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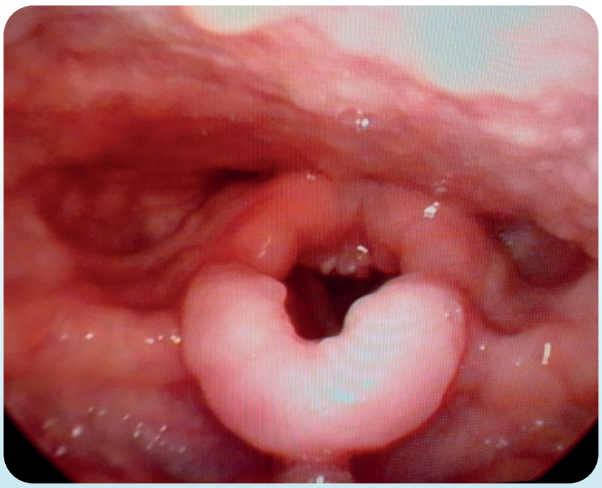

Health of intraoral soft tissues in children with cerebral palsy and associated factors

Laugier-Hunziker syndrome: a rare case report and review of the literature

Lipoid proteinosis

A case of syphilis followed as alopecia areata

Association of acrodermatitis continua of Hallopeau and fissured tongue

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Contents

Savas Yayli

Murat Cakir

Dear colleagues,

We are delighted to welcome you to the second issue of Mucosa in 2021. It is a great pleasure for us to continue publishing during pandemic period without any interruptions.

In this issue, we have five scientific articles for you. An et al. reviewed the clinical findings, diagnosis, and treatment of lipoid proteinosis in order to pay attention the importance of multidisciplinary approach. Tunali et al. analyzed the oral health and associated factors in children with cerebral palsy. They suggest a rehabilitation program with the interdisciplinary work together with patients and parents.

Ermis reported an interesting case with Laugier-Hunziker syndrome and reviewed the literature to impress the importance of excluding the other conditions with similar mucosal findings for the definite diagnosis. Karaca Ural reported a case with syphilis followed as alopecia areata. Detailed clinical examination is cruical for early and appropriate treatment. Finally, An et al. reported a rare association of acrodermatitis continua of Hallopeau with fissured tongue and its treatment options.

We would like to thank our readers, authors, and reviewers as well as our publisher for their meritorious contributions. We hope to hear good news for leading indexes as soon as possible.

We await your valuable contributions for our forthcoming issues.

Warm regards,

Savas Yayli

Murat Cakir

Editors-in-Chief

Review

mucosa

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Lipoid proteinosis

Lipoid proteinozis

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Abstract

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis characterized by the accumulation of an amorphous hyaline material in various regions of the body, including skin, mucous membranes, brain, internal organs. LP is caused by mutations in the gene encoding the extracellular matrix protein 1 (ECM1) found on chromosome 1q21. Although this disease is rare, it is more reported in areas where consanguineous marriages are common. During the infancy, it begins with hoarseness due to laryngeal infiltration. Gradually, skin and mucous changes become clinically evident. The affected individuals have a normal survey unless laryngeal obstruction develops. A multidisciplinary approach is recommended for monitoring these patients.

Key words: *ECM1, lipoid proteinosis, moniliform blepharosis*

Öz

Lipoid proteinozis (LP) deri, muköz membranlar, beyin, iç organlar dahil olmak üzere vücudun çeşitli bölgelerinde, amorf bir hiyalin materyalin birikmesi ile karakterize, nadir görülen otozomal resesif bir genodermatozdur. LP kromozom 1q21'de bulunan ekstraselüler matriks proteini 1 (ECM1)'i kodlayan gendeki mutasyonlardan kaynaklanır. Bu hastalık nadir görülmekle birlikte ülkemizde özellikle akraba evliliklerinin sık olduğu bölgelerde daha fazla bildirilmeye başlanmıştır. Bebeklik döneminde laringeal infiltrasyona bağlı boğuk bir ağlama ile başlar. Zamanla deri ve mukoza değişiklikleri klinik olarak belirgin hale gelir. Etkilenen bireyler, laringeal obstrüksiyon yaşamadıkça normal bir yaşam süresine sahiptir. Bu hastaların takibi için multidisipliner bir yaklaşım önerilmektedir.

Key words: *ECM1, lipoid proteinozis, moniliform blepharosis*

Introduction

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis characterized by the accumulation of an amorphous hyaline material in various regions of the body, including skin, mucous membranes, brain, internal

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organs.[1] LP was first defined by Urbach and Wiethe with the name "Lipoidosis Cutis Et Mucosae" in 1929.[2] This disease affecting both sexes equally is associated with mutations in the coding gene of extracellular matrix protein 1 (ECM1).[3] During the infancy, it begins with hoarseness due to laryngeal infiltration. Gradually, skin and mucous changes become clinically evident. In face and extremities, vesicles and hemorrhagic crusts recover by leaving the atrophic scarring however it is unclear whether this is a primary or secondary phenomenon. while on the extensor surfaces, verrucous and keratotic lesions occur.[1,4-6] The disease is typically slow progressing, but usually follows a benign course. Almost any organ can be affected.[7-11] The affected individuals have a normal survey unless laryngeal obstruction develops. There is no precise and effective treatment of the disease.[12,13]

In this article, the epidemiology, pathogenesis, clinical characteristics, histopathology, diagnosis and treatment of LP will be reviewed.

Epidemiology

The incidence and prevalence of LP are not fully known. Approximately 400 cases have been reported so far in the literature.[1,4,8,14-17] In particular, it is more often seen in South Africa, in the North Cape Province, including the Namaqualand region where immigrants migrated from Germany in the mid 17th century.[18] The majority of LP patients in the literature are reported from Turkey although real prevalence is not known.[1,4,8,14,19,20] We think that consanguineous marriage rates in eastern Turkey may have an effect on this.

Pathophysiology

LP is caused by mutations in the gene encoding the extracellular matrix protein 1 (ECM1) found on chromosome 1q21.[21] The ECM1 protein plays important biological and physiological roles in the regulation of angiogenesis, epidermal differentiation, and functions of dermal collagen and proteoglycans. ECM1 also shows over-expression in certain malignancies and is abnormally expressed in chronologically aged and photo-aged skin. Its role in wound healing, scarring, and aging is speculated but not yet defined.[3,16] ECM1 proteins have also been shown in liver, heart, lungs, small intestine, prostate, pancreas, testicles, ovary, placenta, kidneys, skeletal muscle.[3,21,22]

The loss of normal function of ECM1 in LP is associated with a wide variety of clinical abnormalities due to infiltration of the skin and internal organs with hyaline-like material. The eosinophilic hyaline- like material is deposited in all affected organs, however it is unclear whether this is a primary or secondary phenomenon. The details of the genotype-phenotype correlation regarding the nature of the hyaline deposits are currently under investigation.[16]

ECM1 has been shown to inhibit MMP-9 activity through protein-protein interaction.[23] Increased MMP-9 activity may contribute to hyaline changes in the dermis in LP patients.[24]

Genetics

LP is a rare and autosomal recessive inherited disease.[5] Hamada et al., performed the first linkage analysis and survey of the ECM1 gene in patients with LP, and identified the localization of the ECM1 gene at human chromosome 1q21 locus.[25] Further studies indicated the role of an ECM1 gene mutation in LP. Systematic surveys across different countries and regions demonstrated variable mutation points of the ECM1 gene in individual patients with LP, suggesting the potential gene polymorphism of the ECM1 gene in patients with LP.[8,21,22,26,27]

Afifi et al., in their study on 12 LP patients from 10 different families in Egypt, had detected 5 new ECM1 mutations in exon 1 (c.10_11insC), exon 6 (c.690_691delAG), exon 7 (c.734G>A), exon 8 (c.1286_1287delAA), and intron 9 (c.1393-1G>T).[26] Dertlioğlu et al., in their study on 19 LP patients from 5 different families in Turkey, had detected ECM1 gene mutations in exon 6 (c.507delT, 658T>G), exon 9 (157C>T, 727C>T), and exon 10 (c.93_94delGCinsTT).[27]

According to the The Human Gene Mutation Database

(HGMD) 71 pathogenic mutations in ECM1 have been reported in LP patients from different geographical areas, including 32 missense/nonsense substitutions, 9 splicing substitutions, 26 small deletions/insertions (indels) and 4 gross deletions/insertions.[28]

Hamada et al., suggested a genotype-phenotype correlation based on the location of the mutation, with a slightly milder phenotype for patients with mutations in exon 7 compared to patients with mutations outside exon 7. The splice variant ECM1b lacks exon 7 and is therefore not affected by mutations located in this exon.[29] However, Youssefian et al., noted phenotypic heterogeneity in three families with 12 LP patients, although all patients were homozygous for the mutation c.507delT in exon 6. While existing features of LP were similar in most patients, severity and expressivity differed substantially between patients, even between patients from the same family.[30] The clinical variability between siblings diagnosed with LP carrying the same homozygous mutation indicates that genotype is not the only factor determining the phenotype. Genetic, epigenetic, and environmental factors probably play a role in the clinical expression of LP.[3,26-28]

Clinical findings

The earliest finding is a weak or hoarse cry that occurs early in life due to the accumulation of hyaline-like material in the vocal cords.[20] (Fig. 1-2) Mucosal symptoms appear at birth or in the first few years of life.[11] Cutaneous manifestations usually arise during the first two years of life.[5] Neurpshychiatric symptoms of LP are more common in patients older than 10 years of age.[15]

