Original Article

Valproate Induced Non Hepatic Hyperammonaemic Encephalopathy (VNHE) — A study from Tertiary Care Referral University Hospital, North India

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Abstract

Objective: To report and discuss twelve cases of Valproate (VPA) induced hyperammonaemic encephalopathy without liver failure in subjects receiving VPA therapy.

Methods: This study was conducted in the department of Neurology, G.B. Pant Hospital, New Delhi from January 2000 to December 2006. The subjects were on treatment with VPA alone or in combination with other anti epileptic drugs and developed symptoms of encephalopathy. The data collected included the type of epilepsy, the dose of VPA and other co-administered anti epileptic drugs (AED), their serum levels, clinical presentation, relevant radiological and laboratory investigations, serum ammonia levels, the measures taken to treat the patient and their outcome.

Results: A total of twelve cases of VPA induced Non hepatic hyperammonemic encephalopathy (VNHE) were studied, out of which six were males and six females. The age ranged from 2-75 years with mean age of 21.33 ± 20.84 years. Four subjects were on VPA alone and the others were also on concomitant AEDs. All the above subjects presented with either confusion or altered sensorium (100%). None of the subjects had any other demonstrable cause of encephalopathy. The serum ammonia level in these subjects ranged from 77.3- 345 μmol/L with mean of 163.98 μmol/L ± 48.67 (normal range 10-47 μmol/L). The serum VPA level in this study group ranged from 63-132.6 μg/ml with mean of 93.44 μg/ml ± 31.77 (normal range 50-100 μg/ml).

Conclusions: In any patient on VPA therapy, who develops signs and symptoms suggestive of encephalopathy, even in the presence of normal liver function, VNHE should be suspected. Fortunately, it has a good prognosis and the early withdrawl of VPA leads to improvement in almost all cases (JPMA 58:627; 2008).

Introduction

Valproate has been used in the treatment of epilepsy for more than thirty-five years. It was approved for use in epilepsy in 1978 in the United States. It has been regarded as one of the first line antiepileptic agents in view of its broad spectrum AED characteristics and safety profile.[1]

VPA may be associated with several side effects like gastrointestinal upset, tremors and weight gain, bone marrow suppression and haemorrhagic pancreatitis. Hepatotoxicity has been reported occasionally, predominantly in children.[1] However, it is also known to cause non-hepatic hyperammonaemia which is mostly asymptomatic and occurs more commonly in children. VPA induced Non hepatic hyperammonaemic encephalopathy (VNHE) is an important, potentially reversible cause of encephalopathy.[2] It is characterized by a decreasing level of consciousness, cognitive slowing, vomiting and increased seizure frequency.[2,3] To the best of our knowledge, since 1979 seventy cases of VPA associated encephalopathy have been reported in English literature. Additional thirteen case of VPA associated encephalopathy have been reported in combination with Topiramate (TPM).[4] However very few cases have been reported so far from Indian population.[5-8] We describe a series of twelve cases of epilepsy from India who developed worsening of sensorium while on VPA therapy without any evidence of hepatic dysfunction indicative of a diagnosis of VNHE.

Patients and Methods

This study was conducted in the department of Neurology, G.B. Pant Hospital, New Delhi from January 2000 to December 2006. The subjects were on treatment with VPA alone or in combination with other anti epileptic drugs and developed symptoms of encephalopathy. Routine general physical examination, detailed neurological examination and relevant radiological and laboratory investigations were carried out in all subjects. They were investigated to rule out other co morbid conditions that could have resulted in encephalopathy. The data collected included the type of epilepsy, the dose of VPA and other co-administered anti epileptic drugs

Table I: Clinical features and management of subjects who developed Valproate induced Non-Hepatic Hyperammonemic Encephalopathy.

