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Fatal Fulminant Hepatic Failure Due to Sodium Valproate in an Adolescent

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Since its introduction in 1973, sodium valproate (VPA) has been used extensively due to its efficacy against a wide range of seizure disorders. It appears to be well tolerated at therapeutic doses. Severe hepatotoxicity, resulting in death, is extremely rare(l-3). Till date all reports of fatal hepatotoxicity have come from Europe and North America(l-3). We report one such case involving an Indian adolescent.

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Case Report

A 14-year-old boy with past history of seizure disorder was referred to us, for jaundice and encephalopathy in March 1993. In January 1993 he was put on valproate (600 mg/day) and phenobarbitone (60 mg/day) following a second episode of right focal seizure with secondary generalization. There was no recurrence of seizures while he was on this therapy for the next 10 weeks. In March he developed moderate grade fever and vomiting. Two days later he developed altered sensorium and lapsed into coma. Jaundice was also noted at this stage and he was shifted to this hospital. Both anticonvulsants were stopped after the onset of jaundice. Examination revealed him to be deeply comatose. Vital signs were normal except for tachycardia (120/min). Icterus was present; stigmata of chronic liver disease were absent. Liver span was 12 cm. There was no splenomegaly or free fluid in the abdomen. Pupillary size was 4 mm bilaterally, oculocephalic reflexes were elicitable. All deep tendon reflexes were exaggerated. Planters showed bilateral extensor response.

Investigations were as follows: hemoglobin 12.2/dl, TLC 12,200/ul polymorphs 72%, lymphocytes 21%), blood sugar 103 mg/dl, sodium 125 mEq/L, potassium 3.6 mEq/L, bilirubin 19.6 mg/dl (conjugated

8.6 mg/dl), AST 964 U/L, ALT 2704 U/L, and alkaline phosphates 451 U/L. Prothrombin time was 21 sec (control 12 sec). Tests for HBsAg, IgM And HAV and Anti HCV (c-100-3) were negative. Examination of the cerebrospinal fluid was normal. CT scan of the head did not show any abnormality.

He was treated with neomycin and mannitol along with other supportive measures for hepatic encephalopathy. During the hospital stay, he had recurrence of seizures which did not respond to parenteral paraldehyde or dilantin. He died within 24 hours of admission. At autopsy the liver was enlarged (15 cm vertical span) and had a smooth surface. Histopathological examination revealed submassive necrosis with extensive microvesicular steatosis *(Figs. 1 & 2)*.

Discussion

This patient presented with rapid onset of encephalopathy after a brief prodromal phase. Presence of an enlarged liver and the temporal relation to the onset of VPA therapy in the absence of serologic markers of hepatitis A, B and C raised the suspicion of VPA induced bepatotoxicity which was confirmed by the characteristic liver histology at autopsy.

Clinical spectrum of VPA associated hepatotoxicity varies from asymptomatic mild increase in transminases to fatal liver failure(4). Nearly, 11% of patients on regular VPA therapy show transient rise in aminotranferases which usually resolves spontaneously or after a temporary reduction in dosage(3). Severe hepatotoxicity, which is much less common(l,2), manifests with a brief prodromal phase of lethargy, anorexia and vomiting followed by overt manifestations of liver injury such as jaundice, ascites, hypoglycemia and hemorrhagic phenomena. Hyperammonemic comma occurs in the terminal phase.

Histologically VPA hepatotoxicity is

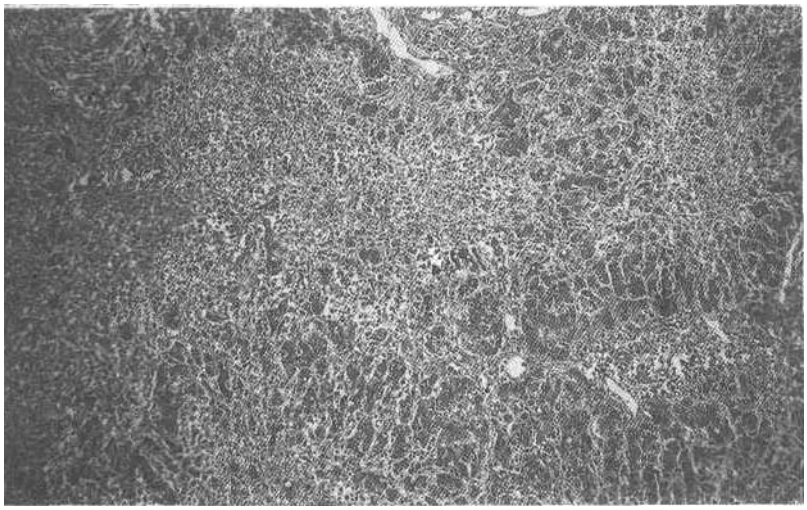

Fig. 1. Postmortem liver biopsy specimen showing submassive hepatic necrosis. (H & E stain, 64 x).