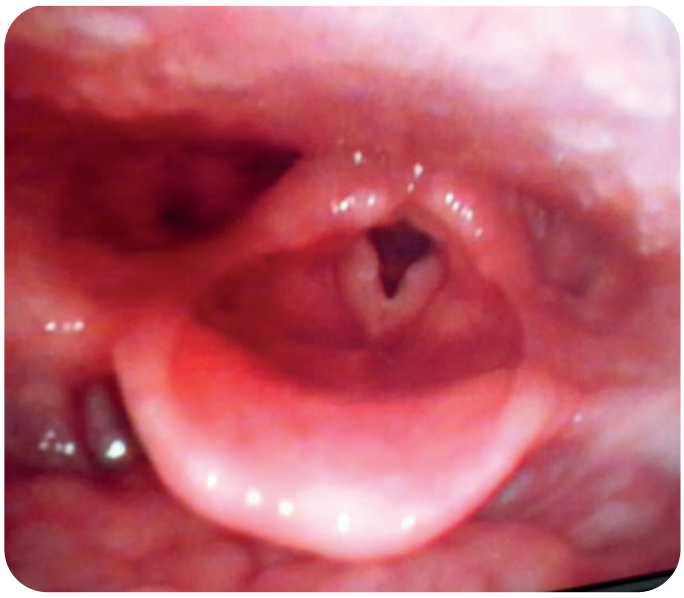

Fig. 1. Thickening of the vocal cords

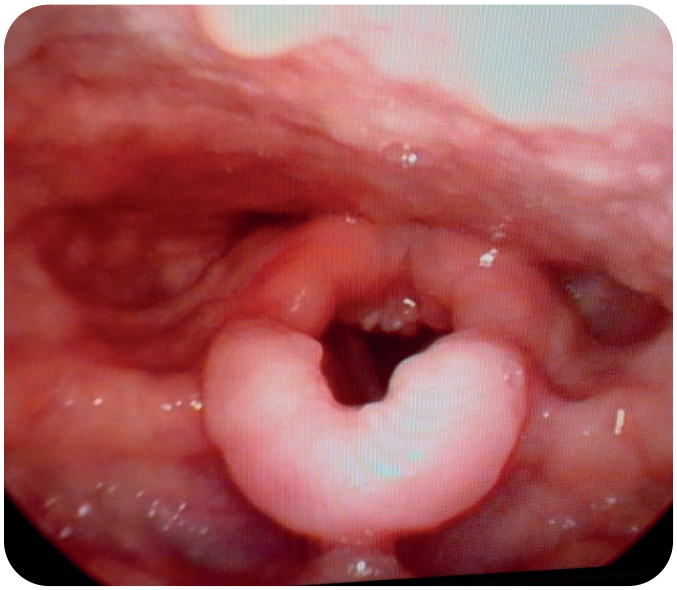

Fig. 2. Thickening of the vocal cords and hypertrophic changes in the arytenoid and interarytenoid region

Cutaneous findings

Cutaneous findings usually begin in the early stages of the disease, usually in the first two years. Lesions such as vesicles and bullae usually begin with hemorrhagic crusts in areas of friction or trauma such as the face and extremities (Fig. 3) and heal leaving atrophic scarring (Fig. 4).[14] A thickened skin is formed, which creates a waxy appearance due to dermal accumulation of amorphous hyaline substance, often on the facial skin, eyelids, axillae and scrotum. Finally,

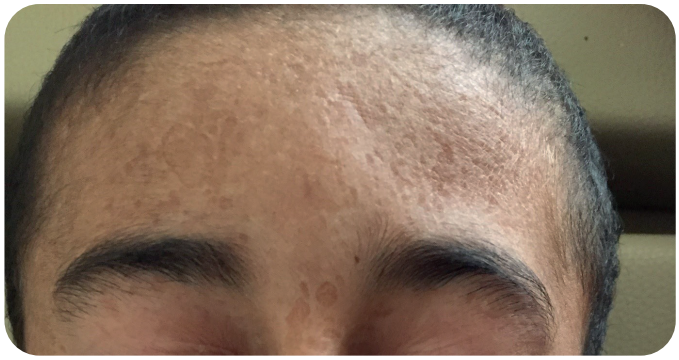

Fig. 4. Facial skin thickening and multiple atrophic scars

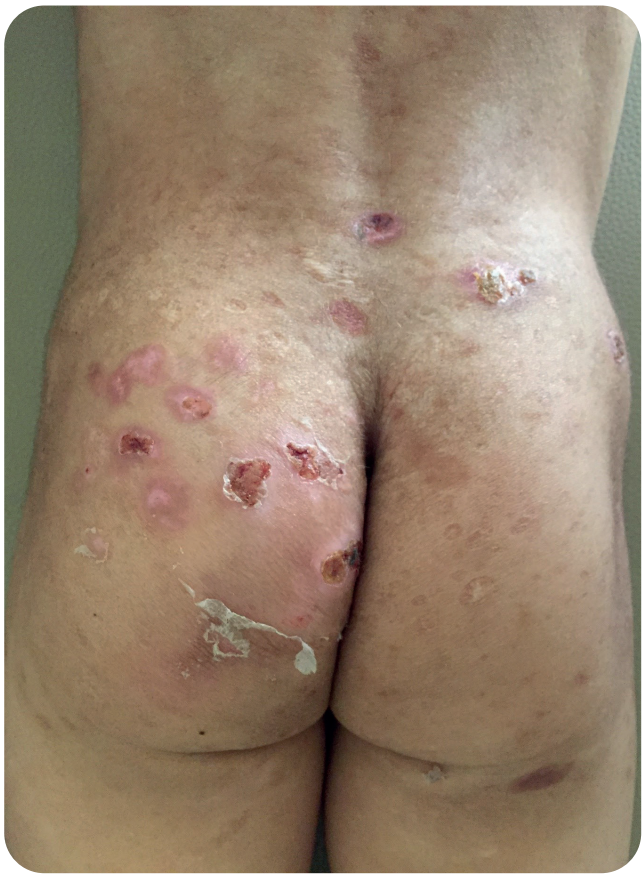

Fig. 3. Ulcerated lesions with hemorrhagic crusts and multiple atrophic scars on the back and buttocks

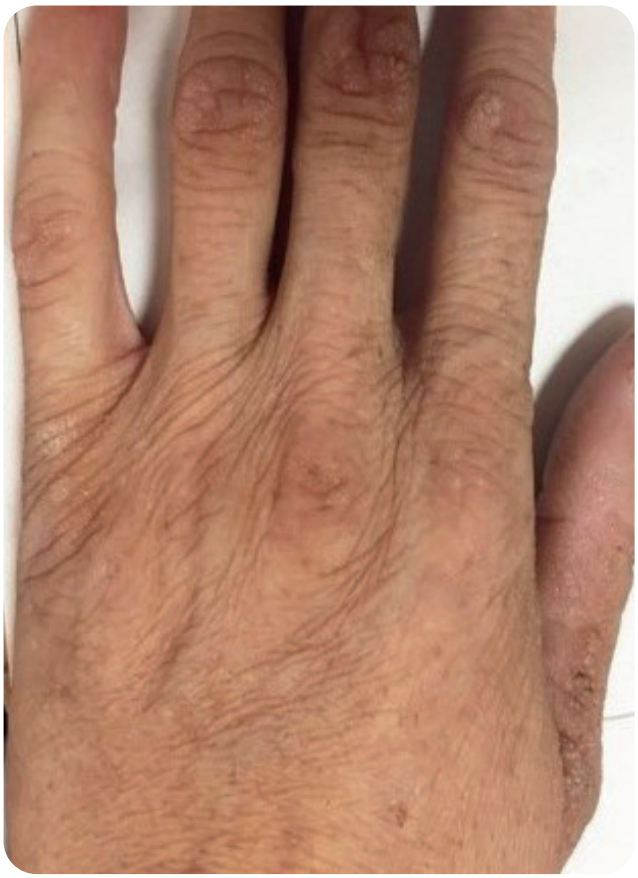

Fig. 5. Verrucous lesions on the dorsum of the hand

hyperkeratotic, verrucous papules (Fig. 5) and plaques occur on surfaces exposed to trauma such as elbows, knees and hands.[5,6,14] Papules, plaques, and nodules may be found primarily on the face, but also in the axilla and scrotum. Irregular or widespread alopecia may be seen due to the involvement of the scalp, but alopecia is not a finding in most cases. Nail dystrophy due to nail bed involvement may be seen in some

cases.[1,4,14,15,31] Nico et al., stated that the first symptom before the development of characteristic skin lesions in LP is hardening of the lip and stated that a mucosal biopsy from lip including lamina propria may be a good method for the early diagnosis of LP.[32]

Differential diagnosis of skin lesions includes impetigo, herpes infection, papular mucinosis, erythropoietic protoporphyria, epidermolysis bullosa, lichen amyloidosis, lepra, colloid milium, syringoma, cutaneous xanthomatosis, hydroae vacciniforme, pseudoxanthoma elasticum, incontinentia pigmenti, juvenile hyaline fibromatosis, infantile systemic hyalinosis and non-Langerhans cell histiocytoses.[1,4,14,15,31]

Mucosal findings

Mucosal symptoms appear at birth or in the first few years of life. Generally oral mucosa is the most severely affected area. The most commonly affected areas are labial mucosa, tongue, lingual frenulum, buccal mucosa and palate.[11] Cobblestone appearance of the oral mucosa, yellow lip nodules, lipeversion, vegetative lesions, fissures in the lateral commissures and oral ulcers may be seen in patients with widespread disease.[33,34] Involvement of salivary glands, usually submandibular and parotid glands, may cause hyposalivation. Recurrent parotitis (Fig. 6) and dental caries may occur as a result of deposits blocking the Stenson canal. The tongue is usually woody hard with no dorsal papillae, and the frenulum is shortened and thickened. (Fig. 7). Inadequate extension of the tongue as a result of frenulum involvement is diagnostic. Hypoplasia or aplasia may occur in the teeth, especially in the lateral incisors and premolars.[11,32-36]

The largest series of oral findings observed in patients with LP was analyzed by Frenkel et al. They analyzed 133 cases from 1948 to 2016, as well as four cases of their own. In this study, tongue (68%), floor of the mouth (55.8%), lips (43%) and buccal mucosa (40%) were found to be the most frequently affected mouth regions. The palate (25%) and gums (6%) were the least affected areas. It was stated that the gums tended to be affected in older patients, while the palate tended to be affected in younger ones. Skin scars were reported to be significantly less in patients with palate and labial lesions.[11]

