Gingival Hypertrophy in a Child with Hyaline Fibromatosis Syndrome

Gingivna hipertrofija u djeteta s hijalinim fibromatoznim sindromom

Abstract

Hyaline fibromatosis syndrome (HFS) is a rare autosomal recessive genetic disorder characterized by accumulation of hyalinized fibrous tissue with cutaneous, mucosal, osteoarticular, and systemic involvement. The condition is caused by a mutation of ANTXR2 gene that results in a faulty synthesis of a transmembrane protein which leads up to excessive deposition of hyaline material in extracellular space. The first signs may be present at birth or appear during infancy, and joint stiffness is the first, most common, symptom. Other manifestations include joint contractures, hyperpigmented macules over bony prominences of the joints, and gingival hypertrophy. The symptom that raises suspicion of HFS is present later, along with subcutaneous growths. The progression of the disease includes enteropathy with extensive protein loss, chronic diarrhea and frequent infections. We present a case of a five-year-old girl with severe gingival hypertrophy that caused difficulties in eating and speaking. To the best of our knowledge, this is also the first patient in Croatia with a confirmed ANTXR2 gene mutation described in the literature.

Introduction

Hyaline fibromatosis syndrome (HFS) is an extremely rare autosomal recessive disorder which appear in infancy or childhood. It is characterized by excessive deposition of amorphous hyaline substance in numerous tissues and organs, with the exception of brain tissue. HFS is caused by a mutation of the ANTXR2 gene (Anthrax Toxin Receptor - 2) located on chromosome 4q21, which encodes a transmembrane cell receptor that participates in strengthening and supporting connective tissue by reacting with the extracellular matrix (1). This transmembrane protein is called CMG2 (Capillary Morphogenesis Protein Gene - 2) and has four components. The extracellular component of the receptor consists of the von Willebrand type A domain (vWA), which continues to the immunoglobulin-like domain, followed by the transmembrane domain and finally the intracellular cytoplasmic tail (2).
ANTXR2 was named after primarily being discovered as a receptor for the anthrax toxin of *Bacillus anthracis*. The pathogenesis of HFS has not been fully explained, but it seems that the mutation of the ANTXR2 causes the synthesis of a receptor that has impaired ability to interact with extracellular matrix components, leading to the accumulation of hyaline deposits in tissues (3). The first clinical signs may be present at birth or appear during infancy. Given the time of the disease onset, the severity of the clinical picture and survival, two syndromes with similar clinical presentation and pathological findings were described in the literature: Infantile Hyaline Fibromatosis (IHF) and Juvenile Hyaline Fibromatosis (JHF). IHF occurs earlier with more pronounced clinical picture and shorter survival, whereas JHF develops later, with milder clinical picture and longer survival. Today, after the discovery of a common genetic cause, it is clear these are stages of the same disease. In 2012, HFS was classified into 4 stages, according to severity, incidence, and survival (1,4). Multiple nodular subcutaneous lesions, painful progressive joint contractures, hyperpigmentation of the skin, enteropathy with extensive protein loss and chronic diarrhea, frequent infections, bone lesions, gingival hypertrophy and thickening of the lip and cheek tissue belong to the characteristic manifestations of HFS (4). In this report we present a five-year-old girl with HFS who, to the best of our knowledge, is the first patient in Croatia with a confirmed ANTXR2 gene mutation described in the literature.

Case report

A 5-year-old girl was referred to the Department of Maxillofacial and Oral Surgery from the pediatric clinic having the chief complaint of difficulty feeding and speaking due to extensive generalized gingival hypertrophy. She was previously diagnosed with HFS, during early infancy. Although she was born in the third trimester of pregnancy, there was an increased risk for preterm delivery managed by medications. The baby was born after full term pregnancy, without complications during delivery. The family history revealed no similar illnesses. The non-consanguineous parents already had one healthy female child. The first symptoms appeared at the age of two months, in the form of upper extremities joint stiffness. This progressed to joint contractures (Figure 1.A). At the age of two years, the patient presented hyperpigmented macules over bony prominences and stunted growth, hypotonia with normal cognitive development (Figure 1.B). As the disease progressed further, pink pearly skin papules appeared on the skin of the neck, condyloma-like growths in the perianal region, and subcutaneous nodules on the trunk and lower extremities (Figure 1.C). A biopsy of the skin and subcutaneous nodules revealed a normal structure of the epidermis and dermis with hyaline deposits in the subcutaneous tissue along with multiplied fibroblasts and blood vessels. A molecular analysis confirmed the mutation of the ANTXR2 gene. The patient underwent orthopedic correction of knee contractures at the age of three.

