Original Article

Infantile Systemic Hyalinosis: Variable Grades of Severity

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Abstract

Background: Infantile systemic hyalinosis (ISH) is an autosomal recessively inherited disorder. The classical natural history of the disease is characterised by hypotonia, multiple contractures, skin lesions, osteopenia, joint pain, bone fractures, persistent diarrhoea and growth deficiency. **Materials and Methods:** Two children manifested the severe type of ISH underwent genotypic confirmation. In order to identify which other family members have inherited the disease. We included siblings and cousins in this study. The baseline tool to study other family subjects was based on the phenotypic characterisations of each child. **Results:**. Two children with the severe type of ISH showed craniosynostosis (brachycephaly and scaphocephaly) associated with multiple contractures, progressive joint osteolysis ending up with multiple joint dislocations. The full exome sequencing was carried out, revealing a previously reported heterozygous nonsense mutation c.1294C>T and a novel heterozygous non-synonymous substitution c. 58T>A in *ANTRX2* gene. Three children (sibling and cousins) manifested variable clinical manifestations relevant to ISH. Specifically, asymptoamtic skin and skeletal abnormalities of hypoplastic clavicles and 'shepherd's crook' deformity and coxa vara. **Conclusion:** It is mandatory to perform extensive family pedigree search to detect asymptomatic clinical features in siblings and cousins in families with first degree related marriages. Interestingly, in the mild and the moderate types of ISH, we observed undescribed combination of asymptomatic skin and skeletal abnormalities. This is a comparative study between the severe and the mild/moderate types in a group of children from consanguineous families. Our current study extends the phenotypic characterisations of ISH.

Keywords: ANTXR2 gene mutation, infantile systemic hyalinosis, phenotype, radiology

Introduction

Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disorder characterised with early onset skin lesions followed by multiple contractures. Progressive deposition of amorphous hyaline material in various tissues such as skin, gastrointestinal tract, cardiac muscle, adrenals, skeletal muscles and other vital organs.[1,2] ISH typically presents at birth or within the first few months of life with reduced spontaneous movements secondary to severe pain and progressive joint contractures. Progressive skin thickening, gingival hypertrophy, appearance of hyper-pigmented patches over bony prominences and joints are the main dermatological manifestations.[3] Clinical presentation usually appears at birth or within the first few months, with painful, swollen joint contractures and livid red hyperpigmentation over bony prominences. Pearly papules (predominantly of the face, scalp and neck) and fleshy nodules (particularly in the perianal region) then develop. Gingival hypertrophy and thickened skin are also characteristic features. Osteopenia is often present and results in increased susceptibility to bone fractures. Affected children are susceptible to infections and/or intractable diarrhoea due to protein-losing enteropathy, and many die in infancy from resulting multisystem failure.[1,3,4] Histologically, ISH is also

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characterised by hyaline deposition, but this is more widespread than in JHF and can affect many tissues, including skin, skeletal muscle, cardiac muscle, gastrointestinal tract, lymph nodes, spleen, thyroid and adrenal glands.[5-7] The underlying pathogenesis ISH was previously unknown. Previously, ISH has been postulated to be lysosomal storage disorder.[8] Breier *et al*. referred the disorder to abnormal collagen metabolism and/or defective glycosaminoglycan formation. Hypotonia, osteopenia, bone fractures, deformities, persistent diarrhoea and growth deficiency were a uniform pattern.[1]

