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Original Article

Hyaline fibromatosis syndrome: a rare, yet recognizable syndrome

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ABSTRACT

Background. Hyaline fibromatosis syndrome is a rare autosomal recessive disorder caused by *ANTXR2* pathogenic variants. The disorder is characterized by the deposition of amorphous hyaline material in connective tissues. The hallmarks of the disease are joint contractures, generalized skin stiffness, hyperpigmented papules over extensor surfaces of joints, fleshy perianal masses, severe diarrhea, and gingival hypertrophy. The severity of the disease varies and prognosis is poor. No specific treatment is yet available. Most patients with the severe form of the condition pass away before the second year of age. In this study, we describe the clinical and molecular findings of a cohort of seven hyaline fibromatosis syndrome patients who were diagnosed and followed up at a single tertiary reference center in Turkey.

Methods. Genomic DNA was extracted by standard salting out method from peripheric blood samples of three patients. In one patient DNA extraction was performed on pathology slides since peripheric blood DNA was not available. All coding exons of the *ANTXR2* were amplified and sequenced on ABI Prism 3500 Genetic Analyser.

Results. Sanger sequencing was performed in 3 patients and homozygous c.945T>G p.(Cys315Trp), c.1073dup p.(Ala359CysfsTer13), and c.1074del p.(Ala359HisfsTer50) variants were identified in *ANTXR2*. All patients passed away before the age of five years.

Conclusions. HFS is a rare, progressive disorder with a broad phenotypic spectrum. HFS can be recognized easily with distinctive clinical features. Nevertheless, it has poor prognosis with increased mortality due to severe clinical decompensation.

Key words: Hyaline Fibromatosis Syndrome, juvenile hyaline fibromatosis, infantile systemic hyalinosis, *ANTXR2*, *CMG2*.

Hyaline fibromatosis syndrome (HFS, OMIM #228600) is an autosomal recessive, rare condition, characterized by hyaline deposits in multiple organ systems.[1] The term encompasses two disorders previously known as juvenile hyaline fibromatosis and infantile systemic hyalinosis, the latter representing the severe form of the former.[2] HFS is caused by homozygous or compound heterozygous pathogenic variants in *ANTXR2* (anthrax toxin receptor-2, OMIM *608041), also known as *CMG2* (capillary morphogenesis protein gene-2) localized on chromosome 4q21.[1]

HFS presents in early infancy and clinical features include stiff skin, subcutaneous nodules, and progressive and painful joint contractures due to continuous accumulation of proteinaceous material in the dermis, as well as pearly papules in the face, neck, and perianal region, hyperpigmented patches over bony

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prominences of joints and gingival hypertrophy as the disease progresses. Mild dysmorphic facial features including coarse face, macrocephaly, frontal bossing, ear malformations, and depressed nasal bridge may be seen in patients with HFS, some of which appear gradually as the patients advance in age.[1-5] The disease has a variable course. While some patients present in early infancy with systemic and visceral involvement eventually leading to early demise in the majority, other patients present later in life with a milder form affecting only the face and digits. In this study, the clinic-pathological and molecular features of seven HFS patients are described.

Material and Methods

The study protocol was approved by Hacettepe University Ethics Committee, Ankara, Türkiye (GO 04-30/2022). The patients clinically diagnosed with HFS between the years 2000-2022 were included in the study. The clinical and radiographic findings were reviewed retrospectively and sequence analysis of *ANTXR2* was performed when DNA sample was available. Written informed consents were taken from the parents.

