate therapy, developed severe hyperammonaemic encephalopathy.

Case report
A 16 year old girl was referred to the hospital because of frequent episodes of absence lasting for seconds or minutes, which had started when she was 5 or 6 years old. She showed bizarre and aggressive behaviour followed by amnesia and stereotype actions such as persistent hair brushing. She retired into herself and showed fluctuating confusion, anxiety, and impaired local orientation. Family history and physical development in childhood were normal. Despite mild mental retardation she was able to finish regular school. She avoided eating meat and often vomited. Neurologic examinations showed no focal signs and MRT was normal. Two EEGs disclosed bilateral theta slowing and a delta focus in temporal areas over the left hemisphere but no epileptic activity. Complex partial epilepsy was diagnosed and carbamazepine treatment started. A daily dose of 600 mg (body weight 60 kg) reduced the frequency of seizures only for two months. For this reason, the patient’s physicians added valproate.

Seven days after initiation of valproate therapy (daily dosage 600 mg), severe disturbance of consciousness occurred. The patient was deeply somnolent. Her eyes were closed, movements were unaimed, she showed no verbal response and did not follow commands or react to painful stimuli. Muscle tone was reduced. Cardiopulmonary function was
normal. Blood samples disclosed an excessively high level of plasma ammonia of 480 µM (normal=50–500 µM) with normal serum transaminases and fibrinogen. Diagnosis of OTC deficiency was based on non-detectable serum citrulline and high urinary excretion of orotic acid (urinary orotic acid/creatinine ratio 189 mg/g). Plasma glutamine was 1.37 mM (normal=0.55 mM). EEG now showed diffuse theta/delta slowing and again a left temporal focus. Three cycles of plasma dialysis were done to eliminate ammonia. Concurrent specific therapy of OTC deficiency with low protein diet, treatment with sodium benzoate (6000 mg per day), and sodium phenylbutyrate (6000 mg/day) and substitution of L-arginine (6000 mg per day) were initiated. Oral L-citrulline was not tolerated. Valproate therapy was stopped immediately. Within five days, ammonia serum concentrations fell to 55 µM. Somnolence disappeared within two days and mental status improved, returning to a premorbid level within four days. Specific diet and treatment were continued. However, because of fluctuating compliance of the patient, more episodes of raised ammonia serum concentrations and complex partial seizures occurred after discharge from the hospital. Therefore, anticonvulsive treatment with carbamazepine had to be restarted.

Discussion
Deficiency of OTC is the most common inherited cause of hyperammonaemia. About one out of 30 000 women in the United States is heterozygous for this urea cycle defect. Often, patients present with generalised tonic-clonic or focal seizures. High cerebral concentrations of glutamine and excitatory amino acids such as quinolinic acid and aspartate lead to a loss of cholinergic neurons and seem to play a main part in the pathophysiology of mental retardation and seizures. Diagnosis of OTC deficiency can be based on the X-linked inheritance, high serum concentrations of ammonia, glutamine and alanine, low serum citrulline, raised urine concentrations of orotic acid, and stimulation of urine excretion of orotidine after receiving allopurinol.

To our knowledge, only three patients with heterozygous OTC deficiency who developed hyperammonaemia after initiation of valproate therapy have been described so far.11,15 Two of them were young women,1,12 and one was a 7 year old girl.13 All three patients were treated because of tonic-clonic seizures and showed confusion and somnolence one to six days after starting valproate therapy. The patient with the highest maximum concentration of plasma ammonia (650 µM) was ventilated and remained decerebrate, even though plasma ammonia concentration fell. The other two patients (plasma ammonia concentrations 386 µM and 170 µM) survived but only the second had a remission. There is one short report16 of an 11 month old boy with OTC deficiency who died six weeks after initiation of valproate therapy (ammonia concentration 455 µM). Our patient is the first described who had a remission, returning to the premorbid state despite an excessive plasma ammonia concentration of 480 µM.

Valproate may cause hyperammonaemia in patients with normal concentrations of urea cycle enzymes. The proposed pathophysiological mechanisms are: (a) increment of mitochondrial glutamine transport and inhibition of carbamoylphosphate synthetase by inhibition of N-acetylglutamate synthesis; and (c) reduction of ammonia metabolism by decrement of carnitine availability followed by suppression of fatty acid β-oxidation. The resulting hyperammonaemia may worsen pre-existing increased ammonia concentrations in OTC deficiency.

This case shows that in a patient with a history of recurrent encephalopathy and seizures an inherited disorder of metabolism, such as a urea cycle defect, should definitely be taken into consideration. It is also important to note that ammonia serum concentrations may be temporarily normal when the patient is on a low protein intake. Sufficient diagnostic tests for the detection of metabolic disorders must be done before prescribing valproate in patients with mental retardation or behavioural abnormalities.

Jacobus Schroeder van der Kolk (1797–1862), Professor of Anatomy and Physiology at Utrecht in 1826 performed autopsies and used an early microscope to study the brains of epileptics. His conclusions were given in: *On the minute structure and functions of the medulla oblongata and the proximate causes and rational treatment of epilepsy* (1859).

He found: “dilatation of the veins which appeared filled with blood in the cortex, medulla and spinal cord”. The medulla "showed a fatty degeneration". "The first cause of epilepsy... is exalted sensibility and excitability of the medulla oblongata... liable to discharge upon itself... and followed by involuntary reflex movements...".

Of the origins of the fit, Robert Bentley Todd believed that “in all instances the hemispheric lobes are first disturbed, next follow the corpora quadrigemina, and upon the intensity of the disturbance depends the extent to which the medulla oblongata and the spinal cord are engaged.” Nothnagel had referred to “the convulsive centre” adjacent to the centre for respiration. Hammond in his *A treatise on the diseases of the nervous system* (1871), like van der Kolk thought that the seat of epilepsy lay in the medulla; lesions in the cortex excited the medulla to produce the convulsive fit.

Gowers clearly favoured the cortex: “... all the phenomena of the fits of idiopathic epilepsy may be explained by the discharge of grey matter; that the hypothesis of vascular spasm is as unneeded as it is unproved; ... that epilepsy is a disease of the grey matter, and has not any uniform seat.”

It was Hughlings Jackson (1834–1911) who finally formulated a physiological and rational definition: “A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles.”

Jackson reported that in focal attacks post-mortem disclosed “coarse” diseases of the brain... The site of such lesions could be inferred from the onset of the fit. This was an important early step forward in rational cerebral localisation from clinical signs. His lucid and minute descriptions embraced the diverse intellectual, psychic, dreamy states, sensory, motor, and aphasic contents of various types of seizures, as well as the several postepileptic states. A convulsion was a positive phenomenon as opposed to the negative phenomena of paralysis. His deductions received ample confirmation and acknowledgement from David Ferrier’s experimental work and the galvanic stimulation of the brain carried out by Fritsch and Hitzig.

Pharmacological and surgical treatments were to follow.

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4 Temkin O. The falling sickness; a history of epilepsy from the Greeks to the beginnings of modern neurology. 2nd ed. Baltimore: Johns Hopkins University Press, 1971:60.
9 Pearce JMS, Robert Bentley Todd (1809–60) and Todd’s paralyses. *J Neurol Neurosurg Psychiatry* 1994;57:315.