CASE REPORT

Encephalopathy in an infant with infantile spasms: possible role of valproate toxicity

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SUMMARY

An infant presented with global developmental delay and infantile spasms. EEG was suggestive of hypsarrhythmia. She was started on sodium valproate, clonazepam and adrenocorticotrophic hormone injection. After an initial improvement the child developed vomiting, altered sensorium and increase in frequency of seizures suggestive of encephalopathy. Valproate-induced hyperammonaemia or hepatic encephalopathy was considered and the drug was withheld following which there was a dramatic improvement. Paradoxically, the liver function tests and serum ammonia were normal. However, a complete reversal of encephalopathy, on withdrawal of the drug, strongly suggested an adverse drug reaction (ADR) due to valproic acid. Marginal elevation of serum valproic acid prompted us to use the Naranjo ADR probability score to confirm the diagnosis. This case highlights the fact that valproate toxicity can manifest with normal liver function and serum ammonia levels. This is the youngest reported case with this rare form of valproate-induced encephalopathy.

BACKGROUND

Encephalopathy is a well-documented but uncommon side effect of valproic acid therapy and is usually associated with hyperammonaemia and/or deranged liver function. The infant in this case report developed all the classical features of encephalopathy but with normal liver function and serum ammonia levels. This case is being reported to highlight the fact that, in such situations, the diagnosis can be challenging and requires a high index of suspicion especially as the outcome can be fatal.

CASE PRESENTATION

A 4.5-month-old female infant, born to third degree consanguineous parents, presented with a 10-day history of infantile spasms and irritability. The infant had not attained any milestone and did not focus or turn to sound. There was no history of fever, vomiting or lethargy. She was born at term by caesarean section. There was no perinatal asphyxia and the postnatal period was uneventful. Despite consanguinity, in two consecutive generations, there was no family history of neurological ailments.

Examination revealed an alert infant who was thriving well with no dysmorphic features. On neurological examination, hypertonia with brisk deep tendon reflexes, ankle clonus and extensor plantar response were noted. There were no signs

of raised intracranial tension or meningitis. A presumptive diagnosis of symptomatic infantile spasms was made and the child was investigated. Basic biochemical investigations and cerebrospinal fluid analysis were within normal limits. EEG was suggestive of hypsarrhythmia but the CT and MRI of the brain were normal. Workup for metabolic disorders, that is, blood tandem mass spectrometry, urine metabolic screening, serum copper, caeruloplasmin and biotinidase levels were normal. Serum lactate, pyruvate and ammonia were also normal.

The infant was started on sodium valproate and clonazepam initially. At a review after 2 weeks, the seizure frequency had come down slightly hence valproate was optimised (30 mg/kg/day) and adrenocorticotrophic hormone (ACTH) was started. After 2 weeks of this therapy, the mother complained that the child had excessive somnolence, vomiting, no response to pain (ie, during ACTH injection) and significantly increased frequency of seizures suggestive of encephalopathy. Valproate-induced hepatotoxicity/hyperammonaemia was considered and the drug was withdrawn. In addition, carnitine was added and supportive care was given.

Liver function tests and serum ammonia were normal but the blood level of valproic acid was elevated (108 ng/dL, normal range 50–100 ng/dL).

OUTCOME AND FOLLOW-UP

On discontinuation of valproate the sensorium improved significantly; within 24 h, the child started crying in response to ACTH injection and seizure frequency reduced. The complete reversal of encephalopathy on withdrawal of the drug and the raised serum valproate level above the therapeutic range made us consider valproic acid-induced encephalopathy despite normal liver function and ammonia levels. This was further confirmed by the Naranjo ADR probability score of 9 in this child.