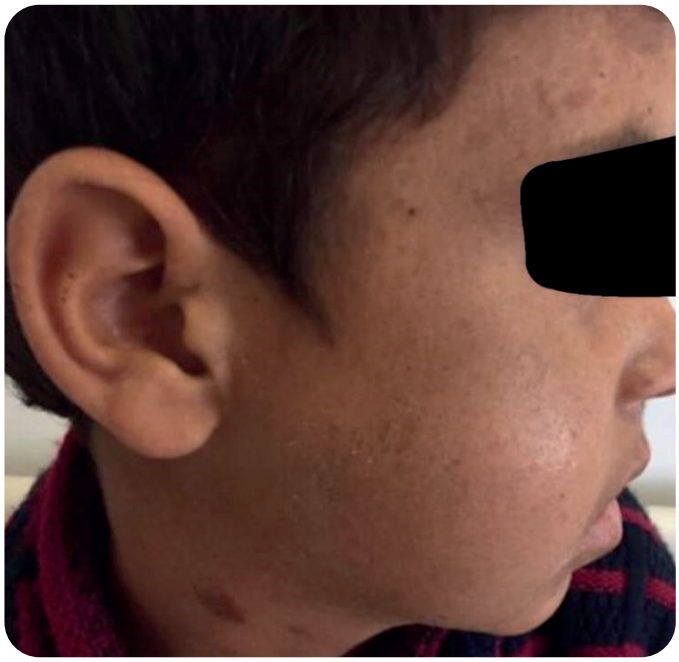

Fig. 6. Recurrent parotitis in a child with lipoid proteinosis

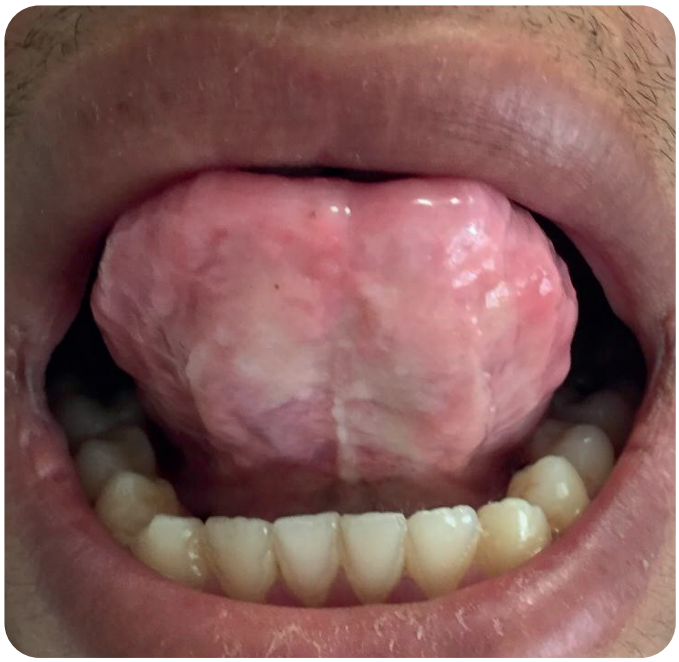

Fig. 7. Decrease in tongue movements due to involvement of the frenulum

Neuropshychiatric findings

Bilateral, comma-shaped symmetrical calcification of the amygdala occurs in 50% of patients with LP and is considered a pathognomonic finding.[37,38] Calcification has also been reported in the hippocampus, parahippocampal gyrus, basal ganglia, uncinate gyrus, pineal gland, and perirhinal and parietal cortexes.[39,40-43] The pathophysiological mechanisms and localization of calcifications are not fully understood. Central nervous system(CNS) infiltration specifically includes hippocampal capillaries, resulting in wall thickening and perivascular calcium deposition.[10] Calcifications develop slowly and are therefore more common in patients older than 10 years of age and those with a longer disease duration.[15] It is estimated that epilepsy occurs in approximately 25-50% of LP patients.[38] In a study evaluating seven LP patients with intracranial calcifications, it was stated that four patients had epilepsy that started in childhood or young adulthood, the most common subtype was focal seizures, and patients with some mutations tended to be resistant to antiepileptic therapy.[40] In a study in which 10 patients with LP were evaluated, decreased perfusion in the medial temporal lobe in three patients was found, and amygdaloid complex calcification and degeneration were found in six patients. Although these nine patients were not different from healthy controls in terms of cognitive functions, they were different from healthy controls in terms of facial expression recognition, emotional processing, and learning and recognition associated with smell.[43]

Neuropshychiatric symptoms of LP may include epilepsy, migraine, varying degrees of mental retardation, depression, anxiety, panic attack, memory dysfunction, abnormal social interaction patterns, dystonia, hallucination, schizophrenia, and spontaneous central nervous system hemorrhage.[10,37-41]

Ocular findings

The most common and pathognomonic ocular finding of LP is linearly sequenced pearly papules on the eyelid called moniliform blepharosis.[9,44] (Fig. 8) In addition to its diagnostic value, moniliform blepharosis may accompany the infiltration of the Zeiss, Moll and Meibomian glands, and consequently cause madarosis, trichiasis and sometimes distichiasis.[44] Another common finding is macular focal degeneration and drusen formation in the Bruch's membrane in approximately 30-50% of patients.[9,45] Uncommon ocular symptoms of LP include cataract, lens dislocation, corneal ulceration, corneal opacities, keratoconus, uveitis, glaucoma, impaired color vision, light hypersensitivity, retinitis pigmentosa, epiphora, dry eye, nasolacrimal duct obstruction, iris and pupillary disorders and temporary blindness.[9,44-47]

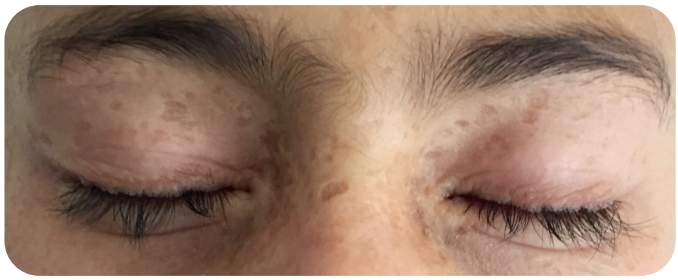

Fig. 8. Moniliform blepharosis in the eyelids

Otolaryngological findings

A weak or hoarse cry from birth or starting in early infancy is typical and remains throughout life.[20] Hofer et al., found hoarseness at birth in 26 of 27 LP patients.[48] Savage et al., reported that hoarseness was present in congenital or early infancy in approximately two-thirds of LP patients.[49]

Although LP is very rare, airway obstruction may be life-threatening, and death due to laryngeal involvement has been reported.[20] Dertlioglu et al., evaluated 10 LP patients with hoarseness and found hyaline deposits, thickened and tuberous vocal cords and decreased movement of vocal cords in indirect laryngoscopic examination of nine patients.[1] On the other hand, Yukkaldiran et al., in their study with 21 LP patients, found thickening in vocal cords in all patients, hypertrophic changes in arytenoids in 13

(61.9%) patients, and thickening in the interarytenoid area in 10 (47.6%) patients.[20]

Differential diagnosis in patients with hoarseness includes vocal cord polyp and nodules, vocal cord paralysis, laryngitis, laryngeal hemangioma, laryngeal cysts and the disease may affect larynx such as laryngeal amyloidosis, congenital dysphonia, hypothyroidism, and gastroesophageal reflux disease.[15,20]

In a study evaluating cochlear function and hearing in LP patients, pure tone audiometry, tympanometry and distortion product otoacoustic emission tests were performed in 20 patients and a healthy control group. It was stated that cochlear functions of patients with LP were affected by the increase in their hearing thresholds, and decreased signal-noise responses, and it was stated that LP patients were candidates for hearing loss in their later stage of life.[8]

Gastrointestinal findings

It has been reported that gastrointestinal system involvement is rare in LP, and hyaline material accumulation is shown in visceral biopsies taken from the esophagus, stomach, small intestine and rectum in autopsy cases.[50,51] Esophageal involvement was not reported in two different studies including 14 and 10 LP patients reported from Turkey.[1,4] Dysphagia has been described as a typical LP symptom in two different cases of LP.[52,53] Al-Bitar et al., stated that a Saudi Arabian patient with LP had esophageal involvement, but the authors did not report the endoscopic findings of that case.[54] Lima et al., observed multiple yellowish nodules along the esophagus, stomach and duodenum in upper gastrointestinal tract endoscopy of a LP patient with epigastric pain, postprandial fullness and dyspepsia without esophageal symptoms. Esophageal manometry was found to be normal in this patient.[7] Caccamo et al., described a patient with typical LP lesions in the small intestine and gastrointestinal bleeding.[55] It has been reported that gastrointestinal involvement in LP is generally asymptomatic and some patients with symptoms tend to improve with age.[7]

Histopathology

In the Hematoxylin-Eosin stained sections of the early skin lesions of LP, pink hyaline-like thickening is observed in the capillaries in the papillary dermis.[16] Rao et al., found non-acantholytic intraepidermal bullae in the histopathological examination of vesicular lesions on the skin of LP patients.[56] Ko et al., on the other hand, detected extensive non-dyskeratotic acantholysis with intraepidermal blister formation in early lesions of LP and stated that this disease may be an acantholytic dermatosis.[57]

The old skin lesions of LP have hyperkeratosis, sometimes papillomatosis, and a thickened dermis with pink hyaline bundles in a diffuse pattern. These bundles are often arranged perpendicular to the dermoepidermal junction. The accumulation of hyaline in the lower dermis is less (Fig. 9-10). The hyaline mantle may surround the hair follicles, sebaceous glands, and rarely the errector pili muscle, as well as the eccrine glands.[16,58] The lesions of 18 LP patients with late-stage skin lesions were examined histopathologically in a study by An et al. In this study, epidermal atrophy, hyperkeratosis, pigment incontinence in the basal layer, amorphous material

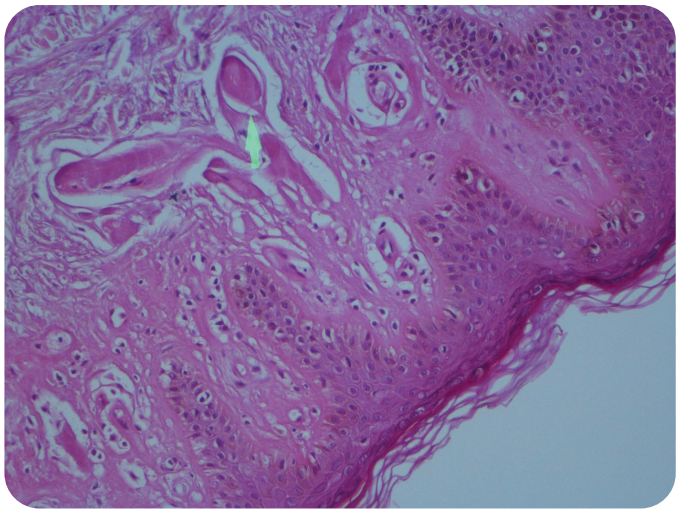

Fig. 9. Hyalinized material stained with PAS around the vessels in the papillary dermis (PASx400)

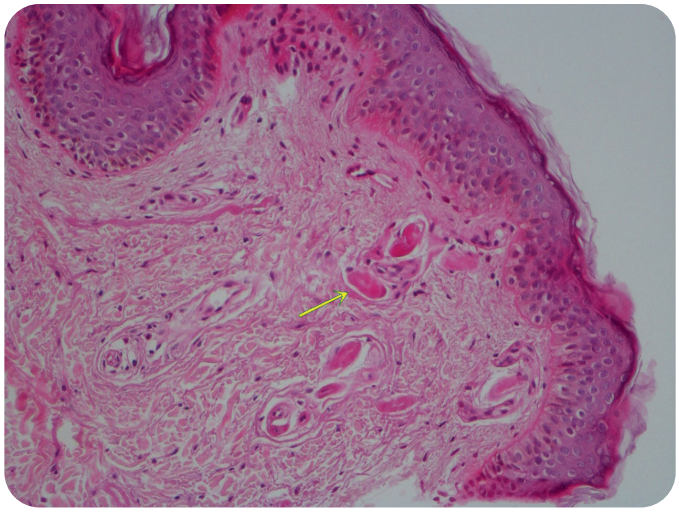

Fig. 10. Hyalinized material around the vessels in the papillary dermis (H&Ex200)

accumulation in the dermis, inflammatory elements in the papillary dermis, fibrosis, papillomatosis, PAS positivity around the perivascular and eccrine glands, flattening and melanophage in the retes were observed in histopathological examination.[16]

