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Indian Childhood Cirrhosis: Case Report and Pediatric Diagnostic Challenges

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Abstract

Introduction

Indian childhood cirrhosis is a chronic liver disease usually seen in pediatric age group and is unique to the Indian subcontinent. The definitive causative factor for the disease is not found till now but excess copper ingestion has been associated with it.

Case presentation

An Indian origin one and half year old premorbidly normal male child presented with history of gradual distension of abdomen for 6 months and jaundice, generalized body swelling, high coloured urine for 20 days. There was no history of any bleeding or feature suggestive of hepatic encephalopathy. On physical examination child was icteric, pale and had anasarca, massive hepatosplenomegaly and ascites. The child was evaluated for various causes of hepatic failure in pediatric age group including infective, metabolic and autoimmune etiologies. Unfortunately the child succumbed to the illness. The post-mortem liver biopsy and copper estimation cleared the air, revealing Indian childhood cirrhosis as the underlying etiology.

Conclusion

Though Indian childhood cirrhosis is a rare entity and reported less frequently in literature, the treating pediatrician should keep this as a differential in case of pediatric hepatic failure. The liver biopsy and hepatic copper estimation are the gold standard diagnostic tests for diagnosing Indian childhood cirrhosis.

Key Words: Childhood cirrhosis, Copper, Mallory hyaline bodies.

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Introduction

Indian childhood cirrhosis (ICC) was prevalent in most parts of India in 1980s, but had quickly disappeared over the last three decades (1, 2). The disease has been considered unique due to geographic localization of this non- Wilsonian copper overload hepatic disorder and characteristic pathologic changes seen during different phase of illness (3, 4). We hereby report a case of one and half year old male child who presented with features of chronic liver failure and the etiology turned out Indian childhood cirrhosis on histopathological examination. The novelty of case report is so early presentation of the children with ICC which was confirmed with biopsy and hepatic copper estimation.

Case presentation

An Indian origin one and half year old premorbidly normal male child presented with history of gradual distension of abdomen for 6 months and jaundice, generalized body swelling, high coloured urine for 20 days. There was no history of any bleeding from any site or feature suggestive of hepatic encephalopathy. The child had predominant vegetarian diet and there was no history of copper utensil use or family history of liver disease in the family.

Child consumed around 800 kilocalories and 21 grams protein from daily dietry intake in premorbid state which was inadequate. On physical examination child was icteric, pale and had anasarca, massive hepatosplenomegaly and ascites. Other systemic examination was within normal limits. Liver function were deranged (total bilirubin 20.7 mg/dl, conjugated 17.3 mg/dl, unconjugated 3.4 mg/dl), total protein 6.1 gm/dl, albumin 2.5 gm/dl, SGOT 591 IU, SGPT 345 IU, alkaline phosphate 211 IU, PT 31.8 control 11.6, INR 2.87. Table 1 shows various investigation of the patient with reference values. USG abdomen was suggestive of chronic liver disease.

USG showed enlarged liver span (12.5 cm) with coarse echo texture and splenomegaly (10.7) cm with gross ascites. Child was worked up for various etiologies of chronic liver disease. Viral markers were normal and workup for Wilson's disease (serum ceruloplasmin normal but 24 hour urinary copper was elevated 182 mcgm/day, slit lamp examination or KF ring) was normal. Markers for autoimmune hepatitis (anti LKM 1 antibody and anti-smooth muscle antibody), tyrosinemia (alpha-feto protein) and inborn error of metabolism (urine reducing substance, serum lactate, urinary ketones, blood sugar) were within normal limits. Liver biopsy was deferred initially because of coagulopathy.

Child was started on supportive management for chronic liver disease. But patient deteriorated on day 3 of admission in form increasing abdominal distension, respiratory distress, shock, seizures and respiratory failure requiring mechanical ventilation. Shock further worsened and child succumbed due to multi organ failure.

Post mortem liver biopsy was taken. Histopathological examination was suggestive of Indian childhood cirrhosis in form of multiacinar hepatocyte necrosis with marked ballooning degeneration, Mallory-Hyaline bodies with inflammatory cells and scattered neutrophilic cells.

Cellular necrosis was seen with reticulum collapse, condensation and collagenization that went around small groups or single hepatocytes resulting in "creeping fibrosis". Post mortem dry copper estimation of liver showed very high copper content of 1598 microgram per gram dry tissue weight of liver tissue (normal range is 15-55 microgram/gram of tissue).