ISH; (OMIM 236490) and juvenile hyaline fibromatosis (JHF; OMIM 228600) are autosomal recessive diseases caused by loss-of-function mutations in the anthrax toxin receptor 2 (*ANTRX2* gene also known as capillary morphogenesis protein 2 (*CMG2*) gene (MIM 228600).[1,9] The two variants now represent the disease spectrum called hyaline fibromatosis syndrome (HFS). The onset can appear anytime between birth and late childhood and more severe types of ISH are accompanied by diarrhoea and recurrent respiratory infections.[10] In addition to HFS, mutations in *ANTXR2* have recently been linked to arthritic disease known as ankylosing spondylitis.[11,12] The *ANTXR2* gene is mapped to chromosome 4q21.21 and encodes a 55 kDa is an integrin-like type I transmembrane receptor (capillary morphogenesis protein, is involved in the homeostasis of the extra cellular matrix and plays a role in normal physiology including vascular formation and angiogenesis.[13,14] ANTXR2/CMG2 is a highly-conserved protein among species and is found in four different isoforms that are generated by alternative splicing. The full ANTXR2 consists of an extracellular von Willebrand factor type A (vWA) domain, followed by an immunoglobulin-like domain, a transmembrane domain with 23 amino acids and a tail of 148 amino acids.[15-17] ANTXR2 was reported to bind laminin and collagen VI via a typical metal ion-dependent adhesion site (MIDAS) motif of the vWA domain and to transmit signal to the inside of the cell and was required for lysosomal degradation of collagen VI in the extracellular matrix.[18-20] Several mutations in the MIDAS of the ANTXR2 vWA domain have been found to cause the severe phenotype in the affected patients, leading to abnormal accumulation of collagen VI in patients' tissues resulting in the clinical manifestations of HFS (IFS) associated with fatality occurring often during infancy.[1,17,21] ANTXR2 is expressed in almost all tissues, however, no expression was observed in the brain and thymus, which is consistent with normal cognitive development of the affected individuals.[22] To-date, more than 40 loss-of-function mutations in the *ANTXR2* gene have been identified in more than 150 cases of HFS, showing no ethnic or geographic predisposition, most of them were missense and frameshift mutations scattered along the *ANTXR2* gene.[16,17,23,24]

Materials and Methods

The study protocol was approved and obtained from the Hospital Ethical Committee (Ethics Committee of the Turner Scientific Research Institute (January 5, No. 3/2016, Saint-Petersburg), in addition, informed consent was obtained from the patients' guardians. The records of five children (two boys and three girls), all came from the same geographical region, from families with high consanguinity and inter-related marriages.

The study and family pedigree research was performed by the first author in collaboration with the co-authors in order to document this group of children.

Parents were mostly of the same geographical origin and all family members were inter-related first cousins.

We studied in detail the antenatal and birth histories as well as major events in gestational history such as feeble or hyperkinetic uterine movements. All children showed feeble uterine movement. Sadly speaking, ultrasound studies did not assist for early diagnosis. Oligohydramnios was criteria in three children, and Polyhydramnios was noted in two children.

Details of unusual events around labour (respiratory distress, cyanosis, neonatal convulsions, jaundice and admission baby care units) have been analysed carefully. All children were confined to baby care units and two children manifested neonatal convulsions.

The subsequent course of development included severe motor and fine motor retardation in all children.

Intractable diarrhoea was a common presenting feature particularly in the severely affected children and to a lesser extent in the mild and moderate forms of ISH.

The average age of admission of the severe type of ISH to our departments was between 6 and 8 months.

The recognition of the moderate/mild types was performed through detailed clinical examination of other family subjects. In other words, family pedigree search and clinical examinations of siblings' relatives who manifested mild, but relevant clinical and radiological abnormalities were carried out meticulously.

Multiple and progressive contractures associated with skin changes were the constant stigmata in two children with the severe forms of ISH. A lesser form of the disease (mild/moderate) was noted after the first year of life in their relatives.

Group I. The severe form of infantile systemic hyalinosis

Clinical examinations showed growth deficiency of − 3SD and Cranio-facial dysmorphic features were characteristic findings.

Case 1

The craniofacial dysmorphic features of a-22-month-old boy manifested the severe form of ISH included extensive and severe papulo-nodular skin lesions extending over the fronto-nasal areas, with massive swelling of the lower face and lips, gingival hypertrophy and the ears were massively involved [Figure 1a and b].