Of seven patients with a clinical diagnosis of HFS, DNA sample was available in four (Patient 1, 5, 6 and 7) of them in whom Sanger sequencing of *ANTXR2* was performed. Segregation analysis was performed in two families (Patient 6 and 7). Sanger sequencing images are shown in Supplementary Fig 1. Genomic DNA was extracted by standard salting out method from peripheral blood samples. DNA was extracted from formalin-fixed paraffin-embedded skin tissue in patients whose peripheral blood samples were not available. The coding sequence of *ANTXR2* including at least 20 bp of adjacent untranslated regions or intronic sequences was amplified from genomic DNA. PCR products were evaluated by agarose gel electrophoresis. After PCR purification, The BigDye Terminator v.3.1 Cycle Sequencing Kit was used for the chain termination method, and reaction products were applied to ABI Prism 3500 genetic analyzer (Thermo Fisher Scientific, Waltham, MA, USA). The detected variants were classified according to the ACMG (American College of Medical Genetics and Genomics) criteria.[6]

For Patient 1, Sanger sequencing of *ANTXR2* did not reveal any pathogenic variant in the exons where PCR amplicons could be formed (except exon 8 and 9). A deletion encompassing exon 8 and 9 was suspected, but MLPA probe for *ANTXR2* was not available. We used control, maternal, paternal, and patient samples and a decreased amplicon was detected in parents compared to that of the control, suggesting the presence of a heterozygous deletion of these regions. So, we designed several primers to reveal the breakpoints of the deletion between the exon 7 and 10. The list of primers is shown in Supplementary Table I. First, intron 7 was divided into six parts. While the amplicons of the first five parts were formed, the sixth part was not observed in the patient. Later, two more primer pairs were designed in part 6, and they formed amplicons. Primers were also designed for a region within intron 9, and no amplicon was formed confirming that a part of intron 9 was also located within the deletion region. Agarose gel appearances of the PCR amplicons are shown in Fig 1. A deletion between intron 7, part 6, section 2 and exon 10 was suspected, but PCR amplicon could not be formed between them.

Microarray analysis was performed in one patient (Patient 1) to investigate copy number variations. Microarray analysis using Agilent Technologies 4x180K platform (Agilent Technologies, Santa Clara, CA, USA) was performed to detect exon and whole-gene deletions or duplications. Data analysis was done using Agilent scanner and Feature Extraction software. Results were processed by Agilent Cytogenomics software. Detected CNVs were analyzed using in-house data and public databases, such as DECIPHER, DGV, and ClinVar.

Table I. Clinical, radiological and genetic features of the seven patients.

Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Summary
Gender	Male	Male	Male	Male	Male	Male	Male	7/7 male (100%)
Consanguineous parents	+ (Same village)	+	+	+	+ (Same village)	+	+	7/7 (100%)
Onset of symptoms	2 months	1 week	3 weeks	6 months	24 months	1.5 months	2 weeks	Median 1.5 months
Survival	16 months	18 months	9 months	18 months	54 months	18 months	10 months	Median 18 months
Weight	4.7 kg (-3.5 SD)	7.1 kg (-1.7 SD)	5.1 kg (-2.5 SD)	4.8 kg (-6.9 SD)		5.6 kg (-1.4 SD)	6.1 kg (-1.9 SD)	
Length		65 cm (-2.2 SD)	64 cm (-0.6 SD)	55 cm (-7.7 SD)	NR	60 cm (-1.2 SD)	61 cm (-2.5 SD)	
(Age at evaluation)	(6 months)	(8 months)	(5 months)	(17 months)		(4 months)	(6 months)	
Coarse face	-	-	-	+	-	-	+	2/7 (28.5%)
Gingival hypertrophy	+	+	-	+	+	-	+	5/7 (71.4%)
Thickened skin	+	+	+	-	+	+	+	6/7 (85.7%)
Hyperpigmented macules	+	+	+	+	+	+	+	7/7 (100%)
Pearly papules	+	+	+	+	+	+	+	7/7 (100%)
Perianal plaques	+	+	-	+	+	-	+	5/7 (71.4%)
Cutaneous nodules	+	+	+	+	+	-		5/7 (71.4%)
Joint contractures	+	+	+	+	+	+	+	7/7 (100%)
Chronic diarrhea	-	+	+	+	NR	+	+	5/6 (83.3%)
Excessive diaphoresis	+	+	-	-	-	-	-	2/7 (28.5%)
Osteopenia	+	NR	-	+	NR	+	-	3/5 (60%)
Periosteal reaction	+	NR	-	-	NR	+	+	3/5 (60%)
Skin biopsy	Amorphous eosinophilic hyaline accumulation	-	-	-	PAS+, amorphous eosinophilic hyaline accumulation	-	-	
ANTXR2								
NM_058172.6	Probable	DNA	DNA	DNA	13	11	13	
Exon	deletion of exon 8 and 9	was not available	was not available	was not available				
Nucleotide change					c.1074del	c.945T>G	c.1073dup	
Amino acid change					p.Ala359HisfsTer50	p.Cys315Trp	p.Ala359CysfsTer13	
ACMG classification					Pathogenic	VUS	Pathogenic	

