

Infantile systemic hyalinosi: A fatal disorder commonly diagnosed among Arabs

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Received on May 19, 2004; accepted in
revised form on April 1, 2005.

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Key words: Infantile, hyalinosi, ribromatosis, Saudi Arabia.

ABSTRACT

We retrospectively reviewed 19 patients (11 male, 8 female) with infantile systemic hyalinosi (ISH) seen at a tertiary care hospital. Fifteen patients (83.3%) presented in the neonatal period. The referral diagnosis was inaccurate in 14 patients (73.7%). Thirteen patients were products of first-degree cousin marriages (68%) and 5 families had more than one affected child. All patients had painful joint contractures and typical mucocutaneous changes (hyper-pigmented sclerodermatous skin over the knuckles and malleoli, gingival hyperplasia, subcutaneous and perianal fleshy nodules). Growth failure was noted in all of them and 39% had profuse diarrhea, 72% had low serum albumin. Radiological findings included osteopenia, periosteal reaction and osteolytic lesions. Tissue biopsy was consistent with the diagnosis in the 8 patients who had the biopsies. Despite aggressive management with physiotherapy and different medications (including NSAIDs, penicillamine and methotrexate), the disorder was progressive and none of them showed improvement. 16 patients died with a mean age of 11 months and only 3 are alive with a mean age of 20 months. This report represents the largest series of ISH. Our data suggests that ISH is a commonly diagnosed disorder in Saudi Arabia and among Arabs.

Introduction

Infantile systemic hyalinosi (ISH) is a rare inherited disease of the connective tissue characterized by widespread deposition of hyaline material. The first report was by Murray in 1873 as "molluscum fibrosum" then in 1962 Puretic et al reported a case under the name of mesenchymal dysplasia (1). Ishikawa and Hori introduced the term of systemic hyaline fibromatosis in 1964. Since then several reports have appeared in the literature (2-4).

Two disease types are recognized in the medical literature, infantile systemic hyalinosi (ISH) and juvenile hyaline fibromatosis (JHF) (5). Both conditions are characterized by painful joint contractures, gingival hypertrophy and subcutaneous and perianal fleshy nod-

ules. However, ISH is distinguished by an earlier onset, more progressive and severe course and death in early childhood. Nonetheless, there are striking histological similarities between the two subtypes; it has been suggested that both diseases represent different expressions of the same disorder (4). Recently this has been confirmed by identification of mutations in the capillary morphogenesis protein 2 (GMC2) causing both JHF and ISH (6, 7).

Cases of systemic hyaline fibromatosis have been described from almost all parts of the world, but most frequently among Arabs, Japanese and Indians (2, 4, 8, 9). We describe here the clinical, radiological and histopathological features of the largest known collection of patients with ISH.

Patients and methods

A retrospective analysis of the charts of all patients with ISH who have been seen at the Pediatric Rheumatology and Medical Genetic Clinics at King Faisal Specialist Hospital and Research Center, Riyadh from 1992 to 2003. To ensure that all charts are reviewed, we coordinated with the Medical Records Department.

The collected data included the demographic, clinical, laboratory, radiological as well as histopathological features, disease course and the outcome of those patients.

Results

Nineteen patients (11 male/8 female) had the typical musculoskeletal and mucocutaneous features in the form of painful joint contractures and hyper-pigmented sclerodermatous skin.

The age of onset ranged from the neonatal period (83%) to 6 months of age while the age of presentation at our hospital ranged from 2 to 23 months with a mean of 14 months. Thirteen patients were the product of first cousin marriage (68%) and 5 families had more than 1 affected child.

During follow up it was noticed that painful joint stiffness is seen in the hips and wrists but later involve all large joints of the upper and lower limbs, leading to a frog-like position (Fig. 1) a few months after the onset of the dis-



Fig. 1. Characteristic flexural contractions of the joints leading to a frog-like position.