Diagnosis

The diagnosis of LP is made by characteristic clinical findings (hoarseness, vesicular lesions in the early period, atrophic scars on the face and extremities in the late period), identification of biallelic ECM1 pathogenic variants in molecular genetic testing, and the presence of characteristic findings in histopathological examination including deposition of an eosinophilic, periodic acid-Schiff positive hyaline material in the papillary dermis and around the blood vessels.[4,16,27,59,60,61]

Treatment

Treatment options are very limited in LP, and although various agents have been used in the treatment, there is no effective treatment option.[1,4,14]

Kaya et al., reported that two years of treatment with 600 mg / day of D-penicillamine provided both clinical and histological improvement in LP.[62]

Wong et al., reported that in a 41-year-old LP patient, after three years of continuous oral dimethyl sulfoxide (DMSO) treatment, the patient's skin lesions, hoarseness, and abnormal esophageal function improved significantly.[63] Ozkaya-Bayazit et al., on the other hand, stated that DMSO had no benefit for skin, mucosal lesions and hoarseness in three LP patients with an average of three years of treatment.[64] It has been reported that systemic retinoids such as acitretin or etretinate may be effective in the treatment of cutaneous and laryngeal lesions by reducing the amount of hyaline-like material in the dermis.[1,4,14,65] Gruber et al., showed the positive effects of 10 mg etretinate treatment on skin lesions in two LP patients.[66] Toosi et al.[67] and Gunduz et al.[68] reported cases of LP who were treated with acitretin and resulted in improvement in voice but had no effect on skin lesions. Bakry et al., showed that acitretin was effective in both cutaneous and mucosal lesions in two LP patients.[12] Acitretin treatment, which is used at a dose of 0.5 mg/kg/d for up to six months in LP, has been reported to improve hoarseness, the appearance of vesiculobullous lesions and palmoplantar hyperkeratosis.[1,67] Systemic steroids may be used in the treatment of oral ulcers associated with LP.[69]

Chemical peeling, dermabrasion and carbon dioxide laser treatment can also be used for the treatment of skin lesions.[14] It has been reported that two sessions of Er: YAG (erbium-doped yttrium aluminum garnet) laser treatment performed every six weeks for facial scars of LP patients provided a good cosmetic improvement during the 2-year follow-up period.[70] Madura et al., successfully treated skin lesions of a patient with LP with a combination regimen of fractional carbon dioxide and non-ablative radio frequency, and stated that this combination therapy was more effective than laser therapy alone.[13]

Microlaryngoscopic excision and carbon dioxide (CO) laser may be successful for patients with vocal cord involvement and phonation impairment. However, there is a risk of postoperative granulation tissue formation. Therefore, surgical intervention should only be considered in patients with risky airway involvement.[15]

Conclusion

LP is an inherited disease that can affect various parts of the body, including skin, mucous membranes, and internal organs. Although this disease is rare, it has been reported more frequently in our country, especially in regions where consanguineous marriages are common. Genetic counseling should definitely be given to these patients and their families. Depending on the symptoms of the disease, a multidisciplinary approach including dermatologist, otolaryngologist, ophthalmologist, psychiatrist, neurologist, dentist, gastroenterologist and geneticist is recommended for the follow-up of these patients.

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Drafting the manuscript or revising the content: IA, MA, MO

Final approval of the version to be published: IA, MO, EA

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Health of intraoral soft tissues in children with cerebral palsy and associated factors

Serebral palsili çocuklarda intraoral yumuşak doku sağlığı ve ilişkili faktörler

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Abstract

Background Cerebral palsy (CP) is a movement and posture disorder caused by damage to the immature brain. Oral health and functions are affected due to developmental disorders in the neuromuscular system of children with CP. The main ones are the hard and soft tissues in the mouth and chewing and swallowing functions.

Objective The aim of our study is to determine the condition of the oral soft tissues and associated factors in children diagnosed with CP in the growth and development period and to lead studies to prevent possible problems.

Methods Fifty-one children who receive service from Metin Sabancı units were included in the study. Diseases concomitant with CP, dietary habits, medications, and medical history forms, including the family status of the children were prepared. Physical examination of tonsillitis according to Brodsky Grading Scale, drooling with Balasco method, swallowing with clinical examination, gingival inflammation according to Modified Gingival Index (MGI) Classification, nutritional status and findings of reflux complaint were performed through face-to-face interviews with parents.

Results 62.7% of children with CP included in our study were boys and 37.3% were girls. The mean age of the children was 9.63 ± 2.40 years. Nutritional disorders were found in 45% of the children, mouth breathing in 57% and gastroesophageal reflux disease in 19%. The rate of children with CP with incorrect swallowing was 63% and the rate of those with drooling was 45%. A significant relationship was found between drooling and incorrect swallowing. 45% of the examined children with CP use medication due to the complaint of epilepsy. In 12% of children, the tonsillar tissue covers 50-75% of the airway patency. In 78% of the children, the MGI value was

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one and above and gingival enlargement was observed in 37%.

Conclusion Providing effective oral hygiene in children with CP is important in terms of preventing gingival inflammation and enlargement. Interdisciplinary studies on mouth breathing, incorrect swallowing and drooling treatments are important. In order to improve oral health, it is necessary to examine the associated factors and administer treatments.

Key words: *cerebral palsy, soft tissue, mouth mucosa, swallowing disorders, sialorrhea, mouth breathing*

Öz

Arka plan Serebral Palsi (SP) immatür beyindeki hasara bağlı oluşan hareket ve postür bozukluğudur. SP'li çocukların kas ve sinir sistemindeki gelişimsel bozukluklar sebebiyle ağız sağlığı ve fonksiyonları etkilenmektedir. Bunların başlıcaları ağız içindeki sert ve yumuşak dokular ile çiğneme ve yutkunma fonksiyonlarıdır.

Amaç Çalışmamızın amacı büyüme ve gelişim dönemindeki SP tanısı almış çocuklarda ağız içi yumuşak dokuların durumunu ve ilişkili faktörleri tespit ederek, olası problemleri engellemeye yönelik çalışmalara öncülük etmektir.

Yöntem Çalışmaya Metin Sabancı birimlerinden hizmet alan 51 çocuk dahil edilmiştir. Çocukların SP'ye eşlik eden hastalıkları, beslenme alışkanlıkları, kullandıkları ilaçlar ve aile durumlarını içeren anamnez formları hazırlanmıştır. Tonsil muayenesi Brodsky Skalasına göre, salya akışı Balasco yöntemi ile, yutkunma klinik muayene ile, diş eti enflamasyonu Modifiye Gingival İndex (MGI) sistemine göre, beslenme durumları ve reflu şikayeti bulguları ebeveynlerle yüz yüze yapılan görüşmelerle gerçekleştirilmiştir.

Bulgular Çalışmamıza dahil edilen SP'li çocukların %62.7s'i erkek, %37.3'ü kızdır. Çocukların yaş ortalaması 9.63 ± 2.40'tür. Çocukların %45'inde beslenme bozukluğu, %57'sinde ağız solunumu, %19'unda gastroözofagial reflü şikayeti tespit edilmiştir Hatalı yutkunma tespit edilen SP'li çocuk oranı %63, ağız dışına salya akışı tespit edilenlerin oranı ise %45'tir. Ağız dışına salya akışı ve hatalı yutkunma arasında anlamlı ilişki bulunmuştur. Muayene edilen SP'li çocukların %45'i epilepsi şikayeti sebebiyle ilaç kullanmaktadır. Çocukların %12'sinde tonsil dokusu havayolu açıklığının %50-75'ini kapatmaktadır. Çocukların %78'inde MGI değeri 1 ve üzeridir, %37'sinde dişeti büyümesi gözlenmiştir.

Sonuç SP'li çocuklarda etkin ağız hijyeninin sağlanması dişeti enflamasyonu ve büyümesinin oluşmaması açısından önemlidir. Ağız solunumu, hatalı yutkunma, salya akışı tedavilerine yönelik interdispiliner çalışma önemlidir. Ağız sağlığının iyileştirilmesi için ilişkili faktörlerin de incelenerek tedavilerin yapılması gereklidir.

Anahtar kelimeler: *serebral palsi, yumuşak doku, ağız mukozası, yutma bozuklukları, sialore, ağızdan soluma*

Introduction

Cerebral Palsy (CP) is defined as a disease that occurs as a result of non-progressive damage to the immature brain and causes posture and movement disorder.[1,2] There are very few studies on CP in Turkey. In these studies, the incidence of CP was found to be 4.4 per 1000 live births and was reported as one of the most common causes of disability in early childhood.[3,4] Studies have shown that 39.8% of pediatric patients with CP in Turkey have diplegic type, 28% hemiplegic type, 19.9% tetraplegic type, 5.9% ataxic type, and 6.4% dyskinetic type.[3]

Epilepsy, mental retardation, respiratory problems, motor function deficits, nutritional disorders, sleep problems, and oral and dental health problems are among the health problems associated with CP. About one-third of children with CP have chewing and swallowing problems. It is very difficult to provide oral care due to tone problems in orofacial muscles. For that reason, they have a high risk of developing oral and dental diseases.[4,5]

Gastroesophageal reflux (GER) is the most common esophageal disorder in children of all ages.[6] In children with neurological disorders, GER has a higher incidence

(15-75%). Chronic dysphagia, loss of appetite, chronic irritability, crying, and more rarely dystonia in the face and neck region are observed in children with CP and GER.[7] At the same time, a high rate of association between GER and dental erosion was found in these children. In a study, it was stated that GER is more common in children with quadriplegic CP, and this condition increases the risk of disease in the mouth area with dental erosion.[8]

Motor and orofacial disorders also significantly affect the ability of children with CP to taste and chew their food. Especially children with advanced motor dysfunction have difficulty in eating hard foods. To improve the standard of oral health in children with CP, it is important to understand the specific roles of sensory structures and functions of salivary glands in food consumption, together with motor function in orofacial structures. Perception deficits in sensory nerves of craniofacial tissues affect the sensory functions of children with CP. This effect limits the motor functions of the tongue, jaws, and orofacial muscles.[9] Dysfunction in the muscles also affects the salivary glands, causing a decrease in saliva production, which provides a basic protection against tooth decay.[10] In patients with CP, saliva production can sometimes be a contributing factor in easier chewing and swallowing of food. Therefore, it should be noted that saliva production in CP patients is important, especially in those with more severe motor dysfunction. Active mouth breathing should be reduced to increase saliva production.[9] Generally, food retention in the buccal and labial sulcus of the mouth in children with CP is due to weak muscles of mastication and poor brushing of these areas due to inadequate in-hand manipulation.[11]

In most children with CP who drool, the etiologic factor is not excessive production of saliva, but the inability to swallow saliva due to oromotor dysfunction. As a result of saliva flowing outside of the mouth; irritation, redness, and infection occur in the perioral region.[12] This situation also reduces the child's adaptation to the social environment and causes psychological trauma for both children and their parents.[13] Oromotor therapy recommended in children with CP is a treatment aimed at increasing the control of muscle functions in the orofacial region.[14] Various tongue, lip and cheek exercises are performed to reduce saliva flow outside of the mouth.[15]

The aim of this study is to determine the conditions of the oral soft tissues and associated factors in children diagnosed with CP in the growth and development period, and to make suggestions to prevent possible problems.