cm: centimeter, kg: kilogramme, NR: not recorded, PAS: Periodic acid-Schiff, SD: standard deviation, VUS: variant of unknown significance.

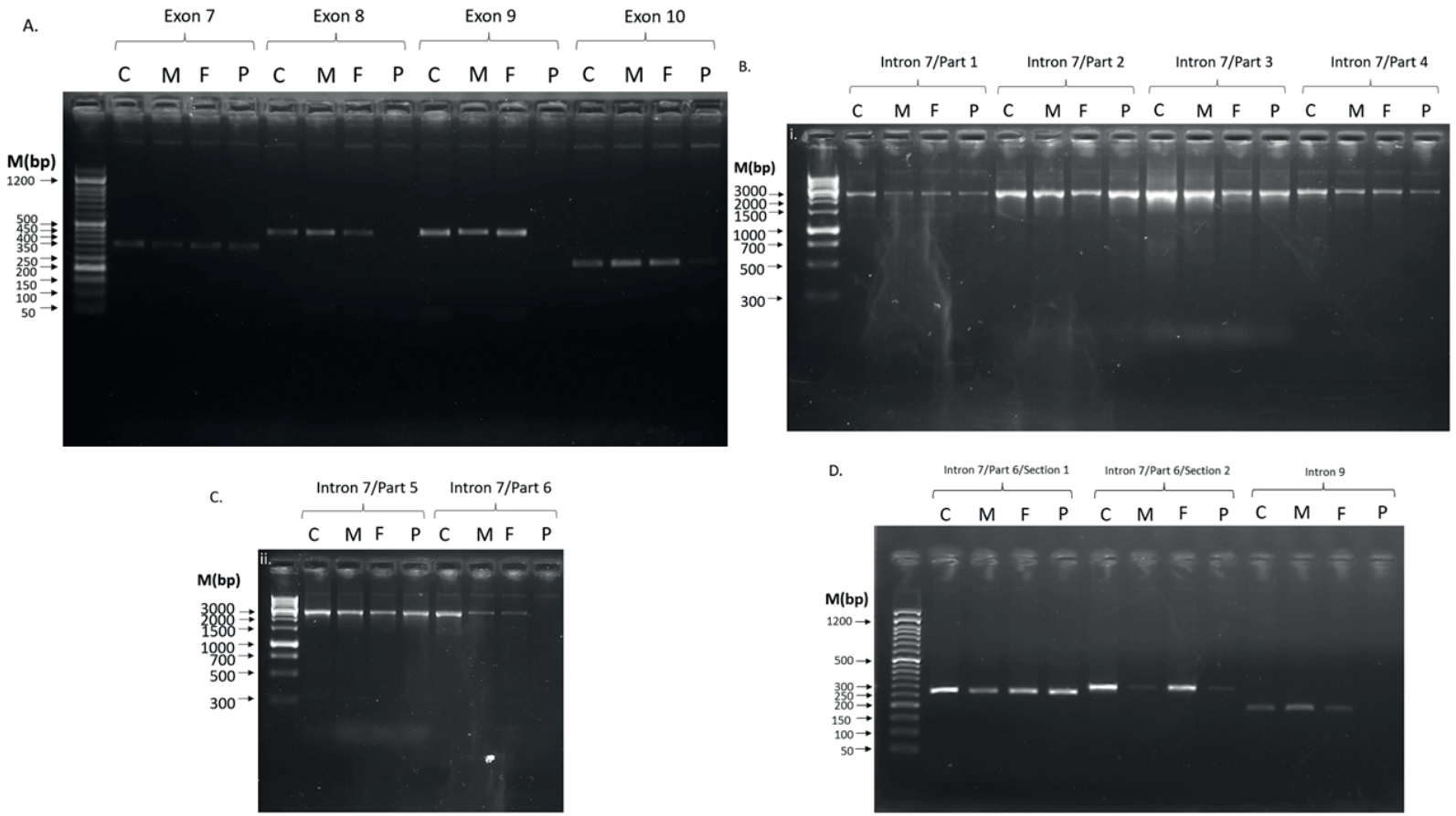

Fig. 1. For patient 1, while PCR amplicons of exon 7 and exon 10 occurred, PCR amplicons of exon 8 and exon 9 were not formed (A). Agarose gel appearance of the PCR reaction were performed with 6 pairs of primers generated from inside intron 7 to find the deletion breakpoint in both panels. PCR reaction was performed with primers designed for the first 4 parts of intron 7 using control, maternal, paternal, and patient samples. At the end of this PCR reaction, the PCR amplicon formed for all samples (B). PCR reaction was performed with primers designed for the last 2 parts of intron 7 using control, maternal, paternal, and patient samples, and PCR amplicons generated of the control, mother, and father samples for both parts (C). However, no amplicon formed in the PCR reaction was performed with the patient sample using the last primer pair. Agarose gel appearance of PCR amplicons was generated with primers designed from part 6 of intron 7 and inside intron 9 to get even closer to the deletion breakpoint. As a result of the PCR reactions performed using these 3 different primer pairs, PCR amplicons occurred in the control, maternal and paternal samples, while no PCR amplicon showed in the region covering intron 9 in the patient (D).

C: Control, M: Mother, F: Father, P: Patient

Results