Fig. 2. Contractions of metacarpophalangeal joints and sclerodermatous skin with pearly papules of the neck and ear.

ease. The small joints of the hands are later affected which leads to severe limitation of range of motion, hyperextension at the metacarpophalangeal joints and fixed flexion contractures at the proximal and distal interphalangeal joints. This leads to a particular deformity (Fig. 2) which is accompanied by hyperpigmented plaque over the

knuckles and malleoli. Skin hardness developed after the first few months and gave rise to sclerodermatous skin. Nodular fibrosis, in the form of subcutaneous nodules (15 patients), gingival hypertrophy (14 patients) (Fig. 3) and perianal fleshy nodules (14 patients) developed later in the course of the disease.

All patients had peculiar features in the form of deep set eyes, depressed nasal bridge, square box head and prominent forehead. All patients had failure to thrive with severe muscle wasting and 39% had intractable diarrhea. Table I shows the frequency of the clinical features.

Only 5 patients were diagnosed correctly before referral and the rest were either not diagnosed or wrongly diagnosed; the most frequent wrong diagnoses were Arthrogryposis multiplex and Farber disease.

Laboratory investigations were not specific. Complete blood count showed low hemoglobin (hypochromic microcytic), a moderately elevated white cell count (WBC) and platelets count in 14 patients. The erythrocyte sedimentation rate was mildly elevated in all patients, while albumin was low in 14 patients. Electrolytes and renal function, liver enzymes and urinalysis were all normal. Few patients had further work-up including antinuclear antibody, rheumatoid factor, complement and immunoglobulin levels, were all within normal limits.

Radiological studies were available for 15 patients. General features (Table II) were: delayed skeletal maturation, severe osteopenia, contractures and deformity involving large and small joints, muscle wasting, soft tissue swelling indicating subcutaneous nodules. Bone erosions were observed more around the shoulder, clavicle and proximal humeri. Proximal tibias showed similar, but less severe changes. Other bone changes include diaphyseal changes in the long bones with slender and contracted diaphyses and abnormal modeling of metaphysis. Lucent defects, different in size and shape, were also noticed.

The skin biopsies showed similar changes; the dermis is thickened and



Fig. 3. Characteristic gingival hypertrophy.

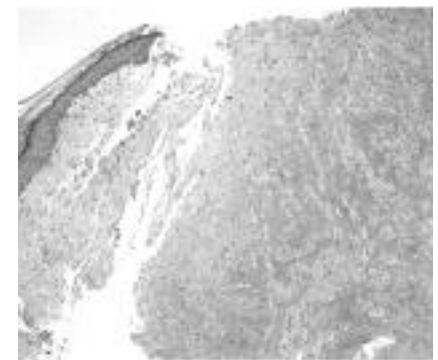


Fig. 4. Skin biopsy showed ill-defined thickened dermis with diffuse hypocellular hyaline areas that stained strongly for periodic acid-schiff and alcian blue.

extended into the subcutaneous tissue and completely replaced by hyaline fibrous material that stained strongly for periodic acid-schiff (PAS) and alcian blue (Fig. 4). By electron microscopy, the PAS and alcian blue positive material showed a granulated ultrastructure. Collagen fibers were found scattered in this material and appeared morphologically normal, and the fibroblasts showed active dilated endoplasmic reticulum and prominent cystic Golgi apparatus containing cystic vesicles filled with a fibrillar, granular material. Others contain large amounts of organelles in the cytoplasm, mainly mitochondria.

The gingival biopsy showed epithelial hyperplasia with infiltration by lymphocytes. The jejunal biopsy showed an edematous lamina propria and multiple dilated lymphatics suggestive of lymphangectasia.

The CMG2 sequencing for one of our patients revealed a new gene mutation, which is a homozygous insertion of a C on exon 13 (p357insC).

Table I. The frequency of clinical features of 19 patients with infantile systemic hyalinosis.

