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Case Report (Pages: 6261-6265)

I-Cell Disease with GNPTAB Gene Mutation

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Abstract

Inclusion-cell (I-cell) disease (mucolipidosis II) is a rare inherited metabolic disorder resulting from a defective phosphotransferase, characterized by coarse facial features, skeletal abnormalities and mental retardation. As clinical feature of this condition mimic that of Hurler disease mutation studies help in the diagnosis. We present a case of I-cell disease in a neonate with N-acetylglucosamine-1-phosphate transferase alpha and beta subunits (GNPTAB) gene mutation.

***Key Words*:** Skeletal anomalies, Mucolipidosis, Mutation, Neonate.

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1- INTRODUCTION

I-cell disease is characterized by coarse facial features, skeletal dysplasia and psychomotor retardation. The frequency of occurrence is about 1 in 100,000 to 400,000 individuals worldwide. It is classified as "mucolipidosis" because of clinical and biochemical similarities to both mucopolysaccharidosis and sphingolipidosis (1, 2). Mutations in the N-acetylglucosamine-1-phosphate transferase alpha and beta subunits (GNPTAB) gene identify the condition. We present an affected neonate with mutations.

2- CASE REPORT

A preterm male neonate with antenatally detected skeletal dysplasia was born out of non-consanguineous marriage to a 21 years old gravida 2 mother by emergency caesarian section at 36 weeks in view of absent end diastolic flow of umbilical artery. There was history of one abortion earlier. There was no family history of skeletal anomalies. The neonate did not cry at birth, but color and cry improved with stimulation. He required non-invasive ventilation in view of moderate respiratory distress. On examination, neonate weighed 1,700gr with length of 37cm, head circumference of 33cm, and upper segment lower segment ratio of 2.08. There was facial dysmorphism, gum hypertrophy, albinism, heterochromia iridis and excessive skin folds (**Figure. 1A**).

Fig. 1A: Excessive skin folds.

Both corneas were clear and normal red glow was present on fundus examination. The skeletal deformities in the form of short narrow thorax, rhizomelia, mesomelia and genu recurvatum were observed. Range of joint movements was restricted with flexion contractures at elbow, wrist, hip and knee joints. Systemic examination revealed mild hepatomegaly. Skeletal radiograph was suggestive of osteopenic short and curved bones (**Figure. 1B**). Investigations revealed leucocytosis, thrombocytopenia and azurophilic inclusion granules on peripheral smear suggestive of Alder Reilly granules (**Figure. 1C**) which are characteristically seen in lysosomal storage disorders. Neurosonogram, ultrasound abdomen and echocardiography were essentially normal. The child was managed symptomatically on non-invasive ventilation, intravenous fluids and

nasogastric feeds after 48 hours. He did not tolerate graded up enteral feeds. By day 7 of life, he was weaned off ventilator support. Parents were explained about the guarded prognosis and the long term morbidity. The child was taken home against medical advice in view of financial constraints, later he was reported to be succumbed within one week. In view of the above clinical features and skeletal survey findings, a provisional diagnosis of lysosomal storage disorder was considered. Blood sent for sequencing of GNPTAB gene was suggestive of homozygous pathogenic variant (c.3503_3504del TC) which confirmed the diagnosis of I-cell disease (I-cell disease, MIM #252500).

