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Rare Diseases

Recent Advances

Edited by John Kanayochukwu Nduka and Sevgi Akarsu

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Meet the editors

John Kanayochukwu Nduka, Ph.D., is a professor in the Department of Pure and Industrial Chemistry, Nnamdi Azikiwe University, Nigeria. He is the head researcher in the Environmental Chemistry and Toxicology Unit with a focus on public health and was a former head of the department. Dr. Nduka has published several scientific articles and is involved in mentoring young academics at Nnamdi Azikiwe University. He has served as head and member of the National University Commission resources verification exercise to various universities in Nigeria for chemistry programmes. In 2020, he received a RULA award for international best researcher in environmental chemistry and toxicology. He was also listed among the top 100 researchers by Nnamdi Azikiwe University. He has attended several local and international conferences and workshops and delivered numerous lectures.

Professor Doctor Sevgi Akarsu graduated from the Faculty of Medicine, Ege University, Turkey in 2000. She completed her specialization at the Department of Dermatology, Faculty of Medicine, Dokuz Eylul University, Turkey, in 2004 and has continued her academic career at the same university without interruption. She has supervised several master's and postdoctoral students at the university, as well as published scientific research articles, case reports, and reviews in different journals. Her special interests are psoriasis, dermato-allergy, acne, urticaria, Behçet's disease, psychodermatology, and photodermatology.

Contents

Preface

We are increasingly exposed to chemicals, toxins, and nuclear and electronic radiation, either through our food or our environment. Environmental and climatic factors can cause disease outcomes, and rates of occupational and technology-induced pathologies have surpassed those of communicable diseases. Globally, people in different work environments and climates are experiencing unexpected health issues not previously envisaged. Office workers who sit for long hours working with computers or other electronic devices report low back and spine pain as well as issues with eyesight. Workers exposed to asbestos and cement dust have been diagnosed with lung diseases and inhalation problems, including some forms of cancer. Those exposed to localized environments of extreme heat may develop heat rash, heat edema, heat syncope, cramps, exhaustion, life-threatening heatstroke, and other related ailments. Some ailments may not yet have a known origin and these diseases require more research to ascertain their causes and treatments. This book provides insight into rare diseases of public health importance.

Chapter 1, "Introductory Chapter: Possible Occupational, Technological and Climatic Contributions to Rare Diseases Occurance", reviews the effects of technology, climate, and occupation on health. For example, contact with environmental toxins such as soot, nitrates, NH3 and nitrogenous gaseous oxides (NOx), sulphur oxides, aerosols, CH3, and particulate matter activate biomarkers that cause enzyme hormonal distortion, inhibition of fetal growth, and DNA damage. The chapter focuses on technology-induced and occupational hazards such as exposure to chemicals, machines, noise, and radiation, as well as climatic causes of rare diseases.

Chapter 2, "A Short Overview of Behcet's Disease", describes Bechet's as a chronic, relapsing-remitting, occlusive vasculitis affecting multiple organ systems characterized by oral and genital aphthous ulcers, arthritis, cutaneous lesions, and ocular, gastrointestinal, and neurological manifestations. Behcet's disease etiology remains uncertain, but various studies suggest an infectious trigger with inflammatory mediators and immune deregulation as the cause of a genetically susceptible host. Environmental factors such as exposure to organophosphates, heavy metals, organochlorides, and allergens exacerbate Behcet's disease.

Chapter 3, "Entero-Behcet: A Challenging Aspect of Behçet's Disease", discusses entero-Behcet's, a primitive vasculitis of unknown origin featuring recurrent oral and/or genital aphthosis, ocular manifestations, and arthritis. Intestinal presentation of the disease is rare; prevalence is about 5%–10%. It may be very severe and is difficult to diagnose and differentiate from inflammatory bowel disease, especially when it is the initial manifestation. Genetic factors, which cannot completely explain the emergence of Behcet's disease, include the human leukocyte antigen (HLA)-B51 allele, ERAP 1, and MHC class I-related gene A (MICA).

Chapter 4, "Genetics of Behçet's Disease," discusses the genetics of Behçet's disease. Although pathogenesis remains uncertain, genome-wide and validation studies have

shown that genetic predisposition is a major factor in disease susