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Arthrogryposis-Renal dysfunction-Cholestasis (ARC) Syndrome---A case report

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ABSTRACT *Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive multisystem disorder. Failure to thrive, icthyosis, dysmorphism, recurrent infections, platelet disorders, deafness, absent corpsus callosum and neurogenic muscular atrophy are some of the features reported in this spectrum of ARC syndrome. Majority of children die within the first year of life and survivors present with severe developmental delay. Germ line mutations in VPS33B gene on chromosome 15q26.1 is the most common defect and identification of this helps in prenatal diagnosis. We report a 3 month female infant with clinico laboratory features diagnostic of ARC syndrome.*

Introduction:
Arthrogryposis-renal dysfunction-cholestasis [ARC] syndrome is an inherited multisystem disorder comprising of the three cardinal features arthrogryposis, renal dysfunction and cholestasis. The variable phenotype and the high mortality are the possible reasons for the under diagnosis of this condition. We report a 3 month old female infant with the classical phenotype of ARC syndrome.

Case Report:
A 3 month old female infant, third born to third degree consanguineous parents with a birth weight 3 kg, was referred with jaundice, high colored urine and pale stools since 20th post natal day. She had been hospitalized earlier for jaundice, fever, sepsis and failure to thrive. There was no history of seizures, altered sensorium, mucocutaneous bleeds, ear discharge or diarrhea. An elder sibling with a similar clinical picture had expired at 40 days of life but another 4 year old sibling was normal. On examination, she was sick looking, weighed 2.2kg (<3rd percentile), head circumference 34cms [microcephaly], heart rate 150/min, respiratory rate 40/min. She was jaundiced, had upward slanting of the eyes and large low set ears. She had redundant skin folds on the neck, scaly and dry hyper pigmented lesions on the forehead, generalized muscle wasting and flexion contractures of knees, hips and flexion deformity of thumbs (Figures 1& 2). Abdomen exam revealed firm hepatosplenomegaly. Cardiovascular and respiratory system were normal. A differential diagnosis of ARC or NISCH syndrome was considered in view of the jaundice and icthyosis.

Investigations revealed total WBC 20,900/cu.mm with lymphocytic predominance, hemoglobin 7.2 g/dl, platelet count of 9.7 lakhs. Serum bilirubin was 8.7 mg/dl, direct bilirubin 5.0mg/dl, SGPT 27IU/L, SGOT 59IU/L, SAP 861 IU/L, γ GTP 4 IU/L(normal range 7-98IU/L), total protein 6.0 g/dl, albumin 2.9g/dl, Prothrombin time 13/14 seconds (normal). Her HCO3 was 14 mEq/L. Urine specific gravity was 1.010 and urine for reducing substances was negative. C-reactive protein was negative and blood culture showed no growth. Ultrasound abdomen showed hepatosplenomegaly, increased renal echogenecity with poor corticomedullary differentiation and small microliths in the renal pelvis. Liver biopsy was not done. This combination of cholestatic jaundice with low γ GTP, icthyosis, arthrogryposis and renal involvement suggested ARC syndrome. Parents were counseled about the lethal nature of the disease and genetic studies though planned could not be done as she succumbed to the illness within 10 days following admission.

Discussion:
ARC syndrome is characterized by a distinctive triad but there may be a wide phenotypic variation and affected siblings sine arthrogryposis has been reported[1]. As majority die within 7 months of age[1] ARC may be under diagnosed.

Arthrogryposis in ARC syndrome occur secondary to neurogenic muscular atrophy. The renal manifestations resemble features of Fanconi syndrome. Renal tubular acidosis is the most consistent abnormality [as seen in our case] while nephrogenic diabetes insipidus and nephrocalcinosis have been reported[2].

Jaundice in ARC is typically a low GTP cholestasis. However when an infant presents with arthrogryposis, renal dysfunction and icthyosis as in this case, the diagnosis is more likely to be ARC. The proportion of ARC to biliary atresia is around 1:7 highlighting that it may not be very uncommon in some ethnic groups[3]. Hepatic histology shows cholestasis, ductopenia, giant cells, lipofuschin granules, fibrosis and features of cirrhosis. Routine liver biopsy is not recommended as fatal hemorrhage may occur and hence we have not performed liver biopsy in our case.

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Platelet dysfunction is the probable cause for bleeds and agranular large platelets may serve as a marker for ARC. These platelets lack alpha granules and have low levels of γ thromboglobulin, platelet factor 4 and thrombospondin[4].

Apart from the arthrogryposis, a striking feature in ARC is the icthyosis which occurs in more than 50 % of the children[1]. Neonatal ichthyosis-sclerosing cholangitis (NISCH) syndrome a rare, autosomal recessive disorder also presents with cholestasis and icthyosis[5]. The differentiating features in NISCH are scalp hypotrichosis and scarring alopecia which was not seen in our case.

Truncated mutations in the Vacuolar Protein Sorting 33 homolog B (yeast)-VPS33B on chromosome 15q26.1 has been reported in 75% of cases[6].VPS 33B involves intracellular protein trafficking by regulation of vesicle-to-target sensory nerve action potential receptor (SNARE) family which may explain the membrane fusion defects at several sites such as epidermis, renal tubules, biliary canalicular membrane, platelet and brain. Recently mutations in VIPAR gene have been identified indicating that the VPS33B-VIPAR complex has diverse functions in the pathways regulating apical-basolateral polarity in the liver and kidney[7]. In the hepatocyte, mutations in VPS 33B affect bile transport and result in a low or normal GTP cholestasis. Management of this rare syndrome involves an early diagnosis, family counseling and supportive treatment. The classical features of ARC syndrome in this infant helped in diagnosis. Awareness of this rare multisystem low GTP cholestatic disorder reveals the complexity of inherited cholestatic liver diseases.

Figure 1: Photograph of the child showing Ichthyosis and icterus

Figure 2: Photograph of the child show ing flexion deformity of thumb and contractures of both knees

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