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CASE REPORT Open Access

Recurrent acute pancreatitis in a Wilson disease patient: an unusual association

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Abstract

Background: Wilson's disease is a multisystem disorder with predominant clinical symptoms depending on the site of copper deposition in the body. Hepatic presentation is usually seen in the younger age group. And pancreatitis is rarely associated with Wilson's disease. To the best of our knowledge, recurrent acute pancreatitis as a presenting manifestation in a WD patient has not been mentioned before in the literature.

Case presentation: We report a 17-year-old boy who presented with recurrent acute pancreatitis and subsequently developed deranged liver enzymes and ascites. Work up for the cause of recurrent acute pancreatitis was normal. Low ceruloplasmin (0.07 mg/dL), high 24-h urinary copper excretion (576 μg/day), and dry copper content in the liver (270 μg/g) clinched the diagnosis of Wilson's disease. The patient was started on a low-copper diet and D-penicillamine therapy resulting in an improvement in symptoms and no further recurrence of pancreatitis.

Conclusion: The possibility of Wilson's disease should be considered in young patients with recurrent acute pancreatitis, who have a protracted and obscure disease course.

Keywords: Wilson's disease, Recurrent acute pancreatitis, Copper metabolism, Serum ceruloplasmin, 24-h urinary copper, D-Penicillamine

Background

Wilson disease (WD) is an autosomal recessive disorder of copper transport causing copper accumulation in the liver and brain primarily [1, 2]. However, copper also accumulates in organs such as the kidney, bone, blood, cornea, and endocrine glands such as the pancreas [3]. WD-associated pancreatitis is described rarely in literature [4–6]. It was attributed to either copper deposition in the pancreas or biliary stones [7, 8]. Acute pancreatitis was index presentation in the earlier case reports. And the presence of gallstones, cholangitis, or anemia with protracted jaundice and positive family history led to suspicion of WD in these cases. In the present report, the index case had recurrent acute pancreatitis (RAP) episodes before developing features of chronic liver disease which lead us to consider the possibility of WD [8].

Case presentation

A 17-year-old boy born of non-consanguineous marriage was admitted 3 years back with epigastric pain radiating to the back associated with vomiting for 1 day. On evaluation, he had elevated amylase 956 U/L (normal < 85 U/L) and lipase levels 635 U/L (normal < 160 U/L). CECT abdomen showed diffusely swollen pancreas with necrosis in the head and tail region. He was managed conservatively. Subsequently, he developed two similar episodes at an interval of 6 months. On being evaluated for the cause of RAP, serum calcium, triglyceride, IgG4, and MRCP were normal. There was no history of drug intake or family history of pancreatitis. Thereafter, he started taking complementary and alternative medicines (*Tinosora caodifoli*a L, Kanchnar guggulu, and one unlabelled) and remained asymptomatic for 1 year. However, he started complaining of right hypochondriac pain with vomiting. Laboratory evaluation showed hemoglobin 12 g/dL, total leucocyte count 7400 per cu.mm, platelet count 1.0 lacs per cubic

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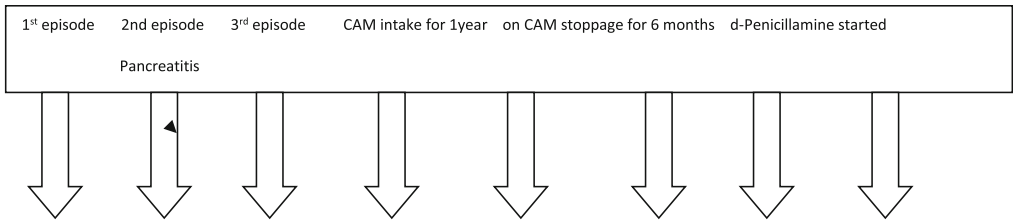
mm, total bilirubin 0.8 mg/dL, SGPT 300 U/L (normal < 40 U/L), and SGOT 305 U/L (normal < 40 U/L) with alkaline phosphatase 217 IU/L (normal < 117 IU/L) and serum lipase 1650 U/L (normal < 160 U/L). USG abdomen suggested a bulky pancreas with normal liver echo texture. The possibility of drug-induced liver injury with pancreatitis was considered. Liver enzymes were continuously monitored and showed a declining trend. He gradually developed jaundice and abdominal distension with bilateral pedal edema and referred to our center.