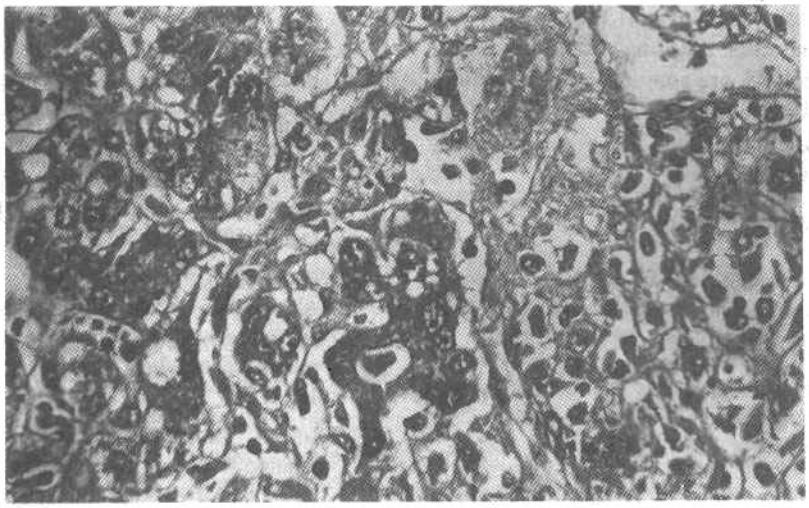

Fig. 2. High power view of postmortem liver biopsy specimen showing microvesicular steatosis. (H & E stain, 400 ×).

characterized by microvesicular steatosis and hepatocellular necrosis of varying severity. Microvesicular fatty metamorphosis consist of small lipid droplets filling the cytoplasm of the hepatocyte leaving the nucleus in a central position. Both steatosis and necrosis occur predominantly in the centrizonal region(2). The combination of these two histological lesions differentiates VPA hepatotoxicity from other causes of microvesicular steatosis such as Reyes syndrome or Jamaican vomiting sickness where hepatocellular necrosis is insignificant.

Hepatotoxicity due to VPA appears to be an idiosyncratic reaction resulting from the production of toxic metabolites. Most cases occur within 6 months of onset of therapy(5). The most toxic VPA metabolite, 4-en-VPA, a product of omega oxidation, leads to microvesicular steatosis by several diverse mechanisms(l). Centrizonal necrosis occurs presumably due to the formation of reactive metabolites in the central zone. Omega oxidation of VPA is mediated by the cytochrome p-450 enzyme system. It is postulated that concurrent therapy with enzyme inducers like phenobarbital and phenytoin is likely to enhance VPA hepatotoxidty. In the two largest series of fatal VPA hepatotoxicity(l,3), more than 70% of the patients were receiving other anti-epileptic drugs. For unknown reasons, younger individuals are more vulnerable to VPA hepatotoxicity(13)- Individuals with high risk for development of VPA hepatotoxicity include children with underlying chronic liver disease(l,5), mental retardation(5) or urea cycle enzyme defects(4). Other independent risk factors for VPA hepatotoxicity are poly-therapy with other anti-epileptic drugs and overdosage(6). Since there are no laboratory tests which detect early toxicity, it is prudent to avoid VPA in these high risk patients.

In conclusion, VPA hepatotoxicity must be considered in the differential diagnosis of jaundice or hepatic encephalopathy in any

child on VPA therapy. Early withdrawal of the drug offers the best hope of survival in these patients. Although data on rechal-lenge with VPA are sparse(7), it is currently believed that patients who manifest VPA hepatotoxicity should be managed with alternative drugs.

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Spread of Scabies and Pediculus Humanus Among the Children at Sivas Orphanage

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Scabies which is caused by *Sarcoptes scabies* is a clinical infection caught as a result of close contact with the infected person(l-3). It can be found all over the world among the age groups(3-5). It has a 30 year cycle where a dormant period of 15 years is followed by another 15 year period of epidemic(3,4).

Even though scabies was a rare diseases during the 1950s(6), the scabies incidence began to increase in Europe and North America during 1960s and reached an epidemic level in 1980(2). In our country, epidemic reports have been submitted from various areas in 1970 and 1972(5,7) and the reasons behind the spread of scabies were

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