Subject	Age(years/ Sex)	Clinical Diagnosis	Treatment Received	Clinical Presentation	Management	Outcome
1.	5/M	Uncontrolled Right SPMS	CBZ 25 mg/kg Seizures uncontrolled Added VPA 20 mg/kg	Altered sensorium	VPA reduced, Clobazam 10 mg added.	Improved
2.	26/F	TBM with GTCS	ATT VPA 20 mg/kg	Altered sensorium	VPA reduced Clobazam 10mg BD.	Improved
3.	2/M	Viral Meningo-encephalitis, SPMS	CBZ 25 mg/kg , VPA 20 mg/kg	Altered sensorium, choreiform and dystonic posturing	VPA tapered Clobazam 20 mg/day added	Improved
4	75/M	GTCS	VPA 12 mg/kg	Confusion , astrexis	VPA reduced	Improved
5	30/F	Occipital seizures with CBZ induced rash	CBZ stopped. VPA 25 mg/kg started	Confusion	VPA tapered PHT started.	Improved
6	10/M	Viral Encephalitis, GTCS	VPA 20mg/kg Clobazam 5 mg PHT 4mg/kg	Confusion and increased frequency of seizures	VPA decreased PHT ,Clobazam increased	Improved
7	44/F	JME	VPA 15mg/kg LTG 100mg	Developed LTG induced SJS, confusion, asterixis	LTG stopped Valproate reduced	Expired
8	17/M	Reflex eating epilepsy.	VPA 20mg/kg Clobazam 20 mg BD	Abnormal behaviour, confusion	VPA reduced	Improved
9.	18/F	GTCS	VPA 25 mg/kg	Altered sensorium, increased seizures	VPA reduced PHT added	Improved
10.	6/M	Refractory GTCS	CBZ 30 mg/kg PHT 6mg/kg VPA 20mg/kg	Drowsiness, vomiting	VPA reduced Clobazam added	Improved
11	6/F	LGS	VPA 46 mg/kg Clonazepam 0.06mg/kg	Confusion , increased seizures	VPA reduced	Improved
12	17/F	Refractory GTCS	VPA 20mg/kg CBZ 25mg/kg	Altered sensorium, increased seizures	VPA stopped Levetiracetam added	Improved

M-Male, F -Female, SPMS-Simple Partial Motor Seizure ,GTCS-Generalized Tonic Clonic Seizures, JME-Juvenile Myoclonic Epilepsy, VPA-VPA, PHT-Phenytoin, LTG-Lamotrigine, TBM-Tubercular Meningitis, ATT-Anti Tubercular Therapy, LGS- Lennox Gastaut Syndrome, SJS-Steven Johnson Syndrome.

(AED), their serum levels, clinical presentation, relevant radiological and laboratory investigations, serum ammonia levels, the measures taken to treat the patient and their outcome.

Results

A total of twelve cases of VNHE were studied, of which six were males and six females. The age ranged from 2-75 years with mean age of 21.33 ± 20.84 years. Eight subjects were on more than one AED and four were on VPA alone. The serum levels of other AED's in all subjects were within therapeutic range. All the above subjects presented with either confusion or altered sensorium (100%).Rest of the details are given in (Table I and 2). None of the subjects had any other demonstrable cause of encephalopathy. The serum ammonia level in these subjects ranged from 77.3- 345 µmol/L with mean of 163.98 µmol/L ± 48.67 (normal range 10-47 µmol/L). The serum VPA level in this study group ranged from 63-132.6 µg/ml with mean of 93.44 µg/ml ± 31.77 (normal range 50-100 µg/ml).

In our study eleven out of the twelve subjects of VNHE improved with discontinuation of VPA and the one with Steven Johnson syndrome expired.

Table 2: Laboratory investigations in twelve cases of VNHE.

Subject	Investigations (Routine-LFT/KFT)	EEG	Baseline CT/MRI Brain	S. VPA Normal Range (50-100 µg / ml)	Serum Ammonia Normal Range (10-47 µmol/L)
1.	Normal	Generalized slowing with frontal predominance	Normal	70.20	118.50
2.	Normal	Generalized slowing in the delta range	Bifrontal tuberculomas with meningeal enhancement	63.30	232.50
3.	Normal	Generalized slowing	Patchy Encephalomalacia	98.30	345.40
4	Normal	Generalized slowing	Normal	98.80	173..60
5	Normal	Generalized slowing	Normal	107.70	77.30
6	Normal	Generalized slowing	Normal	104.80	208.40
7	Normal	Normal	Normal	87.10	132.60
8	Normal	Normal	Normal	125.10	202.80
9.	Normal	Generalized slowing	Normal	132.60	97.50
10.	Normal	Spikes, sharp wave, polyspikes, and slow wave discharges through out the record	Normal	47.70	159.80
11	Normal	Generalized slowing	B/L border zone infarcts	43.90	109.40
12	Normal	Generalized slowing	Normal	139.85	110.00
				Mean 93.44 µg/ml ± 31.77 (63-132.6)	Mean 163.98 µmol/L ± 48.67 (10-47 µmol/L)

EEG-Electroencephalogram, CT-Computerized Tomography, MRI-Magnetic Resonance Imaging, B/L Bilateral, LFT-Liver Function Test, KFT-Kidney Function Test.

