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Case Report

Hennekam lymphangiectasia syndrome

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ABSTRACT

Hennekam lymphangiectasia syndrome is a rare autosomal recessive condition. Onset is usually in childhood. The prevalence is unknown but less than 50 cases have been reported in the literature. Incidence is about 1 in 100000 and occurs in all ethnic groups. The syndrome is characterized by the association of lymphedema, intestinal lymphangiectasia, intellectual deficit and facial dysmorphism. Here is a case presented with distension of abdomen with ascites, bilateral pedal oedema, macrocephaly, left half facial edema, left half hypertrophied tongue, dental anomalies, acanthosis nigricans, acrochordons and syndactyly consistent with a diagnosis of Hennekam syndrome. The diagnosis of Hennekam is suspected on the basis of clinical phenotypic features. This is one of the very few cases reported from India.

Keywords: Hennekam syndrome, Lymphangiectasia, Autosomal recessive, Facial dysmorphism

INTRODUCTION

Hennekam lymphangiectasia syndrome was first described by Dutch physician R.C.M. Hennekam in 1989.[1] The synonym for this condition is Multiple Congenital Anomaly/Mental Retardation (MCA/MR) syndrome. The prevalence is unknown but less than 50 cases have been reported in the literature. Incidence is about 1 in 100000 and occurs in all ethnic groups.[2] Lymphedema usually present at any time from birth to childhood. The syndrome is transmitted as an autosomal recessive trait.[1] Prox-1 gene is required for both emergence of lymphatic endothelial cells from the veins and their differentiation towards the lymphatic phenotype. Critical chromosomal region containing CCBE1 (collagen and calcium binding EGF domains 1) located on long arm of Chromosome 18 (18q21.32) identified as one of few genes causing primary generalized lymph vessel dysplasia in human by Alders et al.[3]

The aetiology remains unknown but the clinical manifestations suggest that the syndrome results from defects in the mechanism of fluid uptake due to abnormal vascular and lymphatic development which disrupts critical events in craniofacial morphogenesis resulting in this phenotype. Hennekam syndrome[4] is characterized by lymphedema, intestinal lymphangiectasia, intellectual deficit and facial dysmorphism.[1] Malformation or dilation of lymphatic channels resulting in lymph blockages and accumulation of fluids occurs affecting mainly the face, lower limbs and genitalia and often leads to complications such as erysipelas. Facial features are characterized by a flat face, broad depressed nasal bridge, hypertelorism, epicanthal folds, a small mouth and low-set ears with a narrow meatus, tooth anomalies and gingival hypertrophy. Seizures, blood vessel anomalies, congenital pulmonary lymphangectasia and a narrow upper thorax have also been reported. Intestinal lymphangiectasia may result in protein-losing enteropathy,[5] mild growth retardation, peripheral oedema and chylous ascites. The degree of intellectual deficit is

highly variable, even within a single family. Less common manifestations include glaucoma, nonimmune hydrops fetalis,[6] chylothorax, brain cysts and craniosynostosis.[7]

The diagnosis is suspected on the basis of the clinical phenotype. Intestinal lymphangiectasia may be suspected by hypogammaglobulinemia, hypoalbuminemia, lymphopenia and increased alpha-1 antitrypsin excretion in the faeces[5] and can be supported by duodenal biopsy. Endoscopy shows dilated lacteals as white opaque spots, nodular lesions and xanthomatous plaques are also seen. The lesions are often patchy and localized.[5] However, several biopsies are often needed before lymphangiectasia is demonstrated. Lymphatic impairment due to malformed, hypoplastic lymphatics can be demonstrated by radionuclide lymphoscintigraphy.[5]

CASE REPORT

A 20 year male patient presented to this hospital with a complaint of progressive distension of abdomen with ascites and bilateral non pitting type of pedal oedema. Incidentally he is the only one child to his parents of a non-consanguineous marriage with no history of radiation exposure, major illness during pregnancy or bad obstetric history. No other family members had similar phenotypic features.