On admission, he was icteric with pedal edema, ascites, and palpable splenomegaly. The rest of the examination was normal. Laboratory values on admission were hemoglobin 8.3 g/dL, total leucocyte count 11,400, and platelet count 1.4 lacs cu.mm. Liver function test values were total bilirubin 5.2 mg/dL (direct bilirubin 3.6 mg/dL), SGOT 167 U/L, SGPT 42 U/L,

Table 1 Timeline of presentation of the index case



	36months prior	30months prior	24 months prior	12 months prior	6 months prior	Day of admission	3 months after d-penicillamine	6 months after d-penicillamine
Hemogram (g/dL)	12	10.2	11.2	12	11.8	8.3	9.3	10.3
Total Leucocyte count (per cu.mm)	13,300	13000	13400	7400	6230	11,400	7,900	6,900
Platelet count (per cu.mm)	2,60,000	3,44,000	3,00,000	1,00,000	1,69,000	1,40,000	1,38,000	1,29,000
Total bilirubin / Direct bilirubin (mg/dl)	1.0/0.3	0.3/0.1	0.8/0.1	Non-icteric	1.4/0.9	5.2/3.6	1.8/0.9	1.00.4
SGOT/SGPT	34/35	39/54	30/44	305/300	205/52	167/42	120/40	62/35
Alkaline Phosphatase (IU/L)	212	135	210	217	184	236	184	121
S. Lipase (IU/L)	635	965	765	1650				
Serum calcium (mg/dL)			9.10					
Serum triglyceride(mg/dL)			203					
Serum ceruloplasmin (mg/dL)						0.07		
24 hour Urinary copper (mcg/day)						576	500	300 mcg/day
Copper content (Liver biopsy mcg/gm)						270		

total protein 6.9g/dL, and serum albumin 2.6 g/dL with prothrombin time 27s (control, 13s). The timeline of laboratory investigations and the disease course is mentioned in Table 1. Ultrasonography of the abdomen showed an enlarged liver with altered echo texture, portal vein 13.5 mm in diameter, splenomegaly (13 cm), and ascites. Ascitic fluid was low protein (1.5g/dL) and paucicellular. SAAG was 0.7 and ascitic fluid amylase was 40 IU/L. Upper gastrointestinal endoscopy examination was normal. He was evaluated for etiology of chronic liver disease. Tests for hepatitis B and C were negative. Antinuclear antibody, anti-smooth muscle antibody, and anti-liver-kidney microsomal antibody were also negative. Total IgG was 15 g/L (N < 16 g/L). Urinary copper was 576 μg/24 h (normal 15–50 μg/day), serum copper 82.26 μg/dL (85–15 μg/dL), and serum ceruloplasmin 0.07 mg% (normal > 0.20 mg%). Keyser-Fleischer ring was negative. Liver biopsy showed liver parenchyma with nodular architecture separated by fibrous strands with bile ductular proliferation and orcein positivity in parasepatal hepatocytes in few nodules suggestive of Wilson's disease (Fig. 1). The copper content in the liver biopsy specimen was 270 μg/g of the dry liver (normal value up to 45 μg/g). Modified Leipzig score was 5.

He was started on a low-fat, low-copper diet and D-penicillamine therapy with zinc. He was started on 250mg of D-penicillamine and increased subsequently to 500 mg twice a day. He was followed monthly for the first 3 months and then every 3 months for 1 year with a complete blood count, liver function test, renal function test, urinalysis, and 24-h urinary copper. His symptoms subsided with no recurrence of pain. Liver enzymes showed improvement in total bilirubin 1.8 mg/dL, direct bilirubin 0.9 mg/dL, SGOT 120 U/L, SGPT 40 U/L, and 24-h urinary copper of 500 mcg per day after 3 months of chelation therapy. No adverse effects were noted during D-penicillamine chelation therapy.