Progressive contractures were noted in the same child with ISH at the age of 3. Attempts for passive movements of the joints causing

painful reactions. Violaceous nodules over the sacral prominences of the same patient were associated with hypertrophy around the anus in the form of nodulous swellings (large tumors and nodules/ polypoid lesions around the anus) [Figure 2].

Case 2

A-2-year-old girl presenting with severe manifestations of ISH, showed sparse hair, frontal haemangioma, a severely depressed nasal bridge, deep-seated eyes, hypertrophy and a congested nasal tip, long philtrum and minimal scattered papulo-nodular skin lesions around the nose were also noted [Figure 3a].

Dentinogenesis imperfecta overwhelmed by massive gingival fibromatosis [Figure 3b].

Group II. The mild/moderate forms of infantile systemic hyalinosis

Case 3

A mild type of ISH in a-14-month-old girl (cousin of case-2) showed mild Papulo-erythemaous rash over the nape of the neck [Figure 4a] and noticeable thickening and hyper-pigmentation of the skin over the elbows with mild joint contractures [Figure 4b].

Case 4

A-4-year-old boy (older sibling of case-2), manifested multiple lipoma-like along the anterior abdominal wall [Figure 5a] and mild hyper-pigmentation over the sacral area associated with a small anal nodule [Figure 5b].

Case 5

A-five-year-old-girl (cousin of case-2) presented with minimal skin lesions, normal intelligence, but with abnormal gait.

All children with severe and mild/moderate types underwent additional radiographic study (included, AP and lateral skull, AP spine, AP shoulder joint and AP hands).

Skull radiographs and three-dimensional (3D) reconstruction computed tomography (CT) scan have been organised. The two children with severe ISH showed abnormal craniofacial contour.

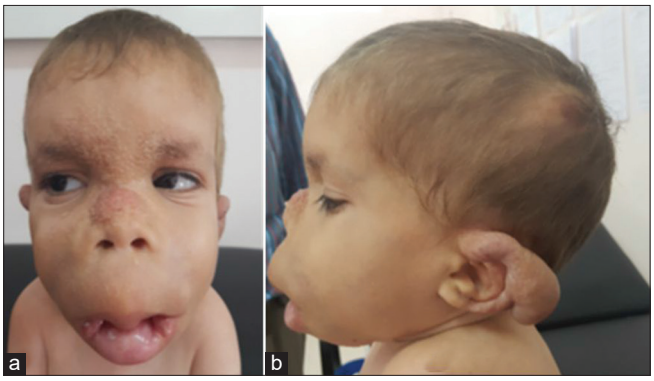

Figure 1: (a and b) The craniofacial dysmorphic features of a-22-month-old –boy (case-1) manifested the severe form of ISH included extensive and severe papulo-nodular skin lesions extending over the fronto-nasal areas, with massive swelling of the lower face and lips, gingival hypertrophy and the ears were massively involved

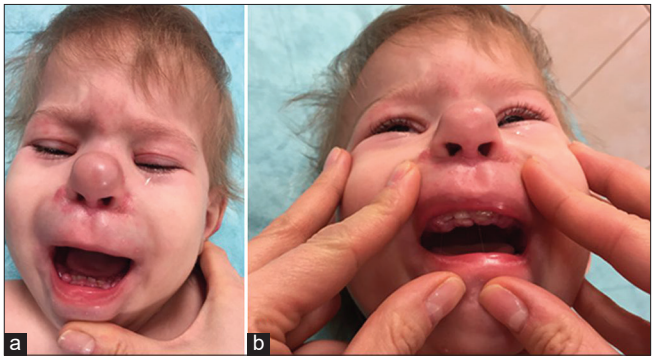

Figure 3: (a and b) A-2-year-old girl (case-2) presenting with severe manifestations of ISH, showed sparse hair, frontal hemangioma, a severely depressed nasal bridge, deep-seated eyes, hypertrophy and a congested nasal tip, long philtrum, and minimal scattered papulo-nodular skin lesions around the nose were also noted (a). Dentinogenesis imperfecta overwhelmed by massive gingival fibromatosis (b)