During a clinical examination of the head and neck, skeletal deformities of viscerocranium and neurocranium (broad prema tome što je primarno otkriven kao receptor za antraks, toksin bakterije *Bacillus anthracis*. Patogeneza HFS-a nije rješena, no vjeruje se da mutacija gena ANTXR2 rezultira sintezom receptora koji ima oslabljeni svojstvo interakcije s komponentama ekstracelularnog matrisa te potiče akumuliranje hijalinih depozita u tkivima (3). Prvi klinički znakovi mogu se pojaviti pri rođenju djeteta ili u dojenačkoj dobi. Obzirom na vrijeme pojavljivanja, u literaturi su se opisivala dva sindroma sa sličnom kliničkom slikom i potomihistološkim nalazom – infantilna hijalina fibromatoza (IHF) i juvenilna hijalina fibromatoza (JHF). IHF se pojavljuje ranije s izraženijom kliničkom slikom i kraćim preživljavanjem, a JHF je spori i ima blazu kliničku sliku i dulje preživljavanje. Današnje, nakon otkrića zajedničkog genetskog uzroka, jasno je da je riječ o stadijima iste bolesti. Godine 2012. HFS je klasificiran u četiri stadija s obzirom na težinu kliničke slike, pojavnost i preživljavanje (1, 4). Multiple nodularne potkožne lezije, bolne progresivne kontrakture zglobova, hiperpigmentacije na koži, enteropatija s ekstenzivnim gubitkom proteina i kroničnim prožetkom, česte infekcije, koštane lezije, hipertrfofija gingive, zabeležavanja tkiva usana i obraz, karakteristične su manifestacije HFS-a (4). U ovom radu opisujemo petogodišnju djevojčicu oboljelu od HFS-a i to je, prema našim spoznajama, ujedno i prvi takav slučaj s potvrđenom mutacijom gena ANTXR2 opisan u Hrvatskoj.

Prikaz slučaja

Djevojčica u dobi od pet godina upućena je iz Klinike za pedijatiju u Kliniku za kirurgiju lica, čeljusti i usta, a razlog je bio otežano hranjenje i govorenje zbog opsežne generalizirane gingivne hipertrfofije obiju čeljusti. U ranoj dojenčakoj dobi dijagnosticiran joj je HFS. Rođena je prirodnom putem u terminu, no u trećem tromjesecju trudnoća je bila zakažena, a zaklapanje otkriveno je prijevremenom porođajem i održavano je lijekovima. Slivne bolesti nisu zabilježene u užoj i široj obitelji. Roditelji nisu u krvnom srodstvu te već imaju jednu zdravu djevojčicu. U dobi od dva mjeseca kod djeteta je zapravo ograničena pokretljivost zglobova gornjih ekstremiteta koja je postupno prešla u kontrakтурu zglobova (slika 1.A). U dobi od dvije godine pacijentica je imala hiperpigmentaciju na koži iznad koštanih prominencija te zastojo u rastu i razvoju, uz normalan kognitivni razvoj (slika 1.B). Kako je bolest napredovala, pojavile su se kožne biserne papule na vratu, promjene slivne kondilomije u perianalnoj regiji, te multiple nodularne potkožne lezije na trupu i donjim ekstremitetima (slika 1.C). U sklopu dijagnostičke obrade učinjena je biopsija kožnih lezija, te se otkrila normalna struktura epidermisa i dermisa s pojavom obilne količine hijalinih depozita u potkožnom tkivu uz umnožene fibroblaste i krvne žile. Molekularnom analizom potvrđena je mutacija gena ANTXR2. U to četiri godine pacijentica je operirana zbog kontrakture koljena.

Kliničkim pregledom glave i vrat pronađene su skelatal deformacije viscerocranijska i neurocranijska (široko čelo, sedlasati korijen nosa, nisko položene uške) (slika 1.D). Intraoral-
forehead, depressed nasal bridge, low set ears) were recorded (Figure 1.D). An intraoral clinical examination showed a limited mouth opening due to diffusely thickened skin of the oral commissures and extensive gingival hypertrophy that completely covered the crowns of the teeth (Figure 1.E).

nim pregledom zapaženo je ograničeno otvaranje usta zbog difuznog zadebljanja kože komisure usana te opsjeorna gingivna hipertrofija u objema čeljustima koja je potpuno prekrivala krune zuba (slika 1. E).
Due to the functional impairments, a gingivectomy with electrocauterity was performed, in general endotracheal anesthesia, resulting in satisfactory postoperative appearance, with healthy deciduous teeth (Figure 1.F and 1.G). During the same anesthesia, subcutaneous nodules from the lower extremities were removed by a plastic surgeon.