Excessive crying/irritability	19
Painful joints contracture	19
Mucocutaneous	19
Gingival hypertrophy	14
Subcutaneous nodules	15
Perianal fleshy nodules	14
Diarrhea	7
Edema	2
FTT	19
Intelligence	19

Table II. Radiological changes in 15 patients with infantile systemic hyalinosis.

Osteopenia	15
Joint contracture	15
Soft tissue masses	10
Abnormal modeling of metaphysis	8
Erosions	9
Lucent defects	8

All patients had progressive disease course and none of them showed improvement in spite of trying different medications (pencillamine, methotrexate). Sixteen patients died due to infection and intractable diarrhea with a mean age of 11 months and only 3 patients are alive with a mean age of 20 months.

Discussion

Infantile systemic hyalinosis (ISH) as described by Landing *et al.* is characterized by widespread hyaline material deposition in skin, musculoskeletal and deep organs in addition to nodule formation and joint contractures (5). It starts appearing in early infancy with progressive course. Usually this form

of hyalinosis is severe and all patients died before 24 months of age (10). Musculoskeletal symptoms – particularly stiff, painful joints – are an important part of the disease and are usually the reason for seeking medical advice. Typically, the patient develops diffuse progressive joint contractures leading to a frog-like position.

There are few disease entities that, mimic the clinical features of ISH, are associated with the early onset of joint contractures including syndromes associated with arthrogryposis such as Faber and Winchester and inflammatory connective tissue disorders, namely neonatal onset multisystemic inflammatory disease (NOMID) (11-13). The similarities and differences among these entities are summarized in Table III.

The important skin lesions consist of thickened skin, small fleshy facial papules, gingival hyperplasia and perianal nodules.

We report 19 patients with ISH who presented the typical musculoskeletal manifestations. Unfortunately there was delay in correctly diagnosing patients with this entity; only 5 patients had the right diagnosis before referral, this was reflected in the delay between the age of onset and age at presentation to our hospital.

Thirteen patients were the product of first cousin marriages and 5 families had more than one affected child not included in this series because they were not evaluated in our hospital and we do not have enough information about them. This data supports the autosomal recessive mode of inheritance. Given the current report and previous reports of Arab children (2, 4, 8, 9), we feel that this disease is prevalent in

Saudi Arabia and among Arab children. Comparing the frequency of consanguinity among the parents of children with ISH in this series (68%) and the consanguinity rate in Saudi Arabia (58%) it appears that parental consanguinity only played a small role in the apparent increased frequency of this disorder in Saudi Arabia (14).

The similarity in the consanguinity rate among the population of the study and the general population suggest a possible high trait frequency in the general population. All biological and histopathological studies including electron microscopy findings are nonspecific (4). Radiological findings also are nonspecific (15). Most of our patients had elevated WBC and platelet count, which is not specific. We report more detailed radiological findings. However, all are nonspecific.

The identification of ISH disease-causing mutation in the CMG2 gene may provide insights into the pathogenesis of this disease (6, 7). The analysis of fibroblasts derived from ISH patient suggests that the CMG2 mutation abrogates normal cell interactions with the extracellular matrix (7). One of our patients was proved to have a homozygous mutation.

Various therapeutic strategies have been used but the outcome remains unsatisfactory (10,16). Pencillamine has been tried with limited success. Surgical procedures have been considered as well as intra-lesional steroid injection but with disappointing results (17).

In summary, we have described the largest collection of patients with ISH in the literature. This report confirms that ISH is a systemic progressive inherited lethal disease.

Table III. Differential diagnosis of infantile systemic hyalinosis.

	Winchester syndrome	Farber syndrome	NOMID**	ISH*
Coarse face	+	-	-	-
Corneal opacity	+	+	-	-
Subcutaneous nodule	-	+	-	+
Arthropathy (joint contracture)	moderate	mild-moderate	moderate	severe
Age of onset	infancy	early infancy	birth – early infancy	early infancy

+ present; - absent.

* ISH: infantile systemic hyalinosis, **NOMID: neonatal onset multisystemic inflammatory disease.

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