In this study, all seven patients were male. The parents of the patients were either consanguineous or from the same village. The most common complaints of the patients on admission were progressive joint contractures and irritability, with symptoms manifesting as early as 1 week (median age: 1.5 month). Four patients had dysmorphic features including coarse face, wide and depressed nasal bridge, anteverted nares, long philtrum, thin lips or gingival hyperplasia. All patients exhibited joint contractures, hyperpigmented macules over extensor surfaces of joints and pearly papules in face, neck or perianal region. Thickened skin was detected in six patients and cutaneous nodules were detected in five patients. Two patients also experienced excessive diaphoresis, while chronic diarrhea was present in five patients. Radiographic findings revealed osteopenia in three patients and periosteal reaction in three patients. In Patient 3, intestinal wall thickness was detected on x-ray, which was further confirmed with ultrasound. Furthermore, skin biopsies from two patients showed Periodic acid-Schiff (PAS) positively stained amorphous eosinofilic hyaline accumulation in the papillary dermis. Unfortunately, all patients died before reaching the age of 5 (median age at death: 18 months), due to respiratory infections, septicemia or electrolyte imbalance.

Three variants in the *ANTXR2* gene were detected in three patients (Patient 5: c.1074del, p.Ala359HisfsTer50, Patient 6: c.945T>G, p.Cys315Trp and Paitent 7: c.1073dup, p.Ala359CysfsTer13). Sanger sequencing and microarray analysis did not reveal any pathogenic variant in Patient 1.

The clinical, radiographic, and genetic findings of patients with a clinical diagnosis of HFS are summarized in Table I. The patient photographs, radiographies and microscopic evaluation of the skin biopsy for patient 5 are shown in Fig 2, Fig 3, and Fig 4 respectively.