**Discussion**

J. Murray (1873) was the first to mention HFS, under the name of “molluscum fibrosum” as an unusual form of neurofibromatosis (5). B. Puretić et al. (1962) described a patient with similar manifestations and named the disease mesenchymal dysplasia. For the years to come, different names have been used for the same disease, until Y. Kitano (1972) concluded that it was the same syndrome with variable clinical presentation and introduced the term hyaline fibromatosis (3). To date, 84 cases of HFS have been described in the literature. It is equally common in males and females. Forty-six ANTXR2 gene mutations have been identified so far, divided into four classes, depending on the receptor domain affected by the mutation. Recent studies showed that mutations affecting the transmembrane, immunoglobulin-like domain and von Willebrand type A domain cause a more severe disease (formerly called JHF), while mutations in the gene responsible for the intracellular part of ANTXR2 receptor cause milder disease (formerly referred to as JHF) with later onset, milder clinical presentation and longer survival (4). In 2012, R. Denadai et al. developed a 4-grade classification system. The first stage is the mildest form of the disease and involves skin changes and gingival hypertrophy. In the second stage, changes in the joints and bones are present, while in the third stage, the internal organs are affected. The fourth stage is the most severe (severely shortened life expectancy). It is, usually, diagnosed earlier than the first three stages, during the first three months of life, the first symptom being joint stiffness. The median survival in stage 4 is 15 months (6). Although our patient was diagnosed very early, at the age of two months, internal organs were not affected which would indicate that her condition is most likely stage two.

Clinically, the two most common manifestations are subcutaneous nodules (85.7%) and gingival hypertrophy (92.9%). Although subcutaneous nodules are most often found on the scalp, they were present only on the hands of our patient, on her feet and behind her ears. In the majority of cases reported in the literature these signs were the ones that led to the diagnosis (4).

Gingival hypertrophy results in impaired oral hygiene that can cause odontogenic infections and difficulties in feeding. Our patient had great difficulties in eating, however, gingival hypertrophy didn’t cause tooth decay. Perhaps, the fact that the gingiva covered the entire crowns of the teeth completely acted as a protective mechanism. Hypertrophic gingiva was enlarged but painless, hard and normal in color. Gingival hypertrophy can cause difficulties in permanent teeth eruption. In older children, it can cover the entire occlusal surfaces of the teeth, causing difficulty in chewing and speaking. As a part of HFS, gingival hypertrophy can be localized

**Rasprava**

HFS prvi put u literaturi spominje J. Murray 1873. godine pod nazivom molluscum fibrosum kao neobičnu formu neurofibromatose (5). Godine 1962., B. Puretić i suradnici opisali su pacijenta sa sličnim manifestacijama te su bolest nazvali mezenhimalna displazija. Godinama su se upotrebljava- vali različiti nazivi za istu bolest, dok Y. Kitano 1972. nije zaključio da je riječ o istom sindromu s varijabilnom kliničkom slikom te je uveo pojam hijalina fibromatoza (3). U literaturi su dosad opisana 84 slučaja pacijenata obojlih od HFS-a. Podjednako je čest u oba spola. Danas je poznato 46 mutacija gena ANTXR2 koje se klasificiraju u četiri razreda, ovi- sna o domeni receptora koja je pogodena mutacijom. Prema najnovijim spoznajama mutacije koje zahvaćaju transmembransku domenu i domenu sličnu imunoglobulinu te von Willebrandov tip A domenu uzrokuju teži oblik bolesti (prije nazvan IHF), a mutacije gena koji dijagnosticira ANTXR2 uzrokuju blagi oblik bolesti (prije nazvan JHF) s kasnijom pojavom simptoma, blazom kliničkom slikom i dužim preživljenjem (4). R. Denadai razzradio je sa svojim suradnicima 2012. godine sustav stupnjevanja težine bolesti u četri stadija od kojih je četvrti najteži (iznimno skraćen životni vijek). Prvi stadij je najbolji oblik bolesti i uključuje promjene na koži i hipertrofiju gingive. U drugom stadiju pojavljivaju se promjene na zglobovima i kostima, a u trećem su zahvaća- ni unutarnji organi. Četvrti stadij je najteži te se dijagnosti- cira ranije negoli prva tri, tijekom prva tri mjeseca života, a prvi simptom je najčešće ukočenost zgloba. Medijan preživljenja u četvrtom stadiju je 15 mjeseci (6). Iako je našoj pacijentici dijagnoza bila postavljena već s dva mjeseca, bolest nije zahvatila unutarnje organe što bi upućivalo na to da se njezina bolest najvjerojatnije može uvrstiti u drugi stadij. Dvije najčešće manifestacije su potkožni čvorovi (85,7 %) i hipertrofija gingive (92,9 %), te su u većini slučajeva opisani u literaturi te su bolesti dijagnosticirane i uz ucijenjenom postoperativnom analizi sa zdravim mliječnim delom.