Examination

Patient was conscious, oriented with no stunted growth or mental retardation. His vital data like blood pressure, pulse rate were within normal limits. There was no pallor, icterus, cyanosis, clubbing or lymphadenopathy. General examination showed facial features like macrocephaly with facial edema on left side and hypertrophy of tongue on left side and dental anomalies like oligodontia with only 28 teeth. Acanthosis nigricans and acrochodons were seen. Bilateral non tender and non-pitting type of pedal oedema present with varicose veins in both lower limbs. Pes planus of both feet with syndactyly of left 2nd and 3rd toes present. Abdomen distended with free fluid in the peritoneum and no organomegaly. Chest examination showed diminished breath sounds in bases bilaterally suggesting pleural effusion. Examination of cardiovascular system and central nervous system were normal.

Investigations

Routine blood investigations were within normal limits. Severe hypoalbuminemia (1.5 g/dl), hypoglobulinemia (2.5 g/dl) and proteinuria were seen. Serum creatinine, haemoglobin, platelet and leukocyte counts were normal. Ascitic fluid milky white in appearance with triglycerides levels 356 mg/dl, proteins 2 gm/dl and sugars 144 mg/dl suggestive of chylous ascites. Chest X-ray showed mild bilateral pleural effusion which is serous in nature. CT Chest showed mild bilateral pleural effusion and thoracic duct found to be normal. Ultrasonography of abdomen (USG) and CT abdomen showed chylous ascites, cholilithiasis, left hydroureter nephrosis and cystitis changes. Duodenal mucosal biopsy from multiple sites twice found to be normal. Echocardiography was normal.

Management

Treatment is symptomatic. Many patients require Total Parenteral Nutrition (TPN) with a medium-chain triglyceride-rich diet and albumin infusions. Fat soluble vitamins and electrolyte supplements together with a high-protein diet have been reported to be beneficial. The lymphedema may be severely disabling and require repeated surgical intervention.

Prognosis

The prognosis is variable and few patients have been described with very severe manifestations leading to early death.

Follow up

Duodenal biopsy could not be repeated as we lost the follow up of patient. Radionuclide lymphoscintigraphy was not done due to financial limitations and non-availability in our region to demonstrate malformed and hypoplastic lymphatics. These investigations might have given an additional support in diagnosis of this syndrome.

DISCUSSION

R.C.M. Hennekam, a Dutch physician first described a syndrome of intestinal lymphangiectasia with severe lymphedema of the limbs, genitalia, face and severe mental retardation in 1989.[1] Hennekam syndrome is a developmental disorder of the lymphatics with autosomal recessive inheritance.[1] Patients with congenital disease may present at any time from birth to adulthood. The aetiology remains unknown but the clinical manifestations suggest that the syndrome results from abnormal vascular and lymphatic development which disrupts critical events in craniofacial morphogenesis resulting in this phenotype.

The syndrome[4] is characterised by the association of lymphoedema, intestinal lymphangiectasia, intellectual deficit and facial dysmorphism.[1] The characteristic features of the syndrome are facial and dental anomalies. Facial anomalies include flat face, upper lip and nasal bridge, hypertelorism, epicanthal folds, small mouth, narrow palate, mild retrognathia, craniosynostosis, dysmorphic pinnae, atresia of ear canal, oligodontia, and conical crowns. The dermatological anomalies described are severe lymphedema of the limbs, face and genitalia, infection of oozing lymphatics (erysipelas), alopecia areata and frontal upsweep. Other systemic features reported are of thorax (pleural effusion, narrow upper

thorax), cardiovascular system (ventricular septal defect) and central nervous system (severe mental retardation, seizures).

The prominent anomaly reported with gastrointestinal tract is intestinal lymphangiectasia. Tortous, dilated mucosal and submucosal lymphatic vessels due to increased lymphatic pressure are the hallmark of primary intestinal lymphangiectasia.[5] As a result of obstruction and increased pressure in lymphatics, intestinal lymph leak into the intestinal lumen. Lymphatic fistulae may form and lymph containing chylomicrons, proteins and lymphocytes drain directly into the intestinal lumen. Patients present with steatorrhea, lymphocytopenia, hypogammaglobulinemia and hypoalbuminemia.[5] Blockage of serosal and mesenteric lymphatics may lead to chylous ascites.[5] Renal lymphangiectasis[8] is most often asymptomatic and characterized by presence of fluid collections in the perinephric, peripelvic spaces which are detected on routine imaging. Urogenital anomalies described are genital lymphedema,[9] duplicated ureter, hydroureter nephrosis, chyluria(rupture of renal lymphangiectasis lacteals) and cystitis due to vesicoureteral reflux.