Methods

The Spastic Children's Foundation of Turkey (SCFT), which is part of the Sabancı Foundation is the only center in Turkey that specifically provides interdisciplinary rehabilitation support to children with CP. For that reason, the research was carried out in this center. After the subject was determined, the details of the study were determined by meeting with the physiotherapist, speech therapist, osteopath and family counselors working with children with CP under SCFT. The research team was informed about the methods of cooperation with children with CP by the center. Ethics committee approval was obtained from the Hamidiye Scientific Research Ethics Committee of the University of Health Sciences (05.06.2020, 19/163) and research permission was obtained from the the Academic Committee of the Spastic Children's Foundation of Turkey. According to the result of the power analysis made by taking the strength of the study as 95% and the margin of error α=0.05, the number of people who would participate in the study was determined as at least 45. The study included 51 children in the 6-14 age group diagnosed with CP, who benefited from the service units at Metin Sabancı Center affiliated to SCFT. Informed consent forms were obtained from all parents by explaining the content of the study. Briefings and examinations were performed face to face and sterile examination kits were used. Medical history forms containing personal and sociodemographic information (age, sex, diseases concomitant CP, types of CP, dietary habits, medications, etc.) were prepared.

Physical examination of tonsillitis was performed according to Brodsky Scale when the patients were in sitting position.[16] Saliva flow was checked in the resting position without stimuli. Mild drooling was analyzed using the Balasco method, according to which saliva was detected to drop onto the vermilion border of the lips, moderate drooling onto the chin, and severe drooling onto clothes.[17] The swallowing pattern was evaluated by occlusion of posterior teeth during swallowing, control of temporal and masseter muscle contraction with fingertips, and other clinical observations.[18] Gingival inflammation examination was performed using the Modified Gingival Index evaluation system.[19] Reflux complaints and nutritional status were evaluated through face-to-face interviews with parents. Gingival enlargement was graded according to McGaw et al.[20] classification system.

Results

62.7% (n=32) of children with CP included in our study were boys and 37.3% (n=19) were girls. The mean age of the children was 9.63 ± 2.40 years. The most common type of CP in children with CP is spastic CP with a rate of 74.5% (Table 1).

Nutritional disorders were detected in 45% (n=29) of the children (Table 2) and one child was fed with percutaneous endoscopic gastrostomy. Among the factors that cause these disorders in children with nutritional disorders, there are mainly chewing and swallowing problems. There are two or more types of nutritional disorders in eight children.

While mouth breathing was detected in 57% (n=29) of children with CP, nasal breathing was observed in 43% (n=22).

GER complaints were detected in 19% (n=10) of children with CP.

45% (n=23) of children with CP have varying degrees of drooling outside of the mouth. The rate of children with CP who were found to have incorrect swallowing (simple tongue thrust, physiologic tongue thrust, and complex tongue thrust) was 63% (n=32). Incorrect swallowing was present in 91.3% of children with drooling outside of the mouth, and macroglassia was detected in four children with CP. A statistically significant difference was found between swallowing and the level of drooling outside of the mouth ($P<0.05$). In infantile swallowing, severe drooling was found in the first place and moderate salivary flow was found in the second rank. In the complex tongue thrust, on the other hand, drooling was found at the highest level. A higher rate of mild drooling was detected in patients with simple tongue thrust. In patients with adult swallowing patterns, no drooling was observed, or a low level of drooling was observed (Table 3).

53% of the examined children with CP use regular

Table 1. Distribution by gender and CP type

		n	%
Gender	Boy	32	62.7
	Girl	19	37.3
Type of CP	Ataxic	3	5.9
	Dyskinetic	5	9.8
	Mix	5	9.8
	Spastic	38	74.5
Total		51	100

CP, Cerebral palsy

Table 2. Distribution by type of malnutrition

		n	%
Type of malnutrition	Inability to finish the meal	10	34
	Difficulty swallowing food	8	28
	Vomiting after a meal	4	14
	Eating time longer than 45 minutes	7	24
Total		29	100

Table 3. Distribution according to the relationship between swallowing pattern and drooling level

	Mild		Moderate		Severe		None		
	n	%	n	%	n	%	n	%	*P*
Simple tongue thrust	1	33.3	3	27.3	2	22.2	6	21.4	
Adult swallow	2	66.7	0	0.0	0	0.0	17	60.7	<0,001
Infantile	0	0.0	5	45.4	6	66.7	4	14.3	
Complex tongue thrust	0	0.0	3	27.3	1	11.1	1	3.6	
Total	3	100	11	100	9	100	29	100	

medication (Table 4). The most common reason for using medications is epilepsy (45%; n=23), while other reasons for using medications are autism, thyroid and neurological disorders.

Table 4. Distribution by medication use

		n	%
Medication use	Yes	27	53
	No	24	47
	Total	51	100
Reason for using medication	Epilepsy	23	85
	Other	4	15
	Total	27	100

In 12% (n=6) of children with CP, the tonsillar tissue covers 50-75% of the airway patency. In 45 children with CP, it was determined that the tonsillar tissue was not large enough to affect the airway patency (Table 5).

No signs of gingival enlargement were observed in 32 children with CP (Table 6). 17 of 30 children without gingival enlargement (Grade 0) are using medication due to epilepsy. Seven of these children brush their teeth regularly and 10 of them do not brush their teeth regularly. Growth limited to the gingival margin (Grade 1) was detected in 12 children with CP. Seven of the children with Grade 1 gingival enlargement use medication due to epilepsy complaint, three of these children brush their teeth regularly and four of them do not brush their teeth regularly. Gingival enlargement covering the interdental papilla and marginal gingiva (Grade 2) was detected in seven children with CP. Three of the children with Grade 2 gingival enlargement use medication due to the complaint of epilepsy. Two of these children brush their teeth regularly and one of them does not brush their teeth regularly. Gingival enlargement covering 2/3 or more of the gingival crown (Grade 3) was not found in any of the children with CP.

Table 5. Distribution by tonsil size

	n	%
Grade 0	45	88
Grade 3+	6	12
Total	51	100

Healthy gingiva was found in 22% of children with CP, mild inflammation, discoloration and edema in a part of the gingiva were found in 33%. Mild inflammation in all regions of the gingiva was observed in 35% of the children, and moderate inflammation, red and edematous gingiva were observed in 10% of the children. Severe inflammation, marked redness of the gingiva, edema, and spontaneous gingival hemorrhage were not observed in any of the children (Table 6).

Table 6. Distribution by gingival enlargement and modified gingival index

		n	%
Distribution by gingival enlargement	Grade 0	32	63
	Grade 1	12	23
	Grade 2	7	14
	Grade 3	0	0
	Total	51	100
Distribution of modified gingival index	MGI 0	11	22
	MGI 1	17	33
	MGI 2	18	35
	MGI 3	5	10
	MGI 4	0	0
	Total	51	100

Discussion

In our study, since the patients were children with special needs, MGI measurement system was used to detect gingival inflammation. In this evaluation system, problems such as bleeding and pain do not occur, since probing is not performed on the gingiva. At the same time, studies have shown that MGI is as sensitive as the Gingival Index system, which measures by probing, in detecting gingival inflammation.[21] Periodontal problems are frequently observed in patients with CP due to the inability to provide effective oral hygiene and the side effects of the medicines used.[22]

In a study conducted on 105 children aged 14 and 15 with CP, the Gingival Index scores were found to be higher than the healthy children in the control group. It has been observed that the Gingival Index scores of the children who need help from their parents especially during tooth brushing.[23] In a different study conducted by Nouf et al.[24] on children with CP, it was stated that Gingival Index scores increase with age, and the reason for this might be Puberty Gingivitis, similar to normal children. Similarly, in our study, it was found that 78% of children with CP did not have healthy gums, and 31% had gingival enlargement. It has been observed that gingival enlargement is not only related to the medications used for epilepsy, but also due to inadequate oral hygiene of the patient. In addition to inadequate oral hygiene, many factors such as medications, mouth breathing, and nutritional deficiencies affect gingival inflammation. Since gingival inflammation is seen more frequently and more severely in children with CP than in healthy children, it is important to provide oral health education with their parents, to carry out this education in practice, to eliminate other predisposing factors, and to carry out frequent follow-ups and controls.

High incidence of GER in children with CP has been reported.[25] In a study conducted by Guare et al.[26], 43.5% of GER was detected in children aged 3-13 years. In a study conducted by Giudice et al.[27] in children with CP between the ages of 6 months and 12 years, the rate of GER was found to be 92%. The rate of GER in children with CP in our study was 10%. It is thought that the reason for these different results in studies may be due to the different age ranges of children with CP, the higher rate of GER at earlier ages, or the differences in body parts affected by CP among children. If dental erosions are observed in this group of patients, they should be referred to a gastroenterologist, and periodic examinations should be provided, and consumption of acidic beverages should be completely stopped for the health of soft tissues in the mouth.[9]

Rieken et al.[28], stated that the reason for the

underweight of children with CP compared to healthy children in the similar age group is not due to the high basal metabolic rates, but insufficient weight gain. Irregular drug use, discontinuation of drugs, nutrition of children with low-calorie foods, not spending enough time to feed the disabled child, increased calorie needs in the acute period of the disease, or stopping of oral nutrition due to hospitalization are among the possible causes of insufficient weight gain.[29] In our study, nutritional disorders were detected in 45% (n=29) of children with CP. Complaints include inability to swallow food, vomiting after eating, prolonged eating time, and inability to finish the meal. At the same time, the high rate of incorrect swallowing (63%) shows the importance of exercise and the use of appliances for correct swallowing habits in these children.

