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CASE REPORT

An Unusual Association of Caroli's Disease and Niemann-Pick Disease Type-B in a child of 3 Years: A Case Report

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ABSTRACT

Caroli's disease (CD) and Niemann-Pick disease (NPD) both are two rare disorder of autosomal recessive (AR) inheritance. Abnormal dilatation of the intrahepatic bile duct is the characteristic feature of CD. On the other hand, NPD type-B is a lysosomal storage disorder in which accumulation of sphingomyelin occurs in the cells of the monocyte – macrophage system of different parts of the body due to deficiency of acid sphingomyelinase (ASM). CD commonly presents with fever and right upper quadrant pain. NPD is characterized by hepato-splenomegaly, thrombocytopenia, interstitial lung disease, and dyslipidemia. In NPD most of the patients have little or no neurologic involvement. The rarity of co-existence of both the diseases in a single patient is the reason for this case report.

Key Word: *Caroli disease, Niemann-pick disease, Acid sphingomyelinase, Hepato-splenomegaly, Bone marrow transplantation*

INTRODUCTION

Abnormal dilatation of the intra-hepatic bile duct is the main characteristic feature of Caroli's (CD) disease and Caroli's syndrome (CS). Both of the diseases are congenital AR disorder and CD was first described in 1958.[1] The term CD is applied when the ectasia or segmental dilatation is limited to the larger intra-hepatic bile ducts. This form is less common than CS, in which malformations of small bile ducts and congenital hepatic fibrosis are also present.[2] CD is sporadic, its prevalence is one case per 1,000,000 of the population.[3] The clinical course of the disease can be asymptomatic in the first two decades of life; however, typical symptoms may arise throughout the patient's life.[4] Moreover, disease progression may lead to recurrent cholangitis, hepato-lithiasis, secondary biliary cirrhosis and portal hypertension.[5]

On the other hand, Niemann-Pick disease (NPD) is also a rare AR lysosomal storage disorder which has three types: type A, B and C. The deficiency of acid sphingomyelinase is the reason for developing Type A and Type B NPD.[6] However, type C results from defective intracellular trafficking of cholesterol with secondary accumulation of glycosphingolipids.[6] Type A is invariably evident by 6 months of age which is characterized by progressive psychomotor retardation, failure to thrive, hepatosplenomegaly, Cherry-red macula and the type is more common in Ashkenazi Jewish population.[6] Most of the death usually occurs by the age of 2–3 years.[6] In contrast, most of the patients of NPD type-B are diagnosed in infancy or childhood due to detection of hepato-splenomegaly during routine physical examination.[7] Most of them have non-lethal course and little or no neurologic involvement.

NPD is a familial disease. It has been observed that age of commencement of disease as well as disease progression varies markedly from one case to another.[8] Pathologic foam cells is the histological hallmark of the disease which is also known as the Niemann-Pick cells.[9]

We diagnosed our case as CD on the basis of intra-hepatic bile duct dilatation as evident in Magnetic Resonance Cholangiopancreatography (MRCP) along with NPD type-B on the basis of lipid laden foamy histiocyte (Niemann-Pick cell) in bone marrow. Isolated incidences of both two diseases are rare in childhood. Association of these two rare diseases in a single patient is very uncommon. We took account of reporting this 3 year old child because of rarity of the association and absence of any such case report.

CASE REPORT

A 3 year old boy of non-consanguineous parents was brought with complaints of irregular fever (highest temperature 101^0F) and gradual abdominal distension for last 6 months. He had occasional mild-abdominal pain for the same duration but no H/O jaundice, hematemesis and/or melena, early morning food craving or irritability. There was no significant family history. The boy had normal developmental milestone. On general physical examination he was found to have moderate pallor and hepato-splenomegaly (liver was 6 cm from right costal margin and spleen was 8 cm from left costal margin). Liver was firm, non-tender and had regular margin. Anthropometrically he was mildly stunted.

Complete blood count showed moderate anemia (Hb 7.3 gm% with normal total and differential count and platelet count 200,000/L) peripheral blood film was suggestive of microcytic hypochromic anemia. Hb electrophoresis was done with normal report. Liver function tests were also normal (alanine transaminase-21U/L, prothrombin time 12 second, bilirubin 0.4 mg/dL). Ultra-sonogram (USG) showed hepato-splenomegaly, intrahepatic biliary channels were moderately dilated with many cystic dilatations inside liver parenchyma and renal architecture was normal. These findings were suggestive of CD. To confirm the diagnosis, MRCP was done that revealed multifocal cystic dilatation of the intra-hepatic bile ducts more marked in segment vii with a large cystic area suggestive of CD.

As patients also had hugely enlarged spleen we did esophago-duodenoscopy (EGD) to see the presence of esophageal varices which were not found. USG of portal vein was also normal.

