Neurologic deterioration in a child with Wilson’s disease on penicillamine therapy

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Penicillamine is the standard therapy for Wilson’s disease in children. We report an 8-year-old-girl with liver disease due to Wilson’s disease who developed extrapyramidal symptoms following administration of penicillamine. Symptoms resolved within 20 hours of stopping the drug but recurred within 24 hours when gradually increasing small doses were recommenced. [Indian J Gastroenterol 2003;22:104-105]

Key words: Zinc sulfate

Worsening of pre-existing neurologic signs in patients with Wilson’s disease on commencement of penicillamine therapy has been documented in young adults.1 In children, there has been only one report of penicillamine-related neurologic syndrome.2 An 8-year-old girl was brought with complaints of progressively worsening jaundice, abdominal distension and swelling of feet for three months, associated with low-grade fever, bilious vomiting and increased daytime sleepiness for two weeks. There was no history of bleeding from any site. She never had jaundice or blood transfusions in the past. She was treated in a local hospital with repeated transfusions of fresh frozen plasma for associated coagulopathy. She also received 250 mg of penicillamine once daily for three days.

She was the first child of non-consanguineous parents, born at term with a birth weight of 2500 g. Neonatal and developmental events were unremarkable. She had received three doses of hepatitis B vaccine. Her younger brother aged 2.5 years was asymptomatic. There was no family history of similar illness.

On examination, she was deeply icteric, pale, conscious and well-oriented. There was no edema, clubbing, spider nevi, palmar erythema or asterixis. Heart rate was 90/min, respiratory rate 34/min, blood pressure 100/70 mmHg, and weight 22 Kg. The liver was palpable 3 cm below the right costal margin and the spleen palpable 5 cm below the left costal margin.

There was free fluid in the abdomen. Slit lamp examination revealed Kayser-Fleischer ring.

Investigations: elevated 24-hour urinary copper level, low serum ceruloplasmin (Table) and evidence of portal hypertension. Liver biopsy could not be performed since coagulation parameters remained grossly deranged despite repeated attempts at correction. The penicillamine challenge test to measure increase in urinary copper excretion was performed with 1 gram of d-penicillamine (Arthrom Biochemie GmbH, Vienna, Austria) orally along with pyridoxine 25 mg. She developed abnormal jerky movements of the limbs with titubation of the head and dysarthria within 4 hours. These symptoms lasted for 20 hours and hence 24-hour urine collection during this period was incomplete and unsatisfactory.

Oral zinc sulfate was begun as precipitation of neurologic symptoms was suspected to be due to penicillamine. After 3 days, d-penicillamine was restarted in small doses – 62.5 mg once daily, gradually increasing by doubling the dose every two days. When it was stepped up to 250 mg twice daily, she developed similar symptoms within 6 hours of ingestion of the dose. The treatment with d-penicillamine was stopped.

She was started on supportive therapy, with parenteral vitamin K, antibiotics, bowel wash twice daily and oral lactulose to prevent hepatic encephalopathy. She was also given multiple transfusions of fresh frozen plasma and platelet-rich concentrates, with no avail. She developed hepatic encephalopathy probably secondary to hypokalemia on the 15th hospital day, from which she recovered. She also developed spontaneous pneumothorax in the fourth week, for which aggressive antibiotic therapy was instituted.

Liver function worsened progressively (Table) and she died of hepatic encephalopathy precipitated by gastrointestinal bleeding on the 25th hospital day.

Veen et al³ demonstrated that sudden deterioration in neurologic status can occur at the beginning of low-dose penicillamine therapy, while Brewer et al² have shown this to occur at initiation of higher daily doses in young adults with Wilson’s disease. In our patient, the neurologic symptoms occurred both with the high dose as well as when small incremental doses reached a threshold of 500 mg/day (22.7 mg/Kg body weight).

D-penicillamine therapy has been shown to be associated with development of new brain lesions on MRI probably secondary to temporary elevation of blood and brain non-ceruloplasmin-bound copper levels.¹ We were unable to document a rise in serum copper 24 hours after administration of d-penicillamine. The urinary copper concentration was also not reliably measured in the immediate post challenge period, but a week later showed values similar to pre-penicillamine challenge values. These findings were similar to those of Porzio et al²

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P: D-penicillamine, ZS: Zinc sulfate

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in a child with asymptomatic Wilson's disease who had steady deterioration in neurologic symptoms over two months following institution of d-penicillamine therapy. They found only an increase in serum aminotransferase levels concomitant with the neurologic symptoms. There was no rise in serum transaminase levels in our patient.

The pathogenesis of penicillamine-induced neurologic damage is unknown. The mechanism may involve mobilization and redistribution of copper within intracellular compartments but also from liver to other tissues, causing high levels of copper in areas of the brain. When copper bound to intracellular proteins other than metallothioneins is converted to a reduced form by penicillamine, its affinity for the proteins becomes less effective and it can escape chelation of penicillamine, thereby rendering the brain vulnerable. 4

Hoogenraad et al 5 reported the successful initial treatment with zinc of a patient with Wilson's disease with neurologic involvement. Trientine has an action similar to that of d-penicillamine and hence zinc sulfate is probably the only alternative in those with exacerbation of neurologic symptoms. 5 Zinc also improves neurologic symptoms by inducing metallothioneins in other tissues to complex copper in a nontoxic form.

We were unable to locate any literature regarding such a sudden appearance of neurological complications in children with Wilson's disease with hepatic presentation, coincident with d-penicillamine therapy and rapid recovery on discontinuation of the drug.

References

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Received December 11, 2002. Accepted December 22, 2002.

Ectopic pancreas mimicking superior mesenteric artery syndrome

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Ectopic pancreas rarely produces symptoms and often goes undetected. We report a 28-year-old man with ectopic pancreas presenting with symptoms and radiological findings mimicking superior mesenteric artery syndrome. Excision of the lesion and duodenojunostomy led to relief. [Indian J Gastroenterol 2003;22:105-106]

Key words: SMA syndrome

Ectopic pancreas is a rare developmental anomaly. It is usually an incidental finding. Rarely it causes gastrointestinal obstruction or hemorrhage.

A 28-year-old man presented with a five-year history of recurrent abdominal pain and vomiting. On examination he was emaciated. Systemic examination was unremarkable. Barium studies revealed grossly dilated second part of duodenum with abrupt change in caliber of duodenum distally (Fig). Duodenal folds were normal and there was no filling defect. CT scan revealed dilated stomach and duodenum up to mid-third part, with the superior mesenteric artery crossing over.

Laparotomy revealed a grossly dilated stomach and duodenum, with a 4 cm x 3 cm subperitoneal mass at the duodeno-jejunal flexure causing obstruction with collapse of the distal bowel. Excision of the lesion and duodenojunostomy was performed. Postoperative recovery was uneventful. Histology revealed heterotopic pancreatic tissue.

Heterotopic pancreas is defined as the presence of pancreatic tissue outside the usual location without anatomic relation to the pancreas, either by physical continuity or shared vascularization. 1 Theories proposed