While drooling is considered normal in infants and young children, the continuation of this condition after the age of four is considered pathological. The salivary flow rate in children with CP ranges from 10% to 58%.[12,30] Due to this high saliva flow, the fact that the mouth area has to be wiped constantly causes irritation of this area, infection and at the same time, the isolation of children from social environments.[12] In our study, drooling was detected in 45% (n=23) of children with CP. In these children, the Innsbruck sensorimotor activator and regulator (ISMAR), Castillo Morales and Hinz appliance[31], tongue and lip exercises, oral motor therapy (OMAR) are the tools used to regulate saliva flow and gain correct swallowing habits. It is thought that starting the use of appliances and the tongue-lip exercises aimed at controlling the saliva flow of children at an early age of growth and development will provide an advantage in both the exercise of the oral region muscles and the adaptation of the patients to these appliances.

In the study conducted by Garde et al.[32] on 832 healthy children aged 6-12 years, the rate of mouth breathing was 4.3%, while the rate of incorrect swallowing was 4.9%. In studies on patients with CP, it has been found that mouth and facial structure disorders associated with incorrect tongue position, weak swallowing reflex, mouth breathing and orofacial muscle incoordination resulting from these reasons are high.[33] In our study, it was determined that the rate of mouth breathing in children with CP was 57%, and the rate of incorrect swallowing was 63%. It is important to determine the main factor that causes mouth breathing in children with CP. After the medical general evaluation, patients with mouth breathing after eliminating factors such as oral motor disorders, tonsillar hypertrophy, polyps, nasal septum deviation should work together with speech and language therapists, and respiratory physiotherapists.

Causes of mouth breathing in young children include allergic rhinitis and adenotonsillar hypertrophy, which cause mechanical obstruction of airflow.[34] Sakalli et al.[35] found that children with adenoid hypertrophy had higher levels of mouth breathing, drooling during sleep, and sleep disorders than children who had undergone adenotonsillectomy. In our study, adenoid hypertrophy was detected in five children with CP, and mouth breathing was observed in only three of these children. Adenoid hypertrophy was not detected in 26 children with mouth breathing. GER was evaluated only according to patient complaints and findings of intraoral erosion. The lack of a more detailed evaluation is one of the limitations of our study. Detailed investigation of the factors that cause mouth breathing in these children, elimination of the factor, correction of faulty breathing are important for the health of the hard and soft tissues in the mouth and face structure of children with CP and to increase the quality of life of children.

In conclusion, it is possible for these children to improve physically and mentally if the problems and needs of patients with CP are determined at an early age and treated on time. Realistic positive results can be achieved with long-term rehabilitation and correct guidance. A successful rehabilitation program can be carried out with the interdisciplinary work of a team of an orthopedist, a pediatric neurologist, a child psychiatrist, a physiotherapist, a clinical psychologist, an occupational therapist, a speech therapist, a

social service specialist, and an orthotics technician, together with the patient and his/her family.[36] While forming the team, it is important to include dentists experienced in the oral health of children with special needs.

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Case report

mucosa

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Laugier-Hunziker syndrome: a rare case report and review of the literature

Laugier-Hunziker sendromu: Nadir bir olgu sunumu ve literatürün gözden geçirilmesi

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Abstract

Laugier-Hunziker syndrome is a rare, hereditary pigmentary disorder characterized by mucocutaneous lentiginous lesions and melanonychia. The condition is regarded as benign since underlying malignancies or systemic disorders were not reported. Since various malignancy syndromes including Peutz-Jeghers and Cronkhite-Canada syndrome and systemic cause of hyperpigmentation such as Addison disease and drugs are presented with similar mucocutaneous findings, it is of paramount importance to assess the patients to exclude aforementioned conditions.

Key words: *Laugier-Hunziker syndrome, mucocutaneous hyperpigmentation, melanonychia*

Öz

Laugier-Hunziker sendromu, mukokutanöz lentijinler ve melanonişiyle seyreden nadir görülen kalıtsal bir pigment bozukluğudur. Bu sendroma, altta yatan bir malignite ya da sistemik hastalıkla henüz ilişkilendirilmediğinden benign olarak yaklaşılır. Peutz-Jeghers, Cronkhite-Canada sendromu gibi malignite sendromları ve Addison hastalığı, ilaçlar gibi hiperpigmentasyona yol açan durumlar da benzer mukokutanöz bulgularla seyrettiğinden, hastaların bu durumlar dışlanarak değerlendirilmesi önemlidir.

Anahtar kelimeler: *Laugier-Hunziker sendromu, mukokutanöz hiperpigmentasyon, melanonişi*

Introduction

Laugier-Hunziker syndrome (LHS) was first described in 1970 in five cases with acquired asymptomatic melanotic hyperpigmented macules of the oral mucosa, lips and fingers and longitudinal melanonychia without any systemic diseases.[1] To our knowledge approximately 200 cases of LHS were reported to date.

The underlying mechanism leading to the syndrome could not be elicited so far. Moreover, accompanying

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systemic disorders and associated malignancy were not established. Since very similar mucocutaneous lesions are also seen in malignancy syndromes, LHS is an exclusion diagnosis. It occurs predominantly in middle-aged individuals with an approximate ratio of female to male of 2:1. Nonetheless, child and adolescent cases and younger individuals were also reported.[2-4] The inheritance was not proven, however, a familial case of LHS was also reported.[5] Although an underlying systemic disease could not be shown, accompanying thrombocytopenia, anemia, hypocellular bone marrow, rheumatoid arthritis were reported.[6,7]

Case report

A 39-year old, smoker, female patient was admitted to our outpatient clinic due to the increasingly spreading dark pigmented asymptomatic lesions in her armpits existing for nine months. The patient did not describe fever, night sweats or weight loss. She denied abdominal pain, melena, hematochezia, fatigue, malaise as well as any malignancy. Her younger sister and maternal aunt were similarly affected. Her medication was limited to escitalopram 10mg/day. Her father died of larynx and colon cancer and her paternal uncle died of stomach cancer.

Physical examination revealed a Fitzpatrick 4 skin with diffuse hyperpigmented macules in axillae (Fig. 1), intermammary skin, labia majora and minora, and discrete hyperpigmented macules in the vestibulum. Bilateral palmar hyperpigmented macules were also detected. (Fig. 2) Moreover, both discrete and slightly coalescing hyperpigmented macules on the inner lips, gingiva (Fig. 3) and hard plate were observed. Regular longitudinal melanonychia of the index and middle finger was seen. Dermatoscopic examination of lentigines on the inner lips disclosed light brown dots and globules in varying sizes, a curvilinear pattern and a reticular pigment network. (Fig. 4) The mucosal lesion revealed a yellowish background. Neither of a ring-like, fish scale-like nor hyphal pattern, which were described mainly in benign mucosal lentiginous lesions, was observed. Subsequently, the patient has undergone a colonoscopy to exclude any malignancy accompanied by mucocutaneous hyperpigmentation disorders, which revealed no abnormal findings. Endoscopy of the upper gastrointestinal tract revealed antral gastritis and bulbitis without any suspicious findings of malignancy. Laboratory tests including complete blood count with renal and liver biochemistry were normal except for a decreased serum hemoglobin and hematocrit level. A peripheric blood smear was performed and revealed hypersegmented neutrophils as wells as hypochromic erythrocytes with anisocytosis. Accordingly, our patient was given iron and B12 replacement therapy.

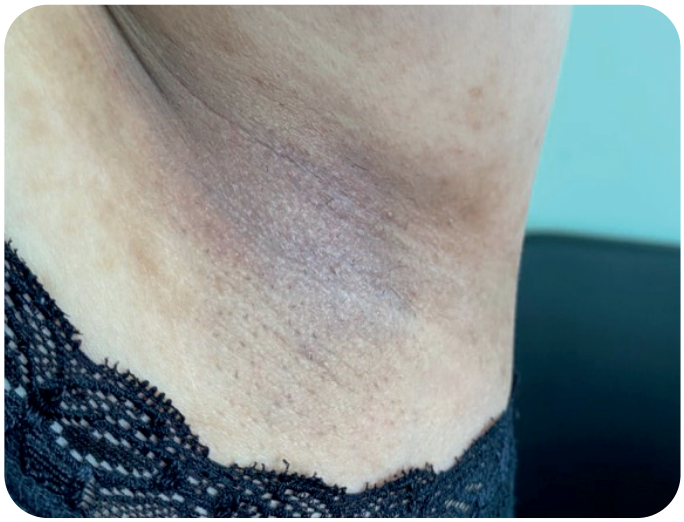

Fig. 1. Diffuse hyperpigmentation of axilla, light-brown discrete macules

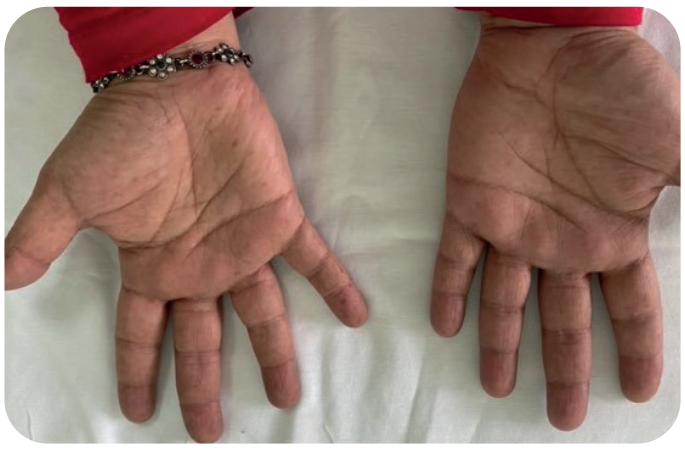

Fig. 2. Discrete macular hyperpigmentation of palms

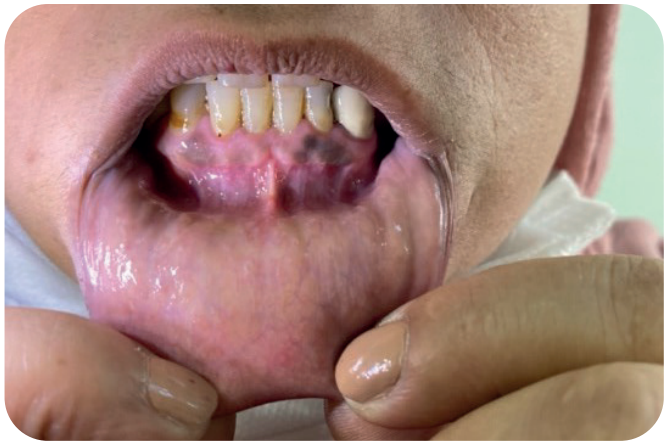

Fig. 3. Hyperpigmented macules on lower gingival mucosa and yellow discoloration of inner lips

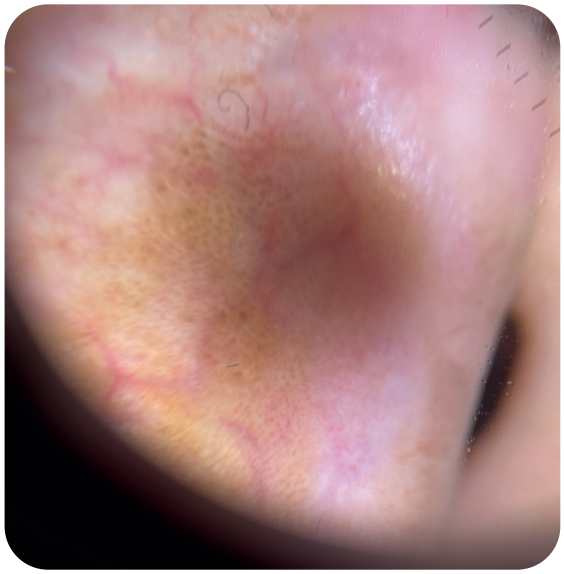

Fig. 4. Light brown dots and globules, a curvilinear pattern and reticular pigment network

A biopsy of a representative lesion on the axillary skin was performed and histopathologic examination displayed hyperkeratosis, a mild spongiosis and increased pigmentation of the basal layer in the epidermis. Pigment incontinence, melanophages and perivascular chronic inflammatory cell infiltration were also reported in the superficial dermis. PAS stain was negative and no spores or hyphae were observed.