DISCUSSION

Infantile spasms are a severe form of epilepsy seen in infancy. This infant presented with infantile spasms associated with a distinct EEG pattern of hypsarrhythmia and psychomotor delay. She was started on sodium valproate, a broad-spectrum anti-epileptic drug which is fairly safe but can rarely cause serious complications such as hepatotoxicity, hyperammonaemia, haemorrhagic pancreatitis, coagulopathies, bone marrow suppression and encephalopathy. Most of the cases of valproate-induced encephalopathy have associated hyperammonaemia

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or deranged liver function. In this case, despite normal liver function and ammonia levels, valproate-induced encephalopathy was considered in view of an elevated serum valproic acid level and the rapid reversal of symptoms on discontinuation of the drug. We decided to substantiate the diagnosis further by using the Naranjo ADR probability scale, which is used to determine the likelihood of whether an adverse drug reaction is actually due to the implicated drug or due to other factors¹ (table 1). This infant had a score of 9 which is indicative of a definite adverse drug reaction.

Encephalopathy is an uncommon side effect of valproate and may be acute or subacute in onset.² The clinical features are decreasing levels of consciousness ranging from lethargy to coma, vomiting, irritability, agitation and a paradoxical increase in seizure frequency.³ The cardinal features of valproate-induced encephalopathy are that it is not dose dependent, develops within days or weeks after initiation of valproic acid or addition of another antiepileptic drug and disappears when valproic acid is withdrawn.³ Three forms of encephalopathy have been described in children taking valproate. The most common forms are due to either deranged liver function or hyperammonaemic encephalopathy.^{2 4 5} Rarely, the encephalopathy may be due to elevated levels of valproic acid causing direct toxicity but with normal ammonia and liver function. The infant, in our case, probably belonged to the last category as there was a documented increase in serum valproic acid level above the therapeutic range with normal liver function and serum ammonia. This form of encephalopathy has been reported very rarely even in the adult population and an extensive literature search revealed only one other report of a child, with a similar condition, in a series by Gerstner *et al.*⁶

The pathogenesis of valproate-induced encephalopathy is not clearly elucidated; a toxic or metabolic origin or a direct intrinsic central nervous system depressant effect have been suggested.⁷ The proposed mechanisms have a direct effect on the neurotransmitters and inhibit enzymes that play a role in the urea/Kreb's cycle, by either valproate itself or its metabolites.^{2 8} The other postulates are related to glutamine synthesis. Glutamine synthetase is a key enzyme involved in cerebral ammonia detoxification as it catalyses the reaction that produces glutamine from ammonia and glutamate. Valproate can lower glutamine synthesis by inhibiting cerebral glutamine synthetase, thus leading to high concentrations of ammonia within the

astrocytes. This inhibits glutamate uptake by glial cells, leading to direct neuronal injury and cerebral oedema.^{8 9} Glutamate is taken up by astrocytes as a protective effect against excitotoxins, thus brain ammonia levels may be a better indicator of valproic acid-induced encephalopathy than serum levels.^{2 9 10} In a study by Gerstner *et al.*,⁶ 5 of 19 patients with valproic acid encephalopathy had normal serum ammonia levels indicating a poor correlation between ammonia levels and the development of encephalopathy. This study group was predominantly adult with only seven children, of which only one child developed non-hyperammonaemic encephalopathy with normal liver function.

What is not clear is why some patients on valproate therapy develop encephalopathy while others do not. In this case, we tried to ascertain the risk factors for encephalopathy—namely urea cycle defects,^{2 11 12} fatty acid oxidation defects and mitochondrial disorders. Primary or secondary carnitine deficiency could not be evaluated for. In this infant, normal tandem mass spectrometry, urine metabolic screen, serum lactate and pyruvate levels ruled out inborn errors of metabolism to a certain degree although valproic acid-induced encephalopathy can be seen in infants without a known metabolic defect. Risk factors such as high-dose, long-term therapy with valproic acid and concomitant topiramate therapy were absent in our case.¹³

Although reports are available regarding enhanced toxicity of valproate when used along with other antiepileptics such as phenytoin, phenobarbitone and topiramate,^{3 13} there is a paucity of literature as regards clonazepam–valproic acid interactions, which are the drugs used in the infant reported. In a report by Yukawa *et al.*,¹⁴ concomitant administration of clonazepam and valproic acid was seen to increase the clearance of clonazepam by 14% and decrease the valproic acid clearance by 17.9% thereby enhancing valproic acid toxicity. Thus, the possible risk factors for valproic acid toxicity in this case may be infancy, developmental delay and concomitant clonazepam use.