Table 1: Table showing investigation of the patient with reference ranges

Investigation	Patient value	Reference range
Haemoglobin	8.6 gm/dl	10.5-14 mg/dl
Total leukocyte count	9100/cumm	6000-14000/cumm
Differential count		
Neutrophil	40 %	54-62%
Lymphocyte	50 %	25-33%
Monocyte	6 %	3-7%
Platelet count	1,32,000/cumm	1,50,000-4,00,000/cumm
Bilirubin		
Total	20.7 mg/dl	0.8-1mg/dl
Conjugated	17.3 mg/dl	
Unconjugated	3.4 mg/dl	
Total protein	6.1 gm/dl	
Albumin	2.5 gm/dl	
SGOT	591 IU	5-45 IU
SGPT	345 IU	5-45 IU
Alkaline phosphatase	211 IU	240-840 IU
Prothrombin time	31.8	
INR	2.87	
Anti LKM1 antibody	1.3 unit/ml	0-15 unit/ml
Anti-smooth muscle antibody	Negative	
Serum ceruloplasmin	0.393 OI/unit	0.2-0.5 OI/unit
Alpha feto protein	39.52 ngm/ml	1.09-8.04 ng/ml
24 hour urinary copper	183 mcgm/dl	0-50 mcgm/dl
Urine for reducing substance	Negative	
Urine ketones	Negative	
Blood lactate	1.2	
Blood Sugar	125 mg/dl	60-100 mg/dl
Serum Calcium	8.6 mg/dl	8-10 mg/dl
Serum Sodium	138 meq/dl	135-145 meq/dl
Serum Potassium	4.2 meq/dl	3.5-4.5 meq/dl
Viral marker Hepatitis B and C	Negative	

Discussion

ICC is difficult to differentiate from other causes of cirrhosis but in majority of established cases of ICC, histological features are helpful in diagnosing case of ICC. Nayak and Ramalingaswami proposed a histologic definition which included necrosis of hepatocytes with ballooning, Mallory's hyaline pericellular intralobular fibrosis and inflammatory cell infiltration. Poor regenerative activity and no fatty changes are characteristic of ICC, cholestasis is present in an advanced stage. This distinctive histologic entity, ICC, was not described in the Western literature, but it was linked to India (5). It generally presents in early childhood but few cases of delayed presentation in later part of life can be found in literature. Patra et al. reported a case series of five children with chronic liver disease who were found to be ICC on retrospective analysis of histologic records. Three children were between 2-6 years and two presented at a later age. The clinical presentation were non-specific and features of hepatic failure in form of direct hyperbilirubinemia, ascites, generalized edema (anasarca), bleeding tendency due to deranged coagulation profile and

hepatosplenomegaly were present (6). The disease is not confined to Indian subcontinent, as previously thought and cases have been reported from other countries well (7-12).

In spite of the rapid progress of clinical and experimental medical research, the exact etiology and causative factors remains a challenge for health care personals and researchers. Many theories had been postulated as causative but none had proven to be definitive. The various postulated etiologies includes ethnic and racial factors, familial cause, genetic factors , nutritional factors linked to vegetarianism, various bacterial or viral infections and different toxins like castor oil, dietary copper toxicity. In some of the reports a protein Chain (NP_116219), a product of the CIRH1A gene had been linked to the etiology of ICC (13).

Till recent past the role of copper in etiopathogenesis of ICC was well established but recent studies have questioned this and now a role of excess zinc is also being postulated (14). The predominance of ICC cases in rural India where use of copper utensils for storing water and milk is very common, makes the bondage of copper and ICC strong but only more studies can exactly tell the role of copper (15). In the recent article published by Nayak et al. questioned the role of copper in their histologically confirmed 225 cases of ICC and 426 controls and emphasized on going for liver biopsy for confirmation of diagnosis rather than relying on copper levels (16). Pencillamine has been used in treatment of ICC and found to effective in some patients. But lack of copper exposure in some patients, normal serum copper level as in our patient challenges the above etiology (17).

ICC is a lethal disease with a mortality of 45% within 4 weeks, 74% in 8 weeks, and 86% within 6 month of clinical presentation. So early diagnosis, good supportive care and pencillamine are the only key for prolonging the survival (11).

Conclusion

ICC is a rare early childhood disease presenting with hepatic failure and having high mortality. The disease is mainly confined to Indian subcontinent but now being reported from different parts of world. Role of excess copper in etiology of ICC once well established but is now being challenged. Good supportive care, pencillamine is the only treatment available. The incidence of the disease has decreased drastically probably because of discontinuation of copper utensils for storing milk and water. The experimental model for causative mechanisms and treatment guidance for this lethal condition can be a game changer and should be actively looked for (18).

Abbreviations

ICC: Indian childhood cirrhosis.
SGOT: Serum glutamic oxaloacetic transaminase.

SGPT: Serum glutamic pyruvic transaminase.

PT: Prothrombin time.

LKM1 antibody: Liver kidney microsomal type 1 antibody.

USG: Ultrasonography.

INR: International Normalized ratio.

Competing interest

"The authors declare that they have no competing interests."

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