Fig 1: MRCP showing multifocal cystic dilatation of intrahepatic bile duct

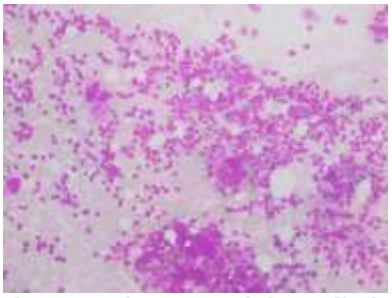

Fig 2: Niemann-Pick cell in bone marrow

However, patient's pallor and splenomegaly could not be explained only with CD, then we went for bone marrow examination and lipid laden foamy histiocytes (Niemann-Pick cell) were found within the marrow. He was found to have mild lipid abnormalities (triglyceride: 200 mg/dl, HDL: 30 mg/dl, LDL: 80 mg/dl). Chest X-ray and eye examination were normal. We could not determine the enzyme analysis due to lack of facilities. As the child had neither neurological nor ophthalmological involvement we diagnosed the case as NPD type B with CD.

DISCUSSION

CD is an uncommon autosomal recessive disorder of unknown etiology that usually presents in childhood and young adults.[2] In CD there are

dilatations of the intra-hepatic bile ducts that are in direct communication with the rest of the biliary tree.[2] This bile duct ectasia is usually accompanied with bile stones. This condition also aggravates the occurrence of recurrent cholangitis. It is the common clinical presentation in half of the patients with CD.[5] Most common symptoms of CD are: fever, right upper quadrant pain and more rarely, jaundice and so on.[4]

Fever and abdominal distention were the primary reasons for our patients to seek treatment. His abdominal pain was occasional. There was a similar report of a 12 year old boy who presented with fever and abdominal pain and had hepatomegaly.[10]

Two cases of CD were reported in two sibs (aged 3.5 years and 7.5 years). Among the two cases the younger case presented with only abdominal lump and another one with abdominal pain and lump.[11] Both the cases had only hepatomegaly.

In our case the boy also had moderate pallor and splenomegaly. But he did not have portal hypertension. To find out the etiology we did bone marrow examination that showed lipid-laden foamy histiocytes (Niemann-Pick cells) within the marrow that made the diagnosis of NPD.

To date no association of CD and NPD have been reported. It could be two separate entities in a single patient.

NPD type B, has variable presentations. Most of the patients of NPD type B are diagnosed in infancy or childhood due to detection of hepato-splenomegaly during routine examination. In addition to hepato-splenomegaly there are also thrombocytopenia, interstitial lung disease, and dyslipidemia in many patients but there is negligible neurological involvement in most of the patients.[8]

The presenting features of reported case were hepato-splenomegaly and mild dyslipidemia with no neurological manifestation. In a case report He et al. found a 5 year old boy with NPD type B who presented only with hepatosplenomegay.[10] The child did not have any pulmonary involvement on chest X-ray. Melissa et al. found pulmonary involvement in about one third of cases of NPD type-B in their 10 years longitudinal study.[4]

Keshavamurthy et al. reported a case of a 2 year old child presented with severe pallor. Our case had moderate pallor and mild growth retardation. The hematologic complications included decreasing leukocyte and platelet counts with age, but hemoglobin concentration remained stable.[10]

Laboratory tests in CD are non-specific and liver function test are usually normal or slightly increased in the early stages of the disease.[12] Our patient had normal liver functions. Definitive diagnosis of CD is made with imaging studies like ultrasonography, MRCP, Endoscopic Retrograde Cholangiopancreatography (ERCP) and Computed tomography (CT).[4] Although MRCP and ERCP are more sensitive in diagnosing CD than USG and CT but because of its invasiveness, ERCP is recommended for therapeutic purposes but not for the diagnosis of CD.[3] The characteristic findings of the disease are intrahepatic bile duct ectasia and irregular cystic dilatation of the large proximal intrahepatic bile ducts and direct communication with biliary tree.[3] In our case USG showed hepato-splenomegaly, moderately dilated intrahepatic biliary trees with many cystic dilatations inside liver parenchyma and MRCP showed multifocal cystic dilatation of the intrahepatic bile ducts more marked in segment vii and a large cystic area suggestive of CD.

The diagnosis of the NPD-B is made either by determination of enzymatic activity in tissue extract or by the detection of two mutations in the ASM gene.[6] We could not determine the enzyme or mutation analysis due to lack of facilities. We found lipid-laden foam cell (Niemann-Pick cells) in bone marrow which is the histologic hallmark of the NPD-B disease.

The treatment of patients with CD depends on the clinical features of the disease and the extent of biliary abnormalities. Cholangitis is treated with appropriate antibiotics. Ursodeoxycholic acid is a useful treatment for cholestasis. In our case, the boy had normal liver functions and treated with antibiotics and ursodeoxycholic acid. Surgical treatment options depends upon the extent of disease that include segmental or lobar hepatic resection and liver transplantation.[5] Malignancy is a complication of long-term CD and

cholangiocarcinoma can develop in 7% of patients.[13]

There is no cure for NPD, treatment is mainly supportive. The treatment options available are bone marrow transplantation or liver transplantation. Although neurological symptoms if presents will not be improved following bone marrow transplantation. Low cholesterol diet and dyslipidemic drug are the treatment options for hypercholesterolemia.[14] Enzyme replacement therapy (ERT) for NPD is a new therapeutic option. ERT for NPD is now under trial.[15]

At present, there is no hopeful therapeutic option to cure NPD patients. Genetic counseling seems to be of great importance and should be offered to the parents of the affected child and other families with positive history.[10]

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