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CASE REPORT

A case of hyperammonaemic encephalopathy due to valproic acid

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ABSTRACT

A patient with valproic acid induced hyperammonaemic encephalopathy is presented. During chronic treatment with valproic acid this patient developed a potentially life-threatening encephalopathy without signs of liver failure. After discontinuing the valproic acid the patient recovered completely. In the case of a patient presenting with hyperammonaemic encephalopathy, the possibility of the use of valproic acid should not be overlooked.

KEYWORDS

Hyperammonemic encephalopathy, valproic acid

INTRODUCTION

We present a case with an unusual cause of hyperammonaemia without signs of liver failure. The patient presented with lethargy and apnoeas and was on chronic valproic acid therapy. After the valproic acid was discontinued, the patient recovered completely. Our diagnosis is a valproic acid induced hyperammonaemic encephalopathy (VHE). Hyperammonaemic encephalopathy is a relatively rare side effect of valproic acid therapy and most case reports describe hyperammonaemic encephalopathy after initiating valproic acid therapy. This case illustrates that life-threatening hyperammonaemic encephalopathy can occur in chronic therapy with valproic acid and without liver failure. If a patient presents with signs of encephalopathy and the use of valproic acid, the ammonia should be checked and valproic acid should be discontinued.

What was known on this topic?
Hyperammonaemic encephalopathy due to the chronic use of valproic acid in the absence of liver failure is relatively unknown and a serious complication of the use of valproic acid. There are several case reports on valproic acid induced hyperammonaemic encephalopathy (VHE) due to an acute overdose of valproic acid. There are only a few case reports on VHE due to the chronic use of valproic acid.[1-3]

What does this case add?
Hyperammonaemic encephalopathy is a rare and serious side effect of valproic acid and can occur without liver failure. Unlike most case reports this case of VHE occurred during chronic therapy with valproic acid. In the case of a patient taking valproic acid and presenting with encephalopathy, regardless of the duration of therapy, ammonia levels should be checked and the valproic acid should be discontinued.

CASE REPORT

A 57-year-old male was brought to the emergency department because of unconsciousness. His medical history revealed alcohol intoxication and epilepsy. The epilepsy was due to intracranial surgery eight years ago because of a traumatic intracerebral haematoma. His list of medication showed the use of 400 mg carbamazepine twice daily and 1500 mg valproic acid three times daily. Because of the somnolence no further history could be obtained. No further information was available at that point.

On physical examination the blood pressure was 97/62 mmHg, temperature 35.1 °C, and the Glasgow Coma Scale was 13 (E3M6V4). He had a flapping tremor. Physical examination was otherwise unremarkable. CT scan of the cerebrum showed no new lesions. Laboratory tests revealed marked levels of γ-glutamyl transferase (144 U/l, normal <45 U/l) and marked ammonia levels (132 μmol/l, normal 9 to 33 μmol/l), alcohol was undetectable. Other liver enzymes and parameters for synthesis function of the liver were in the normal range.

A metabolic encephalopathy was suspected. Because of the apnoeic episodes the patient was admitted to the intensive care unit for observation. He received oxygen, thiamine and lactulose. All antiepileptic drugs were discontinued. In the next six hours the patient regained full consciousness and his physical parameters were stable. Valproic acid levels were revealed to be toxic (168 mg/l, therapeutic range 50 to 100 mg/l).

After discontinuing the lactulose, the ammonia levels remained normal and stable. The patient recovered completely. An ultrasound of the abdomen and endoscopy showed no signs compatible with liver cirrhosis. Our diagnosis is a hyperammonaemic encephalopathy due to valproic acid, a phenomenon which is described in a number of case reports. The cause that led to the hyperammonaemic encephalopathy remains unrevealed. According to our patient he had taken his medication as prescribed and there had been no alterations in his diet.

DISCUSSION

In this case the patient presented with the clinical features of a metabolic encephalopathy, a hyperammonaemia without liver failure and a toxic level of valproic acid during the chronic use of valproic acid. After discontinuation of valproic acid, his symptoms were relieved and the ammonia and valproic acid levels returned to normal. This suggests a causal relationship between the hyperammonaemic encephalopathy and valproic acid.