Our patient is one of the few cases reported from India and suspected to be Hennekam lymphangiectasia syndrome based on clinical phenotypic features.

The characteristic anomalies related to different systems seen in this case are facial anomalies like macrocephaly, facial lymphedema on left side, hypertrophy of tongue on left side, oligodontia with 28 teeth (dental anomalies). The dermatological anomalies seen in this case are left side lymph edema of face, bilateral lymphedema of the limbs with pes planus, left syndactyly of 2nd & 3rd toes, acanthosis nigricans and acrochordons as shown in Figure 1.

Hypoalbuminemia, hypoglobulinemia and chylous ascites due to rupture serosal and mesenteric lymphatics are seen as shown in Figure 2 suspecting intestinal lymphangiectasis. Hydro ureter nephrosis and cystitis changes are seen suggestive of renal involvement.

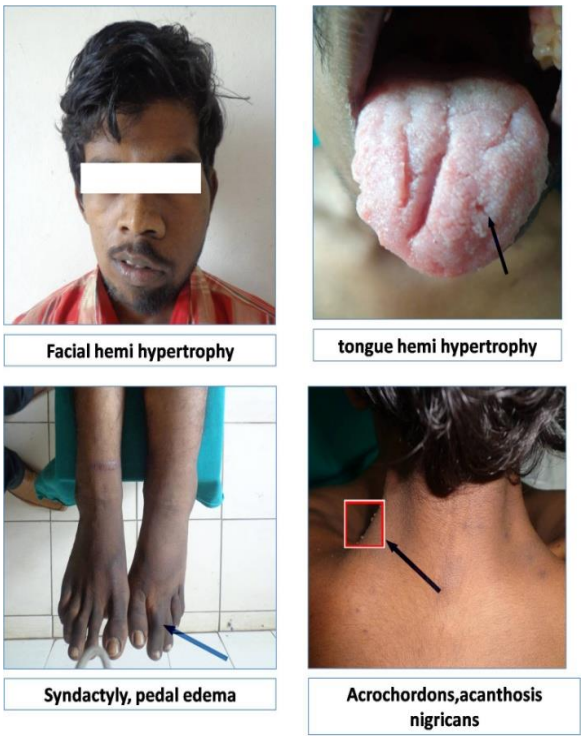

Figure 1: Showing left side lymph edema of face, bilateral lymphedema of the limbs with pes planus, left syndactyly of 2nd & 3rd toes, acanthosis nigricans and acrochordons.

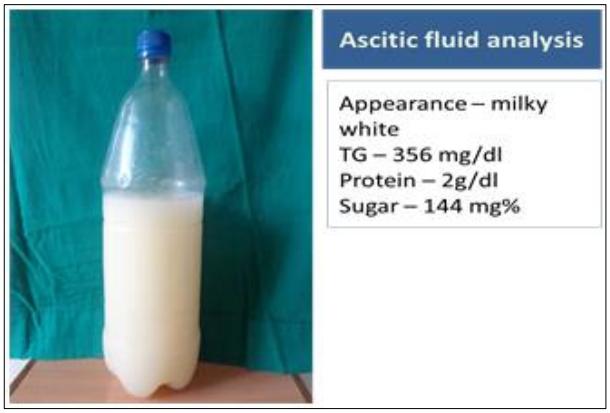

Figure 2: Chylous ascites.

In summary we present a rare case of Hennekam syndrome, a developmental disorder of lymphatics presenting with peripheral limb edema, macrocephaly, left facial edema, left half hypertrophy of tongue, oligodontia, pes planus, syndactyly involving left 2nd & 3rd toes, chylous ascites, hydroureter nephrosis and cystitis. Physicians need to have high degree of suspicion in patients presenting with multiple congenital anamolies involving lymphatics. Diagnosis is suspected based on classical phenotypic features. But lymphatic malformations can be demonstrated by intestinal mucosal biopsy and radionuclide lymphoscintigraphy.

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