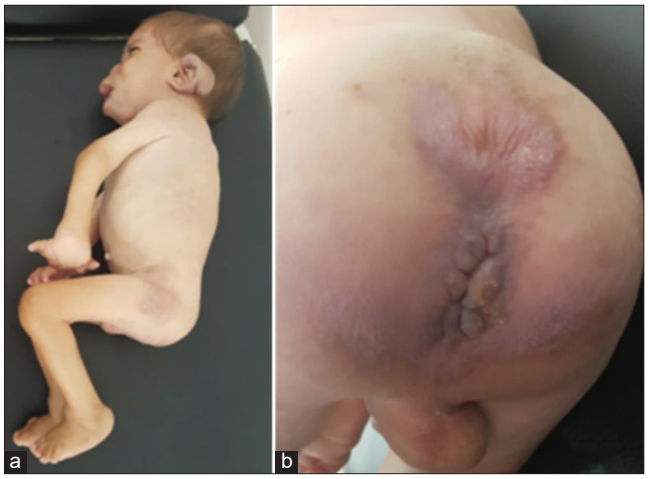

Figure 2: Progressive contractures were noted in case -1 with severe ISH at the age of 3-years. Attempts for passive movements of the joints causing painful reactions (a). Violaceous nodules over the sacral prominences of the same patient were associated with hypertrophy around the anus in the form of nodulous swellings (large tumors and nodules/ polypoid lesions around the anus(b)

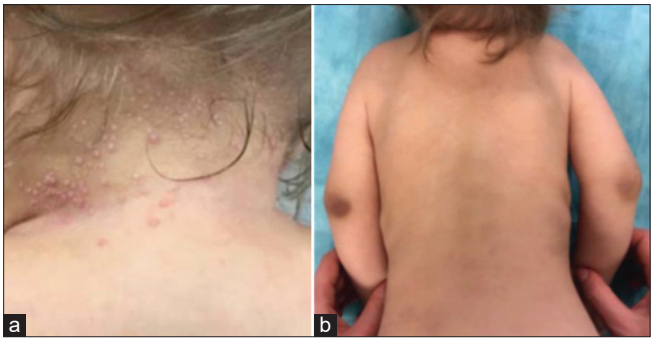

Figure 4: (a and b) A mild type of ISH in a-14-month- old girl (cousin of case-2) showed mild papulo-erythemaous rash over the nape of the neck (a) and noticeable thickening and hyperpigmentation of the skin over the elbows with mild joint contractures (b)

The Lateral skull radiograph of case-1, showed brachycephaly in connection with partial closure of coronals/lambdoid [Figure 6a].

The Lateral skull radiograph of case-2 showed scaphocephaly in correlation with sagittal suture synostosis [Figure 6b].

The 3D reconstruction CT of the skull of case-2 showed total synostosis of the sagittal suture

With mild plagiocephaly [Figure 6c].

AP spine and shoulder radiograph of case-1 showed severe osteolysis of the shoulder and hip joints were noted [Figure 7a]. AP spine radiograph of case-4. Who manifested moderate type of ISH showed a less important malformation complex except for bilateral and symmetrical hypoplasia of the clavicles (arrows) [Figure 7b].

The skeletal phenotype of case-1 with severe type of ISH; AP radiographs of the shoulders, humero-radial and pelvis showed multiple dislocations secondary to massive osteolysis along the major joints of the shoulders, elbows and hips [Figure 8a-c].