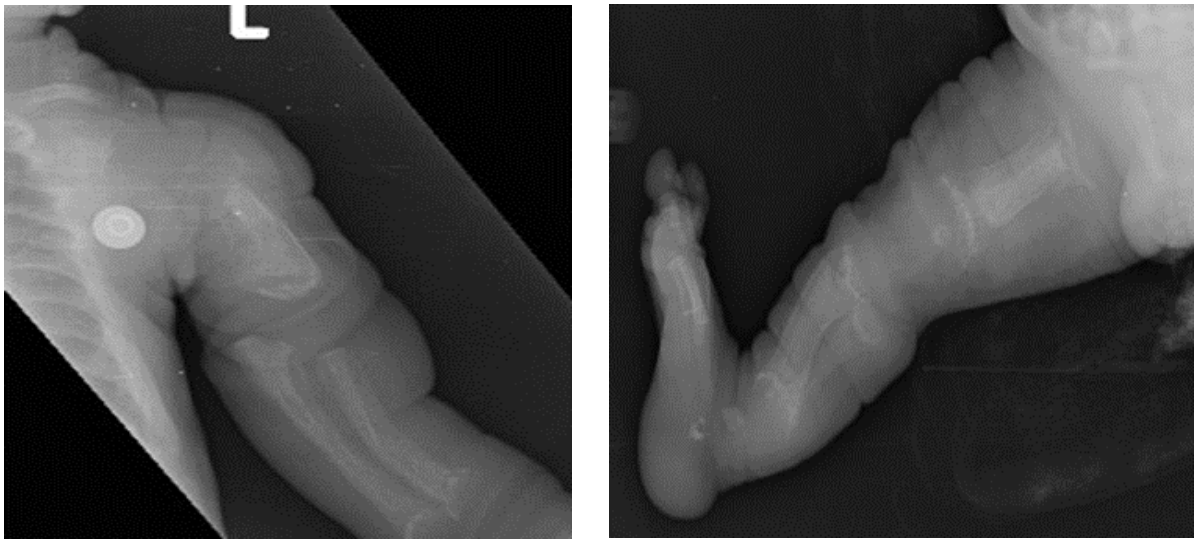

Fig. 1B: Radiograph showing osteopenic short and curved bones.

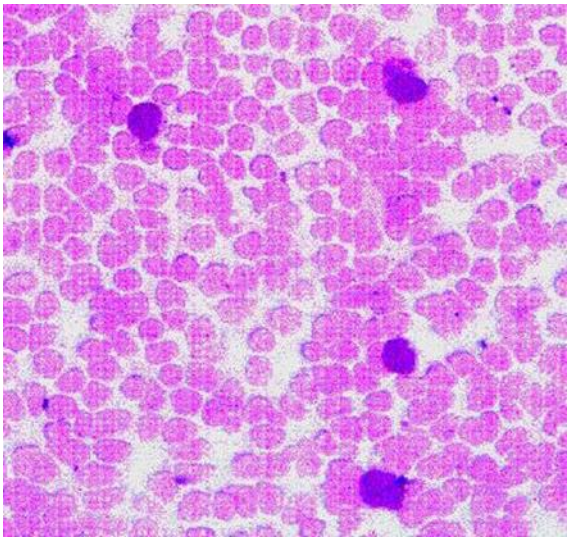

Fig. 1C: Peripheral smear showing Alder Reilly granules.

3- DISCUSSION

I-cell disease or Mucolipidosis II was first described in 1967 by Leroy and DeMars in a patient with clinical and radiographic features resembling those of Hurler syndrome but with earlier onset of symptoms and absence of mucopolysaccharidurіa. I-cell disease is a progressive metabolic disorder caused by a mutation in the GNPTAB gene that leads to a deficiency of Uridine diphosphate-N-acetylgalactosamine (UDP-GalNAc). Disease is inherited as an autosomal recessive genetic trait (1-3).

Mutations GNPTAB gene lead to failure of mannose-6-phosphate synthesis, a marker on the side chain of lysosomal enzymes impairing the lysosomal enzymatic function (1, 2). Deficiencies of a variety of lysosomal enzymes in the cells of the body further lead to an abnormal accumulation of certain mucolipids and mucopolysaccharides within the cells of many tissues of the body.

The clinical manifestations vary. Remarkable variability in age of onset, organ manifestation, radiologic findings and unusual clinical symptoms has been reported. Some features are apparent at birth where as others may become apparent during 6 to 10 months. The skeletal system is most severely affected with an abnormal trabeculation of the bone and cartilage (3).

Coarse dysmorphic facial features, gingival hyperplasia, hip dysplasia, hernia and restricted joint movement were the early manifestations as in the present case. Cardiac involvement most commonly includes the thickening and insufficiency of the mitral or aortic valves. Voice is hoarse and breathing is noisy due to the progressive narrowing of airways and stiffening of all connective tissues. Growth retardation and delayed motor milestones are common. Affected children can never walk due to contractures and postnatal growth usually stops in the 2nd year of life. Cognitive functioning is below normal. Pericardial effusion and profound brain atrophy are the unusual manifestations. The characteristic laboratory finding is abnormal vacuolization and granule formation in the circulating agranulocytes in the peripheral blood. Alder-Reilly anomaly characterized by presence of large azurophilic and basophilic granules in cytoplasm of cells of myeloid and lymphoid series (4) are characteristically seen in mucolipidosis. The cytoplasm of fibroblasts also has cytoplasmic inclusions which are evident on culture. The mutations in GNPTAB gene confirm the diagnosis as in our case.

The treatment of I-cell disease is supportive. Physiotherapy is advised to maintain joint function and mobility. Prompt treatment of respiratory infections and immunization against flu are needed. Prognosis is usually poor; most children do not survive beyond the first decade. Cardiopulmonary complications are the leading cause of death in affected children. Prenatal diagnosis of the particular enzyme defect is possible in the first trimester by chorionic villus sampling or later by estimation of lysosomal enzymes in the amniotic fluid (5, 6).

4- CONCLUSION

Although I-cell disease resembling mucopolysaccharidosis has characteristic clinical and radiographic features, mutation studies are essential for its identification.

5- CONFLICT OF INTEREST: None.

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