Recognising valproic acid-induced encephalopathy is very important since it can result in death due to cerebral oedema and herniation. Diagnosis of this condition becomes difficult since it can occur at any time during therapy and without pronounced symptoms.^{3 8} This can be further confounded by normal liver function and serum ammonia levels. Thus, if altered sensorium develops at any time during valproic acid therapy, serum valproate level, liver function test and venous ammonia should be estimated and valproic acid should be

Table 1 Naranjo Adverse Drug Reaction probability score

SI No		Yes	No	Do not know	Score in this case
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event occur after the suspected drug was administered?	+2	−1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4	Did the adverse reaction reappear when the drug was re-administered?	+2	−1	0	0
5	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	+1	+2	0	+2
6	Did the reaction reappear when a placebo was given?	−1	+1	0	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	+1
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
				Total	9

Definite: 9 or >9.

Probable: 5–8.

Possible: 1–4.

Doubtful: 0.

withheld. Therapy consists of withdrawal of the drug along with hydration, protein restriction, lactulose administration and carnitine therapy.¹³

Thus, we conclude that in any obtunded child on valproate therapy, it is worthwhile to withhold the drug even with normal biochemical parameters.

Learning points

- Reversible encephalopathy induced by valproic acid can be seen even in the absence of deranged liver function and/or hyperammonaemia. Hence, it is advisable to withhold this drug in any obtunded child even in the absence of biochemical abnormalities.
- Valproic acid use in infants is not without risk hence, it should be used judiciously.
- In suspected drug toxicity without markedly elevated drug levels, Naranjo Adverse Drug Reaction probability scale can be a useful diagnostic tool.

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REFERENCES

- 1 Naranjo CA, Busto U, Sellers EM, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
- 2 Guin DS, Biswas S, Saha K, *et al.* A case of nonhyperammonemic valproate-induced encephalopathy. *Neurol Asia* 2006;11:135–7.
- 3 Chen W, Yen D, Yu H, *et al.* Valproate-induced encephalopathy. *Chin Med J* 2001;64:474–8.
- 4 Lheureux PER, Penalzo A, Zahir S, *et al.* Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care* 2005;9:431–40.
- 5 Rath A, Naryanan TJ, Chowdhary GVS, *et al.* Valproate-induced hyperammonemic encephalopathy with normal liver function. *Neurol India* 2005;53:226–8.
- 6 Gerstner T, Buesing D, Longin E, *et al.* Valproic acid induced encephalopathy—19 new cases in Germany from 1994 to 2003—a side effect associated to VPA therapy not only in young children. *Seizure* 2006;15:443–8.
- 7 Zerjav S, Stowe R. Serious neurological complications of valproate therapy. *Psychopharmacol Newslett* 2007;1–5.
- 8 Hamer HM, Knake S, Schomburg U, *et al.* Valproate induced hyperammonemic encephalopathy in the presence of Topiramate. *Neurology* 2000;54:230–2.
- 9 Panda S, Radhakrishnan K. Two cases of valproate-induced hyperammonemic encephalopathy without hepatic failure. *JAPI* 2004;52:746–8.
- 10 Vossler DG, Wilensky AJ, Cawthon DF, *et al.* Serum and CSF glutamine levels in valproate related hyper ammonemic encephalopathy. *Epilepsia* 2002;43:154–9.
- 11 Tariqul Islam MD, Imnul Islam MD, Hogue SA, *et al.* The urea cycle disorders. *Bangladesh J Child Health* 2012;36:46–8.
- 12 Lanpher BC, Gropman A, Chapman M, *et al.* Urea cycle disorders overview. *GeneReviews*, 29 Apr 2003.
- 13 Longin E, Teich M, Koelfen W, *et al.* Topiramate enhances the risk of valproate-associated side effects in three children. *Epilepsia* 2002;43:451–4.
- 14 Yukawa E, Nonaka T, Yukawa M, *et al.* Pharmacoeconomic investigation of a clonazepam-valproic acid interaction by mixed effect modeling using routine clinical pharmacokinetic data in Japanese patients. *J Clin Pharm Ther* 2003;28:497–504.

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