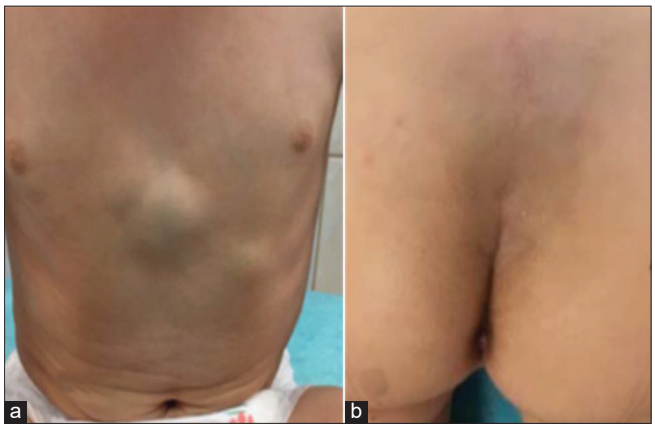

Figure 5: (a and b) A-4-year-old boy (mild type of ISH) (older sibling of case-2), manifested multiple lipoma- like along the anterior abdominal wall (a) and mild hyper-pigmentation over the sacral area associated with a small anal nodule (b)

AP pelvis radiograph of case-5 showed "shepherd's crook" deformity with severe form of coxa vara [Figure 8d].

Results

Laboratory investigations revealed elevated white blood corpuscles (WBCs) in two children with the severe, in addition to hypochromic microcytic anaemia because of the malabsorption, intractable diarrhoea, elevated platelets as well as elevated alkaline phosphatase. Hypo-albuminuria has been detected in one child. WBCs were normal in the mild/moderate types.

Genetic findings

Comprehensive exome sequencing was carried out to look for mutations in the clinically significant part of the human genome based on the clinical picture. Compound heterozygous mutations (c.1294C>T; p. Arg432*/c.58T>A; p. Trp20Arg) were identified in the *ANTXR2* gene: The c.1294C>T in exon 15 is a nonsense mutation resulting in a premature stop codon and protein truncation, which was previously reported in a Mexican patient with milder manifestations of systemic hyalinosis.[25] The c.58T>A (p. Trp20Arg) missense mutation in exon 1 is novel, predicted to result in the replacement of the conserved tryptophan residue by an arginine. The c.58T>A (p. Trp20Arg) mutation has never been reported in the literature or in the 1000 Genomes Project, dbSNP and Exome sequencing databases and so on, so we suggest it is a novel mutation.

Furthermore, the Tryptophan 20 residue of ANTXR2 is highly conserved among various species, suggesting that this substitution may cause a major impairment of ANTXR2 structure and activity. This mutation is also predicted to be probably damaging using online *in silico* prediction programs such as PolyPhen-2 (http://genetics.bwh.harvard.edu/pph 2/) and scale-invariant feature transform algorithm (http://sift.jcvi.org/). We were unable to collect sample and perform whole exome sequencing analysis for the second child.

Discussion

Previous studies by Alfi *et al*. described two Mexican sisters whose parents were second cousins.[26] During the first week of

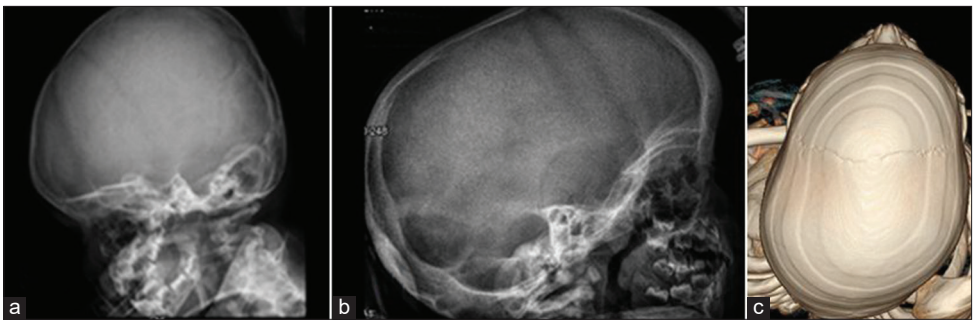

Figure 6: (a - c) Skull phenotypes of the severe types :The Lateral skull radiograph of case-1, showed brachycephaly in connection with partial closure of coronals/lambdoid (a). Lateral skull radiograph of case-2 showed scaphocephaly in correlation with sagittal suture synostosis (b). 3 D reconstruction CT of the skull of case-2 showed total synostosis of the sagittal suture with mild plagiocephaly (c)