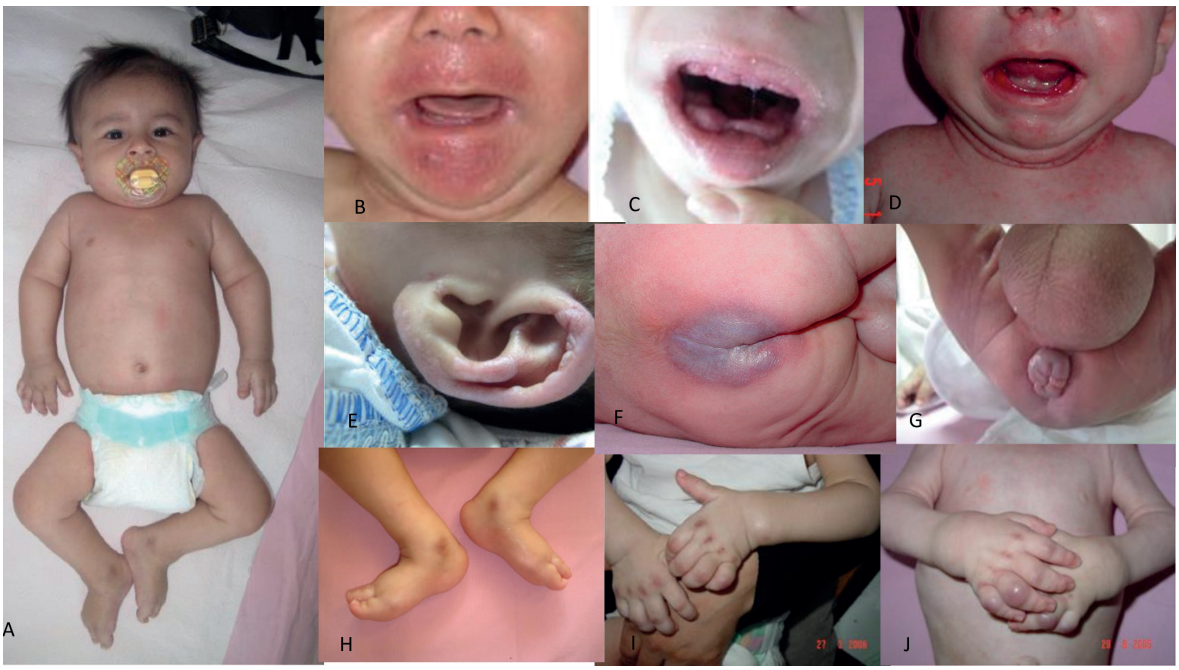

Fig. 2. Photographs of the six patients in this cohort are shown. Note the frog leg position of low extremities, patient 6 (A), perioral erythematous pearly lesions, patient 5 (B), gingival hypertrophy, patient 4 (C), pink pearly papules on perioral region and neck, patient 1 (D), the thickness of auricle, patient 4 (E), perianal purplish plaques, patient 1 (F), perianal fleshy lesion and hydrocele, patient 4 (G), purplish lesions on malleolar region, patient 3 (H), purplish lesions on dorsum of the metacarpophalangeal and interphalangeal joints, patient 2 and 1, respectively (I, J).

