A Case Of Hyperammonemic Encephalopathy Due To Valproate And Topiramate Combination At High Doses

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Citation

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Abstract

A 35 years old male patient was admitted for a mental and behavioral disorder during the last two months. He had been treated for intractable epilepsy with valproate for many years. Topiramate was added in the previous year without any adverse reactions. Due to increased seizure frequency, the dosages of both drugs were increased gradually. Following the adjustment of drug regimen as 2000 mgs valproate and 400 mgs topiramate daily, the patient presented an encephalopaty with prominent delta and theta waves in EEG. Either serum liver enzymes or serum valproate levels showed no abnormality, but ammonia level had had rised up to 2 folds of normal. After withdrawal of topiramate and then valproate the symptoms resolved and ammonia level fell into the normal limits. The diagnosis of hyperammonemic encephalopathy due to treatment with the combination of valproate and topiramate was supposed. In our patient, the halopathic features had extraordinarily appeared after elevation of both antiepileptic drugs to high levels, while no adverse reactions had observed with moderately low doses. While treating patients with intractable epilepsy, complications of combinations should be carefully considered in desicion making not only for initiation but also for follow-up of drug adjustments.

INTRODUCTION

Hyperammonemic encephalopathy (HE) is a nonspecific encephalopathy appearing in patients under valproate (VPA) treatment [1]. Serum ammonia levels are consistently high without any other biochemical abnormality. Recently a few cases were reported under topiramate (TPM) and VPA [2]. Here, we present a case of HE who tolerated this combination well at low doses, but developed encephalopathy following the elevation the dosages of both drugs.

CASE REPORT

A thirty five years old male patient, with a history of intractable epilepsy of 15 years was admitted for aggressive behavior which was going on for the last 2 months. The frequency of complex partial seizures was more than 10 monthly, so that we decided to add TPM 200mgs to existing drug regimen, VPA 1000mgs. During the following year a good control of epileptic seizures was achieved. However the seizures recurred then, which led us to elevate the dosages of VPA to 2000mgs and TPM to 400mgs sequentially. After a short time interval under these high dosages, the patient became drowsy and lost sphincter control. He exhibited abnormal behaviors like playing with his faeces. In the second month of this presentation he's been hospitalized because of gradual worsening of his symptoms.

The neurologic examination at the admission revealed a stuporous man in a good general health. He was oriented for people, but not place and time. Urinary and faecal sphincter control was lost. The rest of neurologic examinations were normal. He had no pathologic reflexes or meningeal irritation.

CBC, blood sugar, BUN, creatinine, AST, ALT, GGT, creatin kinase, potassium, calcium and sodium levels were normal including thyroid function tests. VPA serum level was 64.3 microg/dl, which was also normal. Arterial ammonia level was 196 microgr/dl (N:17-80). Carnitine serum level was normal. A routine EEG showed diffuse slowing of background activity with prominent delta and theta waves (Figure 1). Cranial MRI was normal.

This patient exhibited an encephalopathy with normal liver, renal and thyroid functions. With normal VPA and elevated serum ammonia levels, the diagnosis of HE was supposed. TPM and VPA were stopped with tapering and levetiracetam (LEV) was initiated. The patient gained his consciousness but this resulted in an increase of seizure frequency. Carbamazepine (CBZ) was added. In the last examination,

he was receiving CBZ1600mgs and LEV 2000mgs daily. He was fully oriented with 2-3 seizures monthly. His EEG was also recovered (Figure2). The arterial blood ammonia level was normal (39,8microgr/dl).