Table 3: A Comparison of the two large studies.

Criteria	Gerstner et al (4)	Mehndiratta et al
Number of patients	19	12
Mean age (years)	38.6	21.33 +/- 20.84
Male: Female ratio	8:11	6:6
Mental retardation	10	0
Mean VPA levels	98.05 g/ml (63.6- 170) *	93.44 g/ml (63-132.6)
Number of subjects with Hyperammonemia	9 (47%)	12 (100%)
Number of subjects with deranged hepatic function	6	0
Additional AED	10 (52.60%)	8 (66.66%)
EEG abnormality	18 (94.70%)	10 (83.33%)
Outcome	All recovered with VPA withdrawal	All but one recovered with VPA withdrawal

INR= International normalization ratio, ALP= alkaline phosphatase, TACE= Transarterial chemoembolization, MELD= Model for end stage liver disease.

Discussion

Valproate is an anti epileptic drug commonly used for neurological as well as psychiatric indications. Acute or sub acute onset of decreasing level of consciousness while on VPA therapy with background slowing on Electroencephalogram (EEG) in the presence of normal liver enzymes and elevated levels of serum ammonia, suggest a diagnosis of VNHE. It usually occurs within a few days of administration of VPA, but some subjects are known to develop VNHE with chronic therapy.[2] Other possible manifestations include focal neurological deficits, cognitive slowing, vomiting, drowsiness and lethargy. Behavioural changes may be seen ascribed to post ictal state or non convulsive status epilepticus. An increased frequency of seizures has also been reported, which can lead to a further increase in the VPA dosage causing worsening of symptoms and consequently delaying correct diagnosis.[3] Hyperammonaemia can also be seen in asymptomatic subjects on VPA therapy and encephalopathy can rarely occur with serum ammonia levels in the normal range. Considerable overlap exists in the EEG findings of VNHE and non convulsive status epilepticus. A high degree of suspicion is therefore required to diagnose VNHE. Since serum ammonia level may at times be normal, amelioration of symptoms on withdrawal of VPA may be the only way to clinch the diagnosis. Because of these reasons, VNHE is a grossly under diagnosed entity.[8]

Etiopathogenesis of VNHE is unclear. Decreased level of consciousness may be related to hyperammonaemia or it may be as a result of other compounds including toxic metabolites of VPA. The presence of latter may explain encephalopathy in cases with normal serum ammonia levels. However, recently it has been proposed that brain ammonia concentration may continue to remain high despite normal serum VPA levels.

VPA probably elevates ammonia level both through alterations in hepatic and renal function. Approximately one

fourth of hyperammonaemia may be due to VPA induced stimulation of glutaminase activity in renal cortex. A larger percentage is possibly due to decreased hepatic urea formation through inhibition by VPA of enzyme Carbamoyl Phosphate Synthetase 1(CPS 1).[9] The main inhibitor of CPS 1, the enzyme that begins the urea cycle is a VPA metabolite, propionate which by decreasing the hepatic N-acetyl glutamate (NAG) levels inhibit the hepatic CPS 1 enzyme.[4,9] Subjects with urea cycle enzyme defect and with primary or secondary carnitine deficiency disorders are known to be at a high risk of developing VNHE. VPA reduces carnitine levels and depletes intra mitochondrial coenzyme A, which causes decreased synthesis of NAG, leading to decreased mitochondrial CPS 1 activity.[9]

Hyperammonaemia is believed to produce encephalopathy through inhibition of glutamate uptake by astrocytes. This leads to potential neuronal injury and cerebral oedema. Ammonia is conjugated in the brain with alpha keto-glutarate to form glutamate which also produces damage by excitotoxicity and consequent increase in the seizure frequency.[2,3] This increased frequency of seizures was found in four of our subjects. A number of clinical studies have shown a significant decrease in total or free blood carnitine concentrations or both in subjects taking multiple AEDs, including VPA or VPA monotherapy.[10] VNHE is more common when VPA is used along with phenobarbital, phenytoin or carbamazepine than when used alone.[10,11] This has been explained on the basis of increase in the level of VPA metabolite, sodium 2-propyl-4-pentenoate (4-en-VPA) by these drugs, which produces a decrease in acetyl -coA availability thus causing a decrease in NAG.[3] Eight out of twelve cases in the current series were also receiving concomitant AEDs. The most common co prescribed AED was carbamazepine (50%). The serum levels of concomitant AEDs were within normal limits. The encephalopathy resolved completely on withdrawal of Valproate proving a cause and effect relationship.