A diagnosis of LHS was made according to the distribution of pigmentation, lack of any evidence or suspicion of malignancy and a previous history of malignancy. An informed consent was taken from the patient for publication.

Discussion

LHS clinically presents mainly with mucosal (oral, labial, gingiva, hard palate, buccal mucosa, conjunctiva, glans penis, vulva, labia majora) and acral lentiginous macules. Less often, macules on the neck and trunk are seen. Longitudinal melanonychia is a typical finding, observed in approximately half of the patients.[8] Baran described three types of melanonychia in LHS. The first type was described as isolated longitudinal streaks of varying degrees of pigmentation 1 to 2mm in width while the second type presents as double longitudinal streaking in one or more fingernails, usually involving the lateral parts of the nail plate 2 to 3mm in width. The third variety exerts itself as homogenous staining of the radial or ulnar half of the nail of one or more fingers.[9]

Longitudinal melanonychia is a physiological finding in dark-skinned individuals and can be present in single or multiple pigmented bands in one or more digits. Onychotillomania related traumatic longitudinal melanonychia, drug-induced melanonychia (zidovudine, minocycline, hydroxyurea etc.), lichen planus associated nail hyperpigmentation, exogenous pigmentation (dirt, tobacco, silver nitrate, heavy metals), bacterial infections (P. *aeruginosa*, *Klebsiella* and *Proteus spp.*), onychomycosis, nevus, Bowen's disease and melanoma are the other causes of longitudinal nail hyperpigmentation.[8] Longitudinal melanonychia in malignancies is typically characterized by grey to black streaks with varying colour and width, and occasionally nail dystrophy, onycholysis and bleeding mass could accompany. Hutchinson's sign (pigmentation of proximal and lateral nail folds adjacent to the nail) is another clinical clue for malignant melanoma.[8]

Dermatoscopically, brown reticular pattern with linear-curvilinear vasculature, multiple brown dots, multiple blue-grey granular patterns and a regular

brown reticular pattern, homogenous blue area and fish scale-like pattern in mucosal lesions, parallel furrow pattern, fibrillar pattern in the palmoplantar region were reported previously in LHS.[8]

Pathologically, melanin accumulation of the basal layer of the epidermis (sometimes limited to the rete ridges), an increased number of melanophages and pigmentary incontinence in the upper dermis, occasionally increased numbers of non-nested melanocytes in the epithelial basal layer, acanthosis, hyperkeratosis as in our case and spongiosis were described.[8]

Since LHS is an exclusion diagnosis, the overview of diseases with similar presentations should be evaluated elaborately. Syndromic hyperpigmentation disorders are summarized in table 1.

Regarding differential diagnosis, the mucocutaneous lentiginous lesions in Peutz-Jeghers syndrome (PJS) are present at %95 of cases since birth or develops in infancy, often fade after adolescence. Thereafter buccal lesions usually persist. This autosomal dominant inherited syndrome due to the germline mutation in STK11 gene is associated with gastrointestinal hamartomatous polyps and internal malignancies including colon, breast, pancreas, ovaries etc. In asymptomatic individuals with PJS, a lifetime cancer surveillance including oesophagogastroduodenoscopy and colonoscopy beginning at the age of 8 years, breast imaging and testicular examination are recommended.[8]

Multiple lentigines are also seen in LEOPARD syndrome (lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, deafness). In Carney complexes including LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) and NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides) syndrome, spotty facial hyperpigmentation is prominent. Oral, genital, conjunctival mucosa may also be affected.[8]

In Addison's disease, the primary adrenal insufficiency, generalized hyperpigmentation prominently in sun-exposed and body sites under chronic pressure of friction were main characteristics. Moreover, the vermilion border of the lips, nails, hair and freckles may darken. Buccal, vaginal and anal mucosal pigmentation also occur. McCune-Albright syndrome is another sporadic disorder due to a somatic mutation of GNAS gene. It presents classically with café-au-lait macules which can be unilateral with midline demarcation or following Blaschko lines. They are mainly located to the neck, sacrum and head. Polyostotic fibrous dysplasia, hyperfunctioning endocrinopathies such as puberty precocious, hyperthyroidism, Cushing syndrome are the main features.[8]

Neurofibromatosis type 1 is an autosomal dominantly inherited disease due to a mutation in the NF1 gene and characterized with café-au-lait macules with smooth borders, in contrast to McCune-Albright syndrome, axillary, and inguinal freckling, multiple neurofibromas, optic glioma, Lisch nodules and skeletal malformations.[8] Cronkhite-Canada syndrome is a non-hereditary gastrointestinal polyposis syndrome characterized by cutaneous and oral melanotic macules, alopecia, onychodistrophy and seen mainly in men after the 6th decade.[8]

Regarding labial and oral mucosal lesions, amalgam tattoos, smoker's melanosis, drug-induced mucocutaneous pigmentation (minocycline, chloroquine, ketoconazole, clofazimine, zidovudine, cyclophosphamide, doxorubicin, hydroxyurea, amiodarone, oral contraceptives etc), melanocytic nevus and melanoacanthoma, melanoma and physiological ethnic pigmentation are other causes of hyperpigmented lesions.[8]

Since association with any systemic diseases or malignancies could not be established in LHS, it is regarded as a benign condition and no treatment is required. Regarding cosmetic concerns, several case reports of successful therapies with Q-Switched Alexandrite, Er:YAG and Q-switched Nd:YAG laser were published. However, the recurrence of the lesions rises as a challenge to overcome.[10]

Table 1. A Summary of syndromic hyperpigmentation disorders

Differential Diagnosis	Hyperpigmentation Type	Other Features
Peutz-Jeghers syndrome (PJS)	Mucocutanoeus lentigines mostly present at birth Buccal lesions persist after adolescence	Autosomal dominant inheritance Mutation in STK11 gene Gastrointestinal hamartomatous polyps Malignancies of colon, breast, pancreas, ovaries, etc
Leopard syndrome	Multiple lentigines on the face and trunk Appear at the age of 4-5, increase throughout puberty	Autosomal dominant Inheritance Frequently mutation in PTPN11 gene **L**entigines **E**lectrocardiogram abnormalities **O**cular hypertelorism **P**ulmonary stenosis **A**bnormal genitalia **R**etardation of growth **D**eafness
Carney Complex	Spotty facial hyperpigmentation Oral, genital, conjunctival mucosal hyperpigmentation	
LAMB	Lentigines Blue nevi	Atrial myxoma Mucocutaneous myxoma
NAME	Nevi Ephelides	Atrial myxoma Myxoid neurofibroma
McCune-Albrigt syndrome	Unilateral café-au-lait macules with midline demarcation or following Blaschko lines Located to the neck, sacrum and head	Mutation in GNAS gene Polyostotic fibrous dysplasia Hyperfunctioning endocrinopathies (puberty precocious, hyperthyroidism, Cushing syndrome, etc.)
Neurofibromatosis type 1	Axillary and inguinal freckling	Autosomal dominant inheritance Multiple neurofibromas Optic gliomas Lisch nodules Skeletal malformations
Cronkhite-Canada syndrome	Cutaneous and oral melanotic macules	Non-hereditary Gastrointestinal polyposis Alopecia Onychodistrophy Men after the 6th decade affected
Addison's disease	Generalized hyperpigmentation in sun-exposed areas Darkened vermilion, nails, hair and freckles Buccal, vaginal and anal mucosal pigmentation	Primary adrenal insufficiency

Informed consent: The author certifies that she has obtained all appropriate consent forms from the patient.

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Final approval of the version to be published: HE

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A case of syphilis followed as alopecia areata

Alopesi areata olarak izlenen bir sifiliz olgusu

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Dear editor,

A 33-year-old male patient presented with the complaints of a gray-white plaque lesion on the distal end of the tongue (Fig. 1a) and lower surface which started 2-3 days ago. In addition, there were multiple linearly arranged patchy alopecia areas on the left side of the beard area (Fig. 1b), and he was followed up with the diagnosis of alopecia areata in the outer center. In genital examination, on the dorsolateral side of the penis, a painless, crusted, ulcerated lesion (Fig. 1c), which was noticed before the beard loss and is now healing, was observed. There was a history of painless lymphadenopathy, myalgia, and arthralgia in the cervical and inguinal region. He had a history of suspicous sexual intercourse. He had no known additional disease. The patient was thought to be in the secondary syphilis stage with the presence of syphilitic alopecia and plaque mucous, which started after genital ulcer. Treponema pallidum Haemagglutination Test (TPHA) and venereal disease research laboratory (VDRL) were positive in the patient who was examined for sexually transmitted diseases. A single dose of intramuscular Penicillin G benzathine, 2.4 million U, was planned.