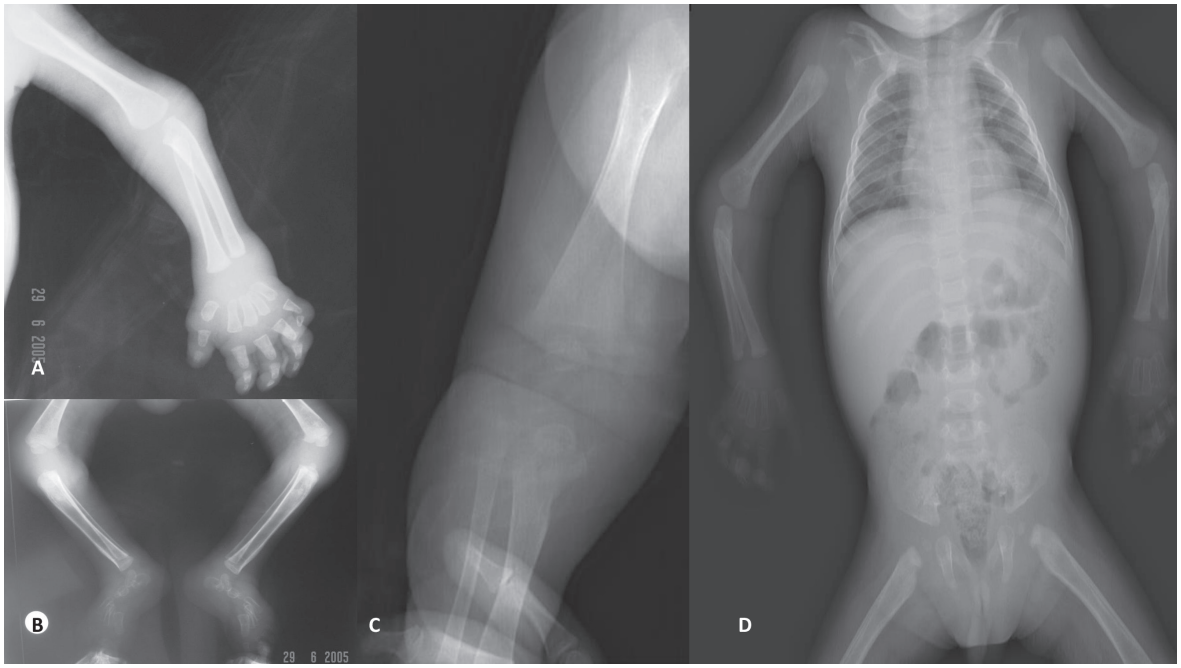

Fig. 3. X-ray images reveal osteopenia, camptodactyly, and periosteal reactions.
(A, B: patient 1, C: patient 6, D: patient 7).

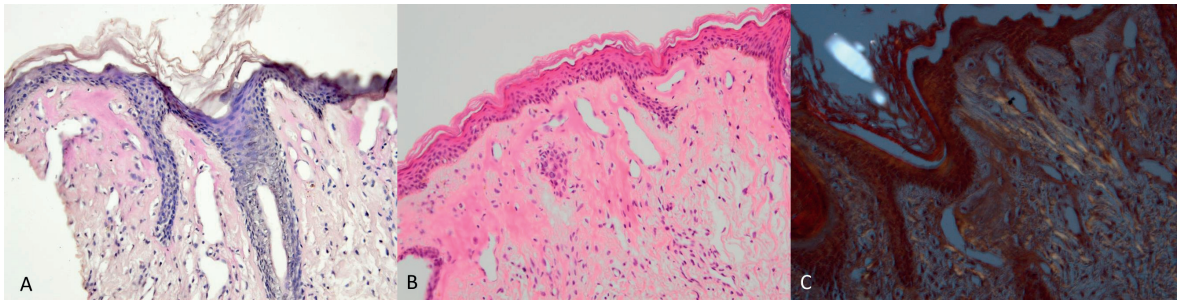

Fig. 4. Microscopic evaluation of skin biopsy for patient 5 is shown. A small amount of PAS-positive (B, 200x), hyalinized amorphous substance accumulated in the papillary dermis accompanied by few (myo) fibroblasts (A, H&E 200x). To exclude amyloid deposition, note the absence of green birefringence under polarized light in Congo red stain (C, Congo red under polarized light, 200x).