Figure 1

Figure 1: The slow background activity during hyperammonemic encephalopathy

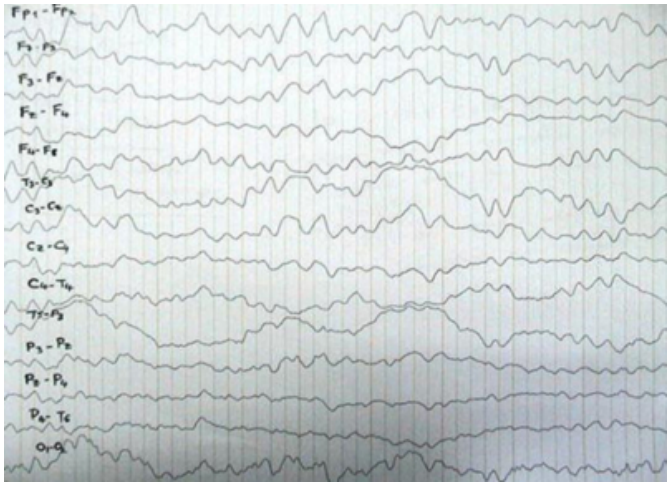
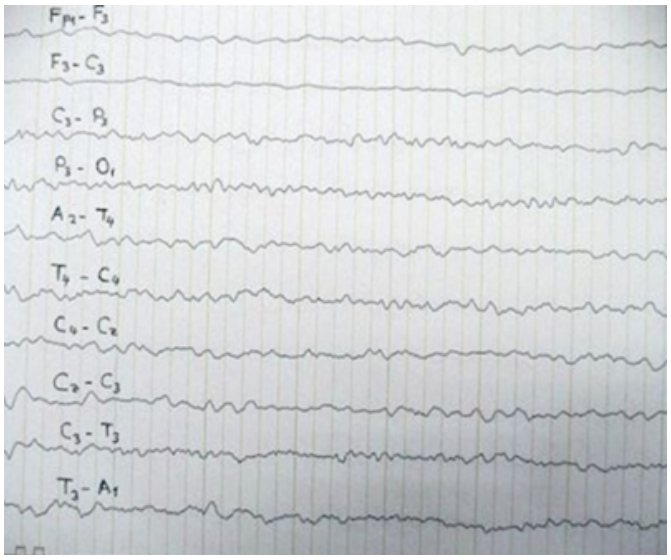


Figure 2

Figure 2:The background activity is improved after TPM and VPA cessation.



DISCUSSION

HE was first described due to VPA alone[1]. Recently a few cases were reported due to combination of TPM and VPA [2,3]. This unusual complication is expected to occur immediately after the initiation of TPM [2]. In our case, unexpectedly it has appeared only after reaching the very high doses of both drugs in one year.

Disturbed conciousness, increase of seizure frequency, behavioral disturbances and an encephalopathic EEG compose the clinical picture [4,5,6]. Two theories are suggested for the mechanism of high ammonia levels under VPA treatment [1]. First, VPA reduces synthesis of glutamine by inhibiting of carbamoyl phosphate synthetase which is the first step of urea cycle. The second, VPA decreases the availability of carnitine which facilitates the transport of long chain fatty acids into mitochondria. The decrease of the effect of carnitine reduces the ammonia metabolism in the liver. Hence the serum ammonia level increases leading HE. Some authors suggest carnitine replacement during VPA therapy, favoring the second hypothesis particularly in youngsters [3].

The role of TPM in the development of HE is still controversial. TPM may decrease the activity of carbonic anhydrase enzyme which has a role in the first step of urea cycle. It also inhibits glutamine synthetase in the brain which helps to the development of hyperammonemia [2].

More than half of the patients receiving VPA hyperammonemia is detected, which is mostly a transitory phenomenon without changing treatment, in a study [7]. The condition observed in our patient, namely development of HE with high doses of the combination of 2 antiepileptic drugs may be explained with Vossler's hypothesis [8]. Following TPM withdrawal cerebral glutamine synthetase inhibition recovers and cerebral ammonia detoxification returns to normal, although absolute serum ammonia concentration may remain high. The measurement of glutamine levels in CSF may prove this hypothesis.

HE may be together with early cytotoxic edema evolving into delayed vasogenic edema as shown by Hantson by means of neuroimaging[10]. Cytotoxic edema develops due to the osmotic effect of glutamine accumulation at the cellular level [10]. A differential diagnosis with edema of status epilepticus (SE) may be required in some patients. The edema of SE is a dominantly subcortical one [7].

MR spectroscobic findings of HE are indistinguishable from hepatic encephalopathy[10]. MRI is mostly normal as in our case but a toxic or metabolic pattern with bilateral T2 hyperintensities in cerebral white matter and globus pallidus are reported in some [11]

The commonest finding is diffuse nonspecific slowing of EEG like in our patient [12].

Several drugs other than TPM may induce HE in patients using VPA. Mostly classic antiepileptic drugs are reported including lamotrigine, primidone, carbamazepine, phenitoin acetazolamide and pivmecillam (an antibiotic) [13,14].

Our patient had completely recovered after withdrawal of VPA and TPM without any sequeal. To recognize the syndrome that may develop after the dose increase carries a big importance.

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