Asymptomatic hyperammonaemia is fairly common with VPA use.[12] Transient symptomatic hyperammonaemic episodes can be triggered by either protein loading or a hypercatabolic state. Hyperammonaemia has been described even with therapeutic serum valproate levels and there is no direct correlation between serum valproate levels and hyperammonemia.[9,12] All the subjects reported here were taking VPA within therapeutic range however, all had raised levels of serum ammonia and five had associated raised serum VPA levels. None of the subjects having raised VPA levels had cerebellar signs or nystagmus thus ruling out VPA toxicity as the cause of their encephalopathy. However, as shown by Rath A et al., an increased level of VPA along with hyperammonemia has a synergistic effect.[5] In our study, neither the absolute dose nor the serum level of VPA was related to the severity of VNHE or to the degree of elevation of serum ammonia. This finding correlates with recent studies, which describe no correlation between absolute dose or serum level of VPA and the severity of VNHE.[9,12] We did not have facilities to investigate for any underlying urea cycle enzyme abnormalities in our subjects.

EEG done in this setting usually shows signs of severe encephalopathy such as diffuse slowing with a predominance of rhythmic theta and delta activity. Occasionally triphasic waves can be found with bursts of frontal intermittent rhythmic delta activity.[3,13] Seven of our subjects had generalized slowing, two subjects had generalized slowing with frontal predominance, one patient had polyspikes, spike and slow wave discharges through out the record and two subjects had a normal EEG.

Recently role of serum and Cerebro Spinal Fluid (C.S.F) glutamate levels in VNHE has been described. Both serum and C.S.F. glutamate were found elevated in majority of subjects with suspected VNHE, even in the absence of hyperammonemia.[9] We did not have the required infrastructure to measure glutamate level. Ziyeh et al reported bilateral T2- hyperintense lesions in the cerebellar white matter and in globus pallidus on MRI in a patient of VNHE. In this study severe depletion of myoinositol and choline, moderately decreased N-acetyl aspartate levels and excess glutamate were found in MR spectroscopy.[14] We did not see any radiological finding described above, attributable to VNHE in any of our subjects. Recently hypersensitivity to Valproate and occurrence of hyperammonaemic encephalopathy has been reported in a child with ring chromosome 20 syndrome (C20A).[15] Administration of L- carnitine in VNHE patients may reduce serum ammonia level. The clinical benefit of reduced serum ammonia however, is not proven. A recently study has shown increased survival from 10 to 48% with L-carnitine administration in subjects with VPA related hepatoxicity.[16] All of our subjects developed encephalopathy while on VPA and the serum levels of concomitant AEDs taken by eight of them was within normal limits. The repeat MRI scan of the subjects did not reveal any new lesions. All this along with the fact that in eleven out of twelve subjects, there was clinical as well as electrophysiological recovery in the form of normal EEGs after withdrawing or reducing the doses of VPA point to the fact that our subjects were most likely having VNHE. However, as already described, there were certain lacunae in our study like we did not have the facilities or means to measure the urea cycle enzymes or C.S.F ammonia levels. Also, the genetic studies were not undertaken in our subjects. The largest series reported in the literature is by Gerstner T et.al. in which 19 cases of VPA induced encephalopathy including

VHHE and VNHE as well as patients with normal levels of serum ammonia were reported.[4] We have compared the various parameters of our study with the above mentioned study (Table 3). Fortunately, almost all patients with VNHE can be expected to improve as shown in both the studies, thus underscoring the importance of early diagnosis of this condition.

Conclusion

The study concluded that if any patient on VPA therapy develops signs and symptoms suggestive of encephalopathy with elevated serum ammonia level or even with normal serum ammonia (where C.S.F. and serum glutamate may be helpful), VNHE should be suspected. These subjects should be investigated with an EEG and blood tests for serum ammonia, liver enzymes and serum VPA levels. VNHE thus forms an important and treatable cause of encephalopathy, and until other forms of treatments are established immediate discontinuation of the drug will promptly reverse the symptoms.

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