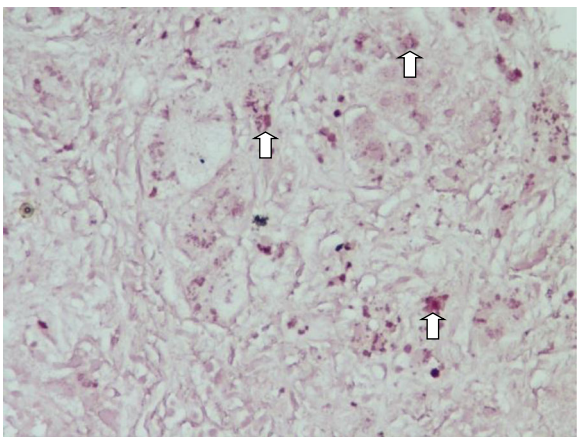


Fig. 1 Liver biopsy showing orcein deposition in granular cytoplasmic inclusion (blank arrow) in hepatocytes (665 × 499 px)

Discussion

Wilson disease is due to absent or reduced function of ATP7B protein leading to decreased synthesis of ceruloplasmin and increased content in the cellular organelle, causing impaired excretion of copper [4]. Over 200 mutations of ATP7B genes are possible. Copper is released into the circulation if the capacity of the liver to store copper is exhausted and taken up by virtually all organs [5]. Symptoms depend on the site of deposition of copper in the body.

Scheinberg and Sternlieb first described that 1 out of 5 WD patients have an excess copper concentration in the pancreas [3]. Along with this, 2 other studies have described abnormal pancreatic secretion in patients with WD [6, 9]. Excess deposition of copper damages each cellular organelle—plasma membrane, cytosolic protein, and other organelles. The accumulated copper disrupts the cell membrane, increases membrane permeability, and causes lysosomal membrane breakages. Such effects may be responsible for the release of proteolytic enzymes leading to autodigestion and inflammation in the pancreas. Such episodes may be transient and self limited [7].

Weizman proposed pancreatic injury because of portal hypertension causing impaired venous drainage of the pancreas or direct cytotoxic effect [8]. Pigmented gallstone due to Coombs-negative hemolysis may also occur, causing pancreatitis, cholangitis, and jaundice [10]. Previously reported cases described index episode of pancreatitis at presentation simultaneously associated with the gallstones, cholangitis, or anemia with protracted jaundice or positive family of WD [8]..

Initial diagnostic tests for recurrent acute pancreatitis were negative. On evaluation of etiology of liver disease, it was found to have decreased serum ceruloplasmin, elevated (> 2 times) urinary copper excretion, and increased (> 5 times) hepatic copper content with a total score of 5 confirming the diagnosis of WD [4]. Following the treatment with D-penicillamine and a low-copper diet, there was no recurrence of abdominal pain. Though molecular study related to pancreatitis genes, the unknown copper content of complementary herb, and no direct evidence of copper deposition in the pancreatic tissue were lacking in the present study. Even then, the temporal sequence of symptoms initially and improvement with D-penicillamine therapy and low-copper diet may suggest a causal association.

Conclusion

The possibility of Wilson's disease should be considered in young patients with recurrent acute pancreatitis, who have a protracted and obscure disease course.

Abbreviations

WD: Wilson disease; RAP: Recurrent acute pancreatitis; CECT: Contrast-enhanced computed tomography; SGOT: Serum glutamate oxaloacetate transferase; SGPT: Serum glutamate pyruvate transferase; USG: Ultrasonography of the abdomen

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Authors' contributions

Dr. HD and Dr. SG helped in analyzing the data and writing the manuscript while Dr. SS and Dr. SB edited the document. All authors have read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during the study are included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Yes; written consent for publication was taken from the parents of the study.

Competing interests

The authors declare that they have no competiing interest.

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