Discussion

HFS is a rare, progressive genetic disorder caused by loss-of-function mutations in *CMG2*, also known as *ANTXR2*.[4,7] The name, *ANTXR2*, stems from its well-documented role in binding and endocytosis of Bacillus antracis toxins.[8,9] To date, 116 HFS patients with a confirmed molecular diagnosis, have been reported.[10] In this report, we aimed to further expand the clinical and molecular spectrum of this rare disorder by presenting seven new patients and a new variant of *ANTXR2* gene.

The gene, *ANTXR2*, encodes a single-pass transmembrane protein and this protein contains an extracellular N terminal von Willebrand A domain, an immunoglobulin-like domain, a transmembrane domain, and a cytosolic tail.[11] von Willebrand A (vWA) domain binds to both laminin and collagen IV, suggesting that the protein interacts with

the extracellular matrix.[3,11] ANTXR2 is an important regulator of collagen VI homeostasis and mediates its intracellular degradation.[12] Accumulation of collagen VI is known to lead to fibrosis in tissues, and inactivating extracellular metalloproteases (MMP).[12] Why some body parts are particularly sensitive to the effects of loss-of-function mutations of *ANTXR2* is still unknown. However, it is suggested that in HFS patients, collagen IV accumulates in certain body parts and tissues and this accumulation leads to progressive loss of tissue integrity and function.[12,13]

HFS was first described by Murray et al.[14] in 1873 as molluscum fibrosum. Since then, many different terms have been used for this disorder. While early-onset severe forms were called 'infantile systemic hyalinosis' mild forms were called 'juvenile fibromatosis syndrome'. These two entities were suggested to represent different degrees of severity of a single clinical entity and therefore were merged under one name: "Hyaline fibromatosis syndrome".[2,15]

It is known that HFS is relatively common in the Turkish ethnicity.[2] Casas-Alba et al.[2] reported a cohort of 84 HFS patients, and Turkish ethnicity was the second most common ethnicity with a total 12 patients (%14.2), after Indians. HFS is equally seen in males and females.[3] Interestingly all seven patients in this study were male probably due to the small size of the patient cohort.

The diagnosis of HFS is based on the clinical features, biopsy findings, and genetic tests. Among the reported 116 patients, the most common clinical feature was joint contracture/stiffness with a frequency of 95%.[10] All seven patients in our cohort had joint contractures consistent with the literature.

Gingival hypertrophy is a common finding and thickened skin can also be seen.[1,3] All seven patients in this report exhibited different degrees of skin findings. Hyperpigmented macules and pearly papules were the most common cutaneous findings in our cohort and detected in all patients (100%), while they were observed in 35% and 37% of the other reported patients, respectively. The frequency of thickened skin was 85.7% and it was also higher than other reported patients (26%). Gingival hypertrophy and cutaneous nodules were detected with a similar frequency to the literature.[10]

Central nervous system involvement is not an expected finding, due to the absence of *ANTXR2* expression in the brain.[4] Intellectual disability has never been reported in HFS.[10] In patient 4, wide anterior fontanelle, preauricular skin tag, ventricular septal defect and cleft palate were detected, additionally. While wide fontanelle and skin tags are reported features in HFS, cleft palate and VSD have never been reported before.[1,16] These findings may be a rare feature of HFS or may be a part of an additional genetic disorder. Since we could not perform other comprehensive genetic tests, we cannot rule out another accompanying disorder.

Failure to thrive is a common finding among HFS patients. Some of them have severe protein-losing enteropathy.[1] Chronic diarrhea was present in 52% of the reported patients[10] and in the present study it was present in five (71%) of our patients. Intestinal biopsy showed villous atrophy, edema, hyalinosis, and lymphangiectasia in these patients.[1]

Biopsy findings are mainly non-specific but worthwhile in the correct clinical setting. Skin biopsy shows a PAS-positive amorphous eosinophilic substance thought to contain glycoproteins and collagen.[1] Hyaline deposits are also seen in many other tissues including the dermis, intestines, skeletal muscles, heart, trachea, esophagus, stomach, lymph nodes, adrenals, thyroid, spleen, and thymus.[4,17] It is important that specific biopsy findings may not be seen in the early stages of HFS[1,13] as was the case in the first biopsy of Patient 5 in the present study. In Patient 5, PAS+ hyaline accumulation was demonstrated in the second skin biopsy.

