

# Primum Non Nocere: A Case of Valproate Encephalopathy

Önce, Zarar Verme!: Valproat Ensefalopatili Bir Olgu

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## Summary

Valproic acid (VPA) is a traditional antiepileptic which is used in the treatment of some types of epileptic seizures. Encephalopathy is a side effect of VPA which leads to rare but serious results and hyperammonemia may be accompanied by one of these statements. It is specified that asymptomatic hyperammonemia which VPA revealed is 20% and the incidence of symptomatic hyperammonemia is 5%. The reason why VPA induced hyperammonemia pathogenesis is not fully understood. In this article we present a 60-year-old male patient who was diagnosed VPA induced encephalopathy. The case presented is the first in the literature, in that, the patient previously taking valproate and whose encephalopathy unmonitored, valproate has been used after repeated seizures; and, after that encephalopathy has emerged.

Key words: Encephalopathy; hyperammonemia; valproic acid.

## Özet

Valproik asit (VPA) bazı tip epileptik nöbetlerin tedavisinde kullanılan geleneksel bir antiepileptiktir. Ensefalopati, VPA'nın nadir ancak ciddi sonuçlara yol açan yan etkilerinden biri olup hiperamoniemi bu tabloya eşlik edebilir. VPA'nın ortaya çıkardığı asemptomatik hiperamoniemi insidansı %20, semptomlu hiperamoniemi insidansı %5 olarak belirtilmektedir. VPA'ya bağlı hiperamoniemi patogenezi tam olarak anlaşılammıştır. Bu makalede, VPA'ya bağlı ensefalopati tanısı konulan 60 yaşındaki bir erkek hasta sunuldu. Sunulan olgu, daha önce VPA kullanan ve ensefalopati tablosu izlenmeyen bir hastada tekrar ortaya çıkan nöbetlerin ardından başlanan VPA tedavisi sonrası ensefalopati ortaya çıkması yönüyle literatürde ilktir.

Anahtar sözcükler: Ensefalopati; hiperamoniemi; valproik asit.

## Introduction

Valproic acid (VPA) which is (2-n-propylpentanoic acid), and used in the treatment of some types of epileptic seizures is a traditional antiepileptic.<sup>[1]</sup> It shows the effect by blocking voltage dependent sodium channels in neuronal membrane, by increasing the level of inhibitory efficient neurotransmitters gamma amino butyric acid (GABA) in the brain and strengthening GABA dependent postsynaptic inhibition.<sup>[2,3]</sup> Encephalopathy is a side effect of VPA which leads to rare but serious results and hyperammonemia may be accompanied by one of these statements.<sup>[4-7]</sup>

## Case Report

A 60-year-old male patient who was started VPA treatment with diagnosis of idiopathic generalized epilepsy and who was examined after his generalized seizures 3 years ago, left using his medication himself about 3 months ago due to the absence of seizures. Firstly, 20 days before the application, self-talk complaint was also added to nervousness, habit changes, dizziness and slowing down in speech. The general condition of the patient seen in neurology clinic was moderately fair and sluggish. He had body ataxia and imbalance; focal neurological signs were not detected.

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The patient had epileptiform discharges which showed a trend of generalization where sharp and slow wave groups mingled each other. He was hospitalized as nonconvulsive status epilepticus. Improvement was observed by diazepam 10 mg IV. The patient was started with 1000 mg/day VPA treatment. Increasing fatigue and sleepiness appeared in the patient's follow-up within two days after VPA treatment had been started. The arterial blood pressure measurements were hypotensive. Biochemical tests and MR imaging of the brain were normal. Measured VPA level was detected as 77.4 micrograms/ml (N: 50-100 micrograms/ml). In the control EEG of the patient, widespread slowing of the ground rhythm was observed. Venous ammonia concentration which was measured in consideration of VPA induced encephalopathy table, was detected high as 143 micrograms/dL (N: 31-123 micrograms/dL) with current clinical and laboratory findings. The patient was diagnosed VPA induced encephalopathy and drug therapy was discontinued. Patient was administered L-carnitine and levetiracetam therapy. Four days later, in a repeat EEG of the patient whose VPA control level was measured as 77.4 micrograms/ml, and ammonia level 83, normal activity was observed. The general physical and neurological examination of the patient was completely recovered.

## Discussion

Despite being one of the agents whose pharmacological and clinical effects are fairly well-known among antiepileptics, VPA induced encephalopathy is an entity which should be diagnosed early, otherwise, could result in death.<sup>[6]</sup> VPA sodium salt is the most widely used one. It shows its effect and also by blocking voltage-dependent sodium channel in neuronal membrane, by increasing the level of inhibitory neurotransmitter gamma amino butyric acid (GABA) in the brain and via strengthening the postsynaptic inhibition dependent. Also, by inducing the competitive inhibition with succinic semialdehyde dehydrogenase and GABA transaminase and by stimulating GABA synthesizing enzymes such as glutamic acid dehydrogenase, it increases the concentration of GABA.<sup>[2,3]</sup> After oral intake, almost all of it is rapidly absorbed and, the sodium salt reaches top concentration in plasma, approximately after 1.5 hours. Uptaking after a meal, may delay absorption. It is bound to plasma proteins in the ratio of 90%. The elimination half-life is 6 to 18 hours (on average 12 hours). After initiation of treatment, time to reach steady state is approximately four days. It is largely metabolized with hepatic UGT enzymes. As well as side effects such as