life both sibs seemed to cry with pain when they were moved, and by the age of 2 months, one sib had developed flexion contractures in the arms and legs. Their skin appeared thick, especially over the hands, with redness at the creases. Over the next year contractures increased in one sib and she developed sausage-shaped fingers. Her gums were hypertrophied and nodules developed on the lips and ears. Hyperpigmentation occurred over the joints of the fingers. Both children were of short stature. At autopsy in one child EM showed distension of the endoplasmic reticulum and mitochondrial changes. Hyaline deposits in the intestinal wall, the thymus, and to a lesser extent elsewhere were noted. A patient reported by Thauvin-Robinet *et al*. survived for 39 months. Intractable infantile diarrhoea was the presenting feature.[27] Stucki *et al*. reported a further case and histological investigations suggested that the amorphous material accumulating in the skin and articular soft tissues may originate from the blood circulation.[28] Three unrelated Brazilian patients reported by Felix *et al*., were also found to have hyaline deposits.[29]

Zolkipli *et al*. described a case with evidence of proximal muscle weakness. Muscle biopsy revealed myopathic changes.[30] Larralde *et al*. reported a form of JHF appears to have the infantile form of the condition.[31] The onset appeared to be around 6 months of age, but at 8 months of age there was severe skin involvement. A case falling between ISH and JHF was reported by Urbina *et al*.[32] Hanks *et al*.[1] demonstrated mutations in the CMG2 gene encoding capillary morphogenesis protein 2. None of the above-mentioned studies showed a similar constellation of deformities of multiple dislocations and a Shepherd's crook deformity as seen in our current patient. Shepherd's crook deformity has been described as a diagnostic radiological feature seen in patients with McCune Albright syndrome (which is characterised by the pathological replacement of normal bone with fibro-osseous tissue).[33]

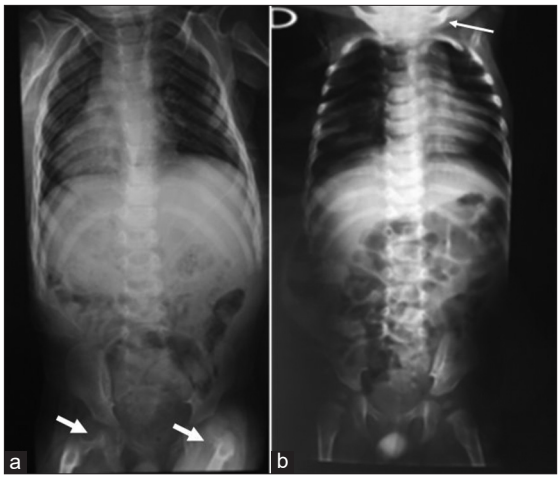

Figure 7: (a and b) Comparing two unrelated male patients (case -1 and case-4) ; AP spine and shoulder radiograph of case -1 (severe ISH) showed severe osteolysis of the shoulder and hip joints (fig 7,a). AP spine radiograph of case-4 (who manifested the moderate type of ISH showed a less malformation complex except for bilateral and symmetrical hypoplasia of the clavicles (arrows) (b)

So far, more than 40 mutations in the *ANTXR2* gene have been reported in the literature. These mutations were classified into four major classes. Class I, consists of mutations within the vWA domain that do not affect plasma membrane folding or targeting but impair ligand binding.[17,34] Class II covers other mutations in either Ig-like or vWA domains that affect folding and stability of the protein.[16,35] Class III contains mutations that insert a premature stop codon resulting in mRNA degradation.[16,17,21] Class IV includes mutations located in the cytosolic tail that affect the function of ANTXR2 but have no effect on either the mRNA level, or the plasma membrane localisation of the protein[1,36-38]