In 2009, Nofal et al.[3] developed a grading system for HFS and Denadai et al.[15] modified

this system in 2012. According to this modified grading system, HFS was classified into four grades: mild, moderate, severe, and lethal.[15] While grade 1 included skin and/or gingival involvement, grade 2 included joint and/or bone involvement, additionally. Internal organ involvement is seen in grade 3. Grade 4 is the most severe form and included organ failure and/or septicemia.[15] According to this grading system, six of the seven patients in this study are classified in group 4, and all passed away before the age of 2 years, due to organ failure or septicemia. Only one patient (Patient 5) survived until 56 months.

HFS has a poor prognosis and most of the patients with severe/lethal form die before the age of two, due to respiratory tract infections, septicemia, organ failure, or intractable protein-losing diarrhea.[3] Today, no specific treatment is available and the treatment is mainly palliative. Pain management and nutritional support are important for these patients. Physiotherapy may not be tolerated due to severe intractable pain. Surgical excision for gingival hypertrophy and large, ulcerated subcutaneous nodules may be performed. Genetic counseling is quite important and it should be explained to parents that this rare disorder has a 25% possibility of recurrence and preimplantation genetic diagnosis may be an option, particularly in countries with a high consanguineous marriage rate like Turkey.

In this study, we demonstrated four variants in the *ANTXR2* gene in four patients whose DNA samples were available. The two frameshift variants in exon13 (c.1073dup and c.1074del) were hotspots for HFS.[2,13] The other missense variant (c.945T>G) has also been previously reported.[13] We described the deletion of exons 8 and exon 9 in the *ANTXR2* gene. Although large deletion and entire exon deletion have previously been reported in HFS patients in the literature[10,15,18], a deletion involving exon 8 and exon 9 has never been reported. When removing the minimum deleted region according to the reference genome, approximately 2000 base amplicon would be obtained in PCR using intron 7 part 6 section 2 forward and exon 10 reverse primers, but we were unable to amplify this region that would show the deletion breakpoint. We suggest that this may be due to an additional structural variant (inversion, repeat sequence insertion, etc.). We could not delineate the breakpoints of a probable deletion in Patient 1 with the aid of other genetic tests (such as MLPA, qPCR, optical genome mapping or whole genome sequencing). In addition, we could not perform Sanger sequencing to three patients since their DNA samples were not available. These are the limitations of the present study.

In conclusion, HFS presents a significant challenge in clinical management, as there is currently no cure for this rare genetic disorder. The focus of treatment is primarily on providing supportive care and addressing the various medical complications that may arise. A multidisciplinary approach involving healthcare professionals from different specialties such as dermatology, orthopedics, algology and genetics is essential in order to effectively manage the diverse symptoms and complications associated with the condition. Symptomatic treatment may include surgical intervention for contractures, physical therapy to improve joint mobility, and management of skin lesions. Additionally, close monitoring and management of potential complications such as growth retardation, joint contractures, and respiratory issues are crucial in providing comprehensive care for individuals affected by HFS. While there is currently no definitive cure, ongoing research and advancements in medical knowledge offer hope for improved management and quality of life for patients with this condition.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2024.4511

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Ethical approval

The study protocol was approved by Hacettepe University Ethics Committee, Ankara, Türkiye (GO 04-30/2022).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: TD, PÖŞK, GEU, KB; data collection: TD, HNG; analysis and interpretation of results: HNG, KK, ÖT, PÖŞK, GEU, KB; draft manuscript preparation: TD, HNG, KK, ÖT, PÖŞK, GEU, KB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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