Hyperammonaemic encephalopathy due to the chronic use of valproic acid in the absence of liver failure is relatively unknown and a serious complication of the use of valproic acid. There are several case reports on VHE due to acute overdose of valproic acid, but only a few case reports on VHE due to the chronic use of valproic acid.[1-3]

CLINICAL FEATURES

Clinical features of VHE are mild to moderate lethargy, increased seizure frequency with progress to stupor and coma.[4] In chronic valproic acid therapy onset can be insidious.[1] Combination with other antiepileptic drugs such as carbamazepine can potentiate the toxic effect.[4]

HYPERAMMONAEMIC ENCEPHALOPATHY

Hyperammonaemic encephalopathy occurs in acute overdose and in chronic therapy with valproic acid and is not dose related.[1,5] Asymptomatic hyperammonaemia is seen in 20 to 25% of the users of valproic acid.[6] The daily dosage of valproic acid and the levels of valproic acid and ammonia are not related to the degree of encephalopathy.[4]

Several mechanisms for the development of hyperammonaemic encephalopathy in valproic acid therapy have been proposed. Changes in dietary protein intake may affect serum ammonia levels. Valproic acid stimulates the production of ammonia in the kidney.[7] Valproic acid is partly metabolised in the liver by oxidation which produces active metabolites. These metabolites inhibit enzymes in the liver (mitochondrial carbamyl phosphate synthetase) necessary for ammonia elimination via the urea cycle.[4] In chronic valproic acid therapy the amount of oxidation and the production of active metabolites increases.[8] Additionally, chronic valproic acid therapy depletes carnitine, an essential substrate for the metabolisation of valproic acid. Depletion can result in a reduced capacity of the ammonia metabolism.[4,9]

Inborn errors in the urea cycle can also result in hyperammonaemic encephalopathy. Ornithine-trans-carbamylase (OTC) deficiency is the most common inherited urea cycle disorder and is X-linked. Affected men usually die young due to an impaired ammonia metabolism. Heterozygote women can be asymptomatic and valproic acid may induce a symptomatic hyperammonia.[1,10,11]

In our patient we found an OTC deficiency very unlikely and did not evaluate this, since he had taken valproic acid for a long time without symptomatic hyperammonia. In addition affected men with an OTC deficiency seldom present at this age. In women presenting with a hyperammonia, however, one should rule out an OTC deficiency. A low clearance of citrulline in urine or an allopurinol test can be of diagnostic use.[10,11]

The pathogenesis of encephalopathy due to hyperammonaemia in valproic acid therapy remains unrevealed. It is suggested that due to high cerebral levels of ammonia, production of glutamine increases and glutamine excretion is inhibited in the astrocytes, what leads to the swelling of astrocytes and cerebral oedema.[4,12] Also, increase in the activation of gamma-aminobutyric acid (GABA) by ammonia induces somnolence.[4,9]

CASE REPORTS

We found five cases of long-term treatment with valproic acid and the development of hyperammonaemic encephalopathy.[1,2,3,12,13] All five cases report altered mental status, stupor or lethargy due to hyperammonaemia and without signs of liver failure. Duration of valproic acid therapy varied from 3 to 11 years. In three of the five cases there was concomitant use of antiepileptic drugs. The ammonia levels measured ranged from 83 to 377 µmol/l, valproic acid levels were within the therapeutic range in all cases, ranging from 48 to 101 µg/ml. Symptoms were relieved after discontinuing valproic acid and prescribing lactulose. In one case report L-carnitine was supplemented.[13] The immediate cause of the VHE remained unrevealed in all five cases.

Our findings are consistent with the cases described above. Only we found a toxic level of valproic acid. The time of ingestion of the valproic acid is unknown in our case. The level measured could have been a peak level after ingestion (1 to 4 hours). We suggest that the cause of VHE is multifactorial, as is outlined above: due to change in dietary protein intake, increase in active metabolites in chronic valproic acid therapy and the combination of other antiepileptic drugs. Also non-adherence of the patient remains a possibility.

CONCLUSION

Hyperammonaemic encephalopathy is a rare and serious side effect of valproic acid and can occur without liver failure. Unlike most case reports this case of VHE occurred during chronic therapy with valproic acid. The cause remains unclear, though we suggest that the combination of risk factors might have potentiated the risk of VHE. In the case of a patient taking valproic acid and presenting with encephalopathy, regardless of the duration of therapy, ammonia levels should be checked and the valproic acid should be discontinued.

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