Genetic analysis of one affected child revealed compound heterozygous mutation (c.1294C>T; p. Arg432*/c.58T>A; p. Trp20Arg) in the ANTXR2 gene. The c.1294C>T was reported once in the heterozygous form in combination with another heterozygous mutation in a Mexican patient manifesting mild HFS.[25] The c.1294C>T is a nonsense mutation belonging to *ANTXR2* class III mutations, resulting in the insertion of a premature stop codon at amino acid residue 432 and predicted to lead to unstable mRNA that is rapidly degraded by the nonsense-mediated degradation (NMD).[17] The c.58T>A transition is a novel mutation resulting in the replacement of a highly conserved amnio acid residue, presumably located in the von Willebrand (vWA) domain that is essential for ligand binding, including collagen VI.[20] This mutation is predicted to be probably damaging using online *in silico* prediction programs, suggesting that this substitution could cause a major impairment of ANTXR2 structure and activity. To the best of our knowledge, the c.58T>A mutation has never been reported and is absent from gene mutation databases. The presence of

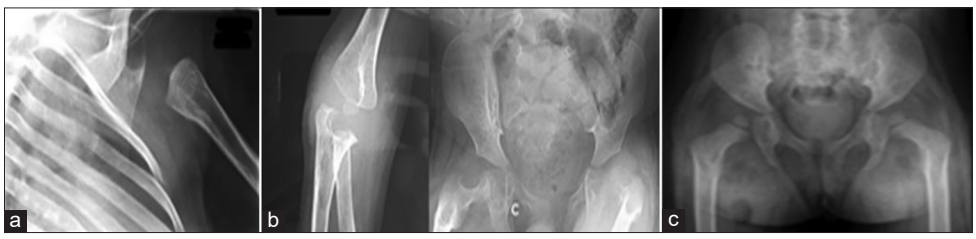

Figure 8: Comparing the joint involvement in the severe type (a,b,c) and the mild/moderate type (d). AP radiographs of case-1 of the shoulders, humero-radial and pelvisshowed multiple dislocations secondary to progressive osteolysis along the major joints of the shoulders, elbows and hips (a,b,c). AP pelvis radiograph of case-5 showed 'shepherd's crook' deformity with severe form of coxa vara (d)

this novel combination of the two mutations could explain the spectrum of ISH manifestations in this patient.

Conclusion

Hypotonia, multiple contractures, skin lesions, osteopenia, bone fractures, persistent diarrhoea

and growth deficiency are the classical signs and symptoms which are usually described in the literature, and mostly reported in patients with the severe type of ISH. Nevertheless, craniosynsotosis and multiple dislocations, are new findings in severe types of ISH. In our current study, we observed a new constellation of skeletal deformities such as hypoplastic clavicles, 'shepherd's crook' deformity (coxa vara), specifically in the mild and the moderate forms of ISH. The severe type of ISH has been encountered in two children. However, nevertheless siblings and cousins manifested less severe skin and articular abnormalities in conjunction with lesser degrees of other symptoms such as diarrhoea. In other words, this sort of diverse clinical manifestations appears to be a multitude of disease manifesting asymptomatic carriers among the siblings and relatives of the index cases. Surprisingly, the genetic carriers (with late manifestation of the disease) are more frequent than the subjects with the severe type of ISH. These findings have been confirmed in our previous publications in families with autosomal recessive pattern of inheritance.

We believe, the term "rare disease" is only applicable to the severe cases. Whereas the mild and moderate types of ISH are more frequent and mostly passed unnoticed. Although there are various studies describing the severe type and the juvenile type of systemic hyalinosis as separate clinical entities. Our findings were based on extensive family pedigree search associated with careful examination of different asymptomatic family subjects. For instance, the mild/moderate types manifest minimal pathological presentations, which represent a real challenge to paediatricians, physicians and geneticists. We wish to stress that the confusing clinical presentation of children with mild ISH has made paediatricians and physicians to underestimate the frequency of such slowly progressing but a serious heritable disorder with a devastating outcome. Genetic tests for the mild group of ISH, almost yielded negative results, thence-fore such a misleading parameter added another burden for these families because of the unexplained skeletal and extra skeletal long term and slowly progressing genetically programmed abnormalities.

Acknowledgements

We wish to thank the families of the patients for their collaboration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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