Gingivna hipertrofija rezultira ostezanom oralnom higiene koja može uzrokovati odontogene infekcije te poteškoća pri hranjenju. Naša pacijentica imala je velike poteškoće pri hranjenju, no kod nje gingivna hipertrofija nije uzrokovala karatje zuba. Možda je gingiva imala protetivni učinak na zube zbog činjenice da je potpuno prekrivala njihove krunu. Hipertrofichna gingiva bila je bezbolna i uveličana, tvrda i nor- malne boje. Hipertrofija gingive može utjecati na otežano ni- canje trajnih zuba. Kod starejih djece može biti toliko izraža- na kao u našem slučaju, te prekrivajut okluzalne površine zuba i uzrokovati poteškoće pri čuvanju hrane. Djece često imaju poteškoće sa govorom. U sklopu HFS-a, gingivna hipertrofija može biti lokalizirana ili generalizirana. Najčešće je lokalizi-
or generalized. Hypertrophy is most commonly localized on the palatal side of the tuber of the upper jaw or the lingual side of the lower alveolar ridge (7, 8).

The characteristic pathological features are the accumulation of amorphous, eosinophilic hyaline substance in many tissues and organs as found in the presented case (Figure 1.H) (9). Although the composition and origin of the hyaline substance is not yet fully known, some studies indicate that mutation of the ANTXR2 gene, due to receptor dysfunction, leads to destabilization and dysregulation of extracellular matrix components. Type IV and VI collagen and laminin have been shown to be the major ligands of receptors, and, in case of ANTXR2 dysfunction, they accumulate in the extracellular space. In addition, there is a proliferation of spindle and inflammatory cells (4). Pathological differential diagnosis includes Farber disease, I-cell disease (mucolipidosis II), Pseudo-Hurler polydystrophy (mucolipidosis IIIa) and lipid proteinosis of Urbach and Wiethe (7). Given that there is no cure for HFS today, treatment is symptomatic and involves surgical removal of the gingiva and subcutaneous nodules. Unfortunately, poor results have been reported in the literature using interferon alfa-2B, corticosteroids, penicillamine and methotrexate (4, 10). Due to the extreme rarity of HFS and the short life span of patients, there is no consensus on treatment modalities to date. The most common cause of death in HFS is persistent diarrhea, frequent infections, and organ failure (6). Due to the recurrence of gingival hypertrophy, additional surgery is needed; however there is no doubt that gingivectomy greatly improves the quality of life in these patients (7, 8). In our case, one year follow up shows satisfactory results without local recurrence. After the procedure, the patient gained weight which is significant considering her stunted growth.

Until the cure for HFS has been found, it is necessary to focus on a multidisciplinary approach in the diagnosis and treatment of these patients and provide psychological support for the family. Although these patients suffer from a range of symptoms, it is necessary to address gingival hypertrophy in the earliest opportunity to allow proper nutrition, which is imperative bearing in mind their slower growth and development.

Conflict of interests

The authors have no competing interests.

Patient consent

Written patient consent was obtained from the patient’s family.
Sažetak
Hyaline fibromatous sindrom (HFS) rijedak je autosomno recesivni genetski poremećaj koji karakterizira nakupljanje hijaline tvari u tkivima s kožnim, sluzničkim, koštanim, zglobnim i sistemskim manifestacijama. Bolest je uzrokovana mutacijom gena ANTXR2 koja rezultira sintezom neispravnog transmembranskog proteina, pa se hijalini depozitiraju prekomjerno talože u međustaničnom prostoru. Prvi znakovi mogu biti prisutni pri rođenju ili tijekom dojenčke dobi, a prvi simptom najčešće je ukočenost zgloba. Ostale manifestacije uključuju zglobove kontrakture, hiperpigmentiranu makulu kože iznad koštanih promene i slijedeća kontrakture ruke i noge. U radu predstavljamo petogodišnju djevojčicu s teškim oblikom gingivreptije koja je uzrokovala potješće s hranjenjem i govorom. Prema našim spoznajama to je prvi pacijent opisan u Hrvatskoj s dokazanom mutacijom gena ANTXR2.

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Ključne riječi
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