Syphilis, caused by Treponema pallidum, is the oldest known sexually transmitted disease.[1] There is an incubation period of 20-90 days after infection.[2] Syphilis is known as the "great imitator" because of a wide variety of symptoms and these differences in the time it takes for the lesions to appear.[1] Primary syphilis is characterized by a mouthless solitary chancre. It is classically located in the genital area. If this self-resolving lesion is not treated, secondary syphilis develops with hematogenous spread. At this stage, many mucocutaneous skin lesions such as condyloma latae, hand and foot lesions, macular rash, alopecia may be accompanied by various symptoms such as diffuse lymphadenopathy, headache, myalgia, arthralgia, pharyngitis, hepatoslenomegaly, and fatigue.[2] In secondary syphilis, slightly elevated and white or grayish plaques are most frequently encountered in the oral mucosa.[3] Alopecia is a rare manifestation of syphilis. It is thought to be between 2.9 and 7%.[4] It is most commonly encountered as a patchy "Moth-eaten" pattern, and this pattern is considered pathognomonic for secondary syphilis.[5] If the diagnosis is not made and treatment is not given in the secondary syphilis

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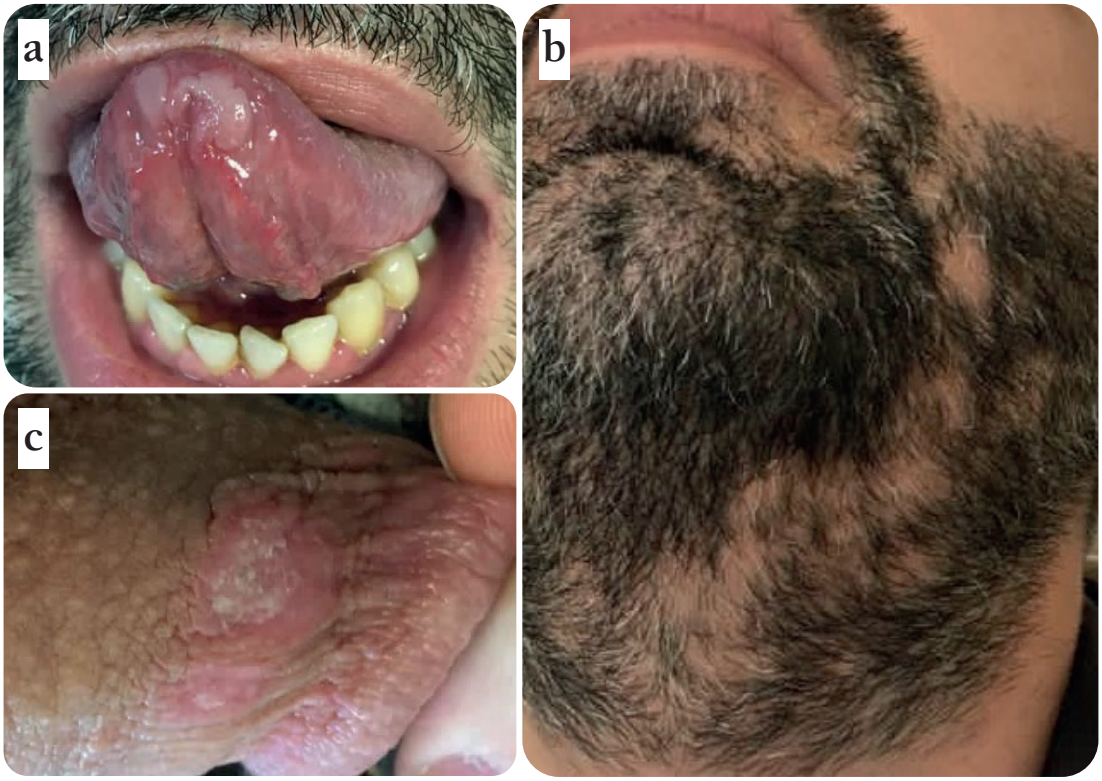

Fig. 1. Gray-white plaque lesion on the tongue (1a), Linearly arranged patchy alopecia areas (1b),Crusted ulcerated lesion (1c)

stage, which can also regress spontaneously, the latent phase is entered. Some patients at this stage develop tertiary syphilis, characterized by cardiovascular syphilis, neurosyphilis, and late benign syphilis.[2]

Immunological tests (treponemal and non-treponemal) are used for diagnostic and follow-up purposes in clinical practice. Treponemal tests such as TPHA detect antigen-specific antibodies that continue to respond throughout life regardless of treatment. Non-treponemal tests detect non-specific antibodies such as cardiolipin antibody detected in VDRL. They are semi-quantitative tests. Titration is determined and followed.[6]

As the first step in treatment; in primary, secondary, or early latent syphilis, intramuscular penicillin G benzathine is administered as a single dose of 2.4 million units; it is done once a week for three consecutive weeks in late latent syphilis and tertiary syphilis.[2]

Early diagnosis and treatment are very important to reduce transmission. Untreated disease can last for decades.[1] Syphilis, which is a great imitator, should always be kept in mind as a differential diagnosis in daily practice. Our patient first applied to the doctor with the complaint of alopecia. He also had an old genital lesion at that time, but the patient did not express this complaint. When questioned later, he said to have had a genital lesion when he came for an oral mucosal lesion. Therefore, our threshold for suspecting syphilis and looking for serology should be low. Suspicous sexual intercourse should be questioned in patients and oral-genital mucosa examination should be performed.

Informed consent: The author certifies that she has obtained all appropriate consent forms from the patient.

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Association of acrodermatitis continua of Hallopeau and fissured tongue

Akrodermatitis Kontinua Hallopeau ile fissüre dil birlikteliği

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Dear editor,

A 32-year-old male patient was admitted to our dermatology and venereal diseases clinic with complaints of periungual erythema and pustular lesions on the fingers. (Fig. 1). The patient had been followed for 20 years with the diagnosis of acrodermatitis continua of Hallopeau. Fissured tongue (FT) was detected in the oral examination of the patient. (Fig. 2). The patient was previously treated with tetracycline 200 mg/d for three months, colchicine 1.5 g/d for six months, dapsone 100 mg/d for one year, methotrexate 15 mg/w for one year, acitretin 35 mg/d for two years, and cyclosporine 200 mg/d for six months, and these treatments were partially effective. The patient was started on adalimumab 40 mg/2 weeks sc. treatment. At the 6th month of adalimumab treatment, the skin lesions healed almost completely, but no change was observed in FT. Written consent was taken from the patient.

FT consists of a deep cleft along the long axis of the tongue on the dorsum of the tongue and usually in the middle of the tongue, and irregular smaller clefts right next to it.[1] FT affects 2-5% of the general population and increases with age, but its incidence has been reported to be up to 30% in some populations.[1-3] Jahanbani et al., reported a three-fold higher incidence of FT in smokers compared to non-smokers.[4] FT appears to be the most common oral lesion in psoriatic patients. The reported prevalence of FT ranges from 6% to 47.5%.[5] Costa et al.[6] showed the presence of FT in 34.3% of 166 patients with psoriasis and geographic tongue (GT) in 18% of patients. Perez et al.[7] reported FT in 47% and GT in 12.5% of 80 psoriatic patients. Pourchot et al., reported tongue involvement in 7.7%, 4.2% as GT, 2.8% as FT and 0.64% as both, of 313 children with psoriasis. No correlation was found between tongue involvement and clinical features of the children.[8] Picciani et al., stated that FT is associated with late-onset psoriasis, but not with psoriasis severity.[9] D'Erme et al., reported a 60-year-

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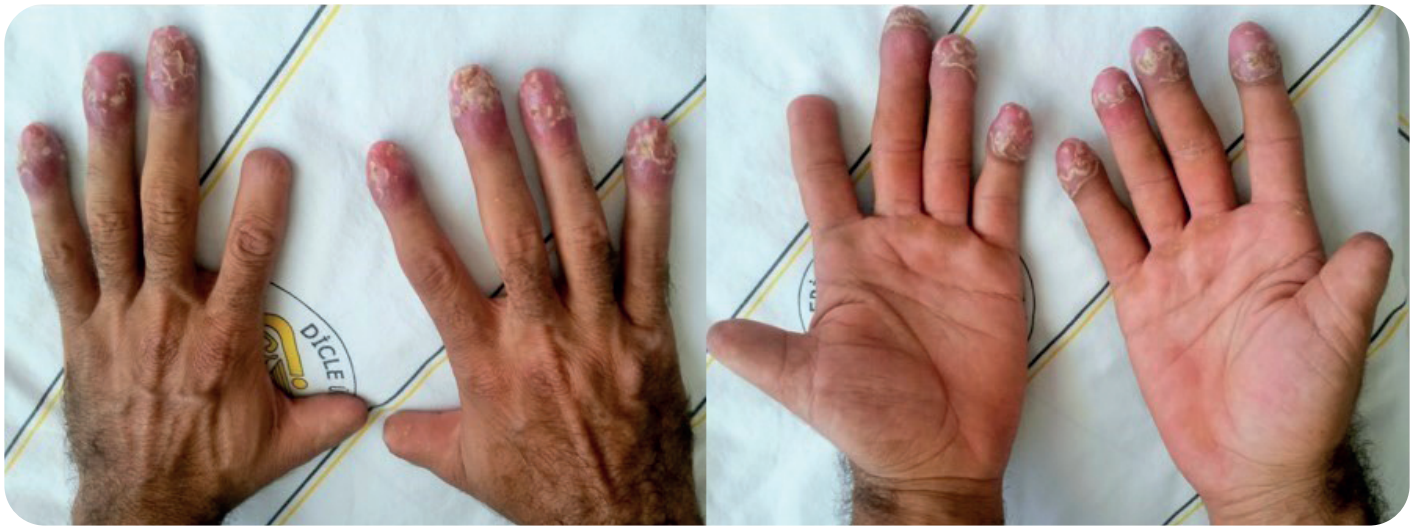

Fig. 1. Periungual erythema and pustular lesions on the fingers

old man with psoriasis who presented with FT at the beginning of the treatment and whose skin and oral lesions improved 5 months after he was treated with infliximab.[10] Similarly, Tonini et al., reported a 16-year-old girl with psoriasis who was treated with ustekinumab and achieved mucocutaneous improvement after 16 weeks of treatment.[11] In our patient, at the 6th month of adalimumab treatment, the skin lesions healed almost completely, but there was no change in FT. We think that FT seems refractory to systemic therapy in psoriasis patients.

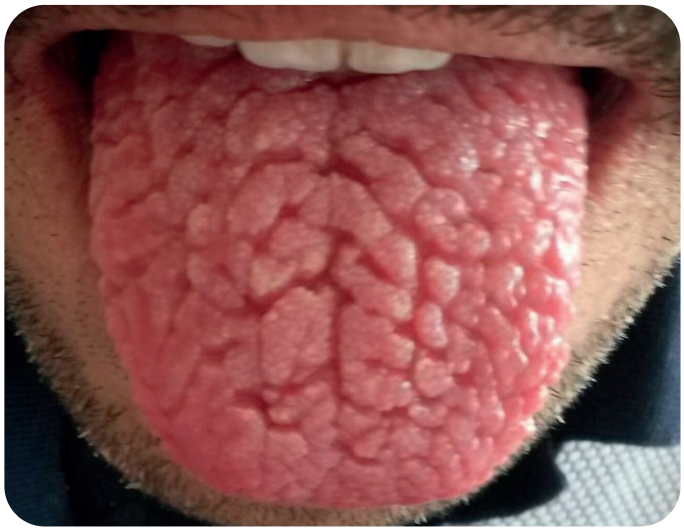

Fig. 2. Fissured tongue

Clinicians should not skip the oral mucosal examination in patients with psoriasis and should be aware of the association of acrodermatitis continua of Hallopeau and fissured tongue.

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