nausea, anorexia, dyspepsia, diarrhoea, weight gain, thrombocytopenia, skin and hair loss, tremor, sedation, hepatotoxicity, PCOS, hyperandrogenism, especially hyperammonemia with high doses can cause encephalopathy and coma.<sup>[2]</sup> It was also reported that coma scene which was accompanied by hipocarnitine and ketosis that were dependant on carnitine deficiency, have emerged.<sup>[8-12]</sup> Slowing down in speaking, sleepiness, psychomotor retardation, progressive dizziness, general weakness, irritability, concentration weaknesses are identified findings in patients with encephalopathy.<sup>[13]</sup>

The physical examination, biochemical, hormonal, serologic tests, blood gas measurement and imaging studies that we do to understand whether clinical findings identified in our patients are related to a systemic or local organ failure, were within normal limits. Although VPA blood level was normal, ammonia levels were identified as high. The patient's clinical examination findings, laboratory investigations, the findings recorded in the serial EEG and VPA induced encephalopathy were taken into consideration.

It is specified that asymptomatic hyperammonemia which VPA revealed is 20% and the incidence of symptomatic hyperammonemia is 5%. VPA induced hyperammonemia pathogenesis is not fully understood. It is thought that the fact that VPA introduced ammonium to urea cycle, interacting with carbamoyl phosphate synthetase and increased ammonia production by increasing the switch of glutamine to mitochondrial membrane in the kidney.<sup>[14]</sup> The fact that the basic mechanism caused to hyperammonemia via drug's direct effects on neurotransmitters has also been emphasized.<sup>[15-17]</sup> Encephalopathy connected to valproate has been identified four subtypes: 1) It ranges between liver enzymes and serious highness of serum ammonia. Hyperammonemia leads to the development of neuronal damage, brain edema, seizures and encephalopathy by inhibiting the uptake of glutamate via astrocytes.<sup>[18]</sup> 2) It is in the form of which can go with normal or moderately high ammonium levels without hyperammonemia or liver failure. It is informed that possible mechanisms cause the increase of the postsynaptic responses by inhibiting the degradation of GABA in the central nervous system of valproate.<sup>[19]</sup> 3. This is the type of which goes with highness of serum ammonia and is explained by the inhibitions in urea cycle with no liver failure.<sup>[20]</sup> 4. There are elevation in the liver enzymes but there is no hyperammonemia.<sup>[21]</sup> In peo-

ple with low serum carnitine levels, VPA induced encephalopathy; severe cerebral oedema and even coma have been reported. While encephalopathy picture associated with carnitine deficiency is observed frequently in VPA usage, carnitine deficiency which is based on short-term VPA usage has also been reported.<sup>[8-12]</sup> Mitochondrial beta-oxidation is inhibited by VPA. It is thought that during chronic use of VPA, the beta-oxidation of fatty acids occurs in another way (omega-oxidation) and meanwhile, free carnitine is consumed. According to another view, VPA itself is a kind of short-chain fatty acid and causes carnitine consumption by entering beta or omega-oxidation.<sup>[22]</sup> Although carnitine deficiency is a picture reported in patients who has longer VPA usage; in people whose basal carnitine levels are close to the lower limit, short-term and high dose VPA usage can lead to fast developing carnitine deficiency. It is alleged that possible mechanisms in this place, are urine decreased carnitine reabsorption and / or are large quantity of carnitine loss in urine in the form of acylcarnitine or valproil carnitine.<sup>[12,23,24]</sup> It has been found that total carnitine level in our patient measured for the purpose of differential diagnosis was 78.50 (34-78) and free carnitine levels were 51.40 (25-54).

### Conclusion

The case presented is the first in the literature, in that, in a patient previously taking valproate and whose encephalopathy unmonitored, valproate has been used after repeated seizures and after that encephalopathy has emerged. None of the possible hyperammonemia causing reasons could be detected in the mentioned patient. The patient's treatment was initiated as valproate 500 mg twice daily. Shortly following the onset of medication the patient presented an ancephalopathic picture that could be easily attributed to hyperammonemia. We suspected, the cause to be an intolerance to instant introduction of valproate in therapeutic doses. It is widely known that drug doses initiated without increasing gradually, increase adverse effects in all drug groups and make the toleration difficult. Especially liver based functional physiological deficiencies or liver's undetectable personal functional insufficiencies may cause this situation in the valproate elimination and distribution mechanisms. In patients who will be started valproate treatment, after detection of individual liver reserve supported by laboratories, if the treatment will be initiated, increasing the valproate dose gradually is going to resolve possible side effects and toleration difficulties additionally provide you a medical comfort in terms of medical doctor.

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