Infantile systemic hyalinosis: Report of a rare inherited disorder from Northern India

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Introduction:
Hyaline fibromatosis syndrome (HFS) is a rare autosomal recessive disorder characterized by abnormal deposition of amorphous hyaline material in the dermis and other tissues. Histopathological examination of skin lesions shows amorphous eosinophilic substance in the dermis with interspersed spindle-shaped fibroblasts. It presents with papular and nodular skin lesions in the scalp, face, ears, neck, hands, feet, and perianal regions. Molecular testing shows a mutation in the anthrax toxin receptor 2 (ANTXR2) gene, also known as the capillary morphogenesis gene 2 (CMG2) located on chromosome 4q21. The clinical severity is variable, mild forms seen during early childhood being known as juvenile hyaline fibromatosis (JHF) and severe forms, seen during infancy, as infantile systemic hyalinosis (ISH). Less than 70 cases of JHF and 20 cases of ISH have been reported worldwide. The two variants, ISH and JHF, represent different degrees of severity of the same disease. Both conditions are progressive, disfiguring, and disabling. We present an infant with features of ISH, with a history of two elder siblings with similar clinical features.

Case report
A 4-month-old male infant, born to a non-consanguineous married couple, presented to us with complaints of restriction of movements of elbows, wrists, ankles and knee joints bilaterally since birth. He is the fourth child of the couple. Regarding gross motor development, partial neck holding was present; child was able to follow objects and was able to recognize his mother; regarding language, child was making incomprehensible sounds.

On examination, child had involvement of both flexor and extensor groups of muscles at elbow, wrist and knee joints and dorsiflexors, planter flexors, invertors, and evertors at ankle joints (Figures 1 and 2) and hyperpigmentation of knuckles (Figure 3). His weight was 4.72kg (<1st centile), length 55cm (<1st centile), head circumference 40cm (<3rd centile), upper segment 34cm, lower segment 21cm (growth centiles according to Indian Academy of Paediatrics growth charts)

Figure 1: showing wrist joint contracture

Figure 2: showing contracture of elbow

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The couple also had two other children whose details were as follows. The firstborn was a female with uneventful antenatal history, who also developed multiple joint contractures a few months after birth, and died due to respiratory distress when she was one year old. The third child was a female, who also died at 1 year of age due to respiratory failure, with similar complaints of multiple joint contractures soon after birth. Genetic analysis of the above two deceased siblings was not done. The second child of this couple is healthy and alive (Figure 4)

Blood investigations revealed iron deficiency anaemia. Biochemical analysis was normal. X-ray of wrist showed looser zones (Figure 5).

Ultrasonographic (USG) screening of joints was grossly normal. Magnetic resonance imaging (MRI) of joints showed generalized muscle atrophy with soft tissue thickening at the right shoulder region and contractures of elbow and wrist joints. Nerve conduction study showed decreased amplitude with normal latency and nerve conduction velocity, indicating decreased compound muscle action potential. Sensory conduction was within normal range. Ear nose and throat (ENT) and ophthalmologic evaluation revealed no abnormality and 2D echocardiography screening of the heart was normal. No skin biopsy was done.

Clinical exome sequencing of the child showed heterozygous single base pair duplication in exon 13 of the ANTXR2 gene (chr4: g.79984832dupG; Depth: 41x) that results in a frameshift and premature truncation of the protein 13 amino acids downstream to codon 359, which was diagnosed as infantile hyaline fibromatosis syndrome. Genetic analysis of parents and live sibling was advised but could not be done due to financial constraints.

Supportive treatment and symptomatic rehabilitation were started with an occupational therapist. Assessment of range of motion in all joints was done passively along with grading of muscle tone. Techniques used to improve mobility of joints were:

- Myofascial release and gentle stretching.
- Passive range of motion of both upper and lower extremities.
- Muscle facilitation and light joint compression.
- Neck rotation (right to left and left to right) both actively and assisted.
- Positioning.

Parents were trained for these exercises and advised to continue on a daily basis. Bilateral whole length lower limb casting was done (Figure 4).
There is an abnormal growth of hyalinised fibrous tissue with cutaneous, mucosal, osteoarticular, and systemic involvement. Clinical features seen in both conditions include multiple joint contractures, nodular and popular skin lesions, gingival hypertrophy and osteopenia with normal brain development. Those with ISH have additional involvement of the gastrointestinal (GI) system with persistent diarrhoea, frequent severe infections and failure to thrive and death usually by 2 years of age. Hyaline deposition in the GI tract causes intestinal lymphangiectasia and thus persistent diarrhoea and protein-losing enteropathy, which may be suspected based on increased stool alpha 1-antitrypsin. The main causes of death in these children are usually intractable diarrhoea, recurrent infections, and organ failure.

Our case report describes a family in which three out of four offspring were affected with abnormal joint contractures. The first and the third born children, both girls, died. They presented with complaints of severe joint contractures at birth and died within the first year of life. The second child, a girl, is 6 years old and is alive and healthy. The fourth sibling, a male child, presented to us with severe joint contractures. Gene mutation analysis done showed heterozygous single base pair duplication in exon 13 of the ANTXR2, confirming the diagnosis of hyaline fibromatosis syndrome.

ANTXR2 gene encodes type I transmembrane protein which contains a signal peptide, followed by an extracellular von Willebrand type A domain (vWA), an immunoglobulin-like domain, a transmembrane domain, and a cytosolic tail; vWA domains interact with extracellular matrix proteins with a metal ion-dependent adhesion site (MIDAS) motif. ANTXR2 may be a receptor for type VI collagen and may mediate its transport to lysosomes for degradation, and hence loss of ANTXR2 function leads to accumulation of type VI collagen in the extracellular matrix. The immunoglobulin-like domain helps proper folding for protein with the help of disulfide bonds formed in the endoplasmic reticulum.

ANTXR2 mutations were classified into four major classes: which include: I- missense mutations in the vWA domain which thus impair ligand binding; II- other missense mutations in exons 1-11 usually affect the Ig-like domain and hence affect folding, leading to endoplasmic reticulum retention and degradation; in some cases Class III mutations contain frameshift mutations that lead to a premature stop codon and splicing mutations, and they have been predicted or proven to lead to unstable mRNA that is rapidly degraded. Class IV mutations affect the cytosolic tail. ISH is associated with missense, truncating, and frameshift mutations, affecting the extracellular vWA domain, whereas in-frame and missense mutations are associated with phenotypically milder JHF.

According to genetic exome analysis, our patient had frameshift and premature truncation of protein 13 amino acids downstream to codon 359 which has been predicted or proven to lead to unstable mRNA that is rapidly degraded. Phenotypically the patient presented to us with joint contractures, pigmentation over the joints, and with a history of recurrent episodes of diarrhoea which belongs to grade 3 (severe) according to Denadai R, et al severity classification. There was a history of recurrent episodes of diarrhoea in first and third siblings who died at the age of 10-11 months. The stool examination was normal.

The treatment is mainly palliative and supportive. Pain is managed with nonsteroidal anti-inflammatory drugs and opiates. Physiotherapy is done for joint contracture to improve the range of movements and for the management of pain. In patients with failure to thrive, nasogastric tube or gastrostomy feeding should be considered. In severe conditions such as in cases of intestinal...
Infantile systemic hyalinosis: Report of a rare inherited disease—lymphangiectasia and protein-losing enteropathy, we can consider albumin infusions, hydration and dietary therapies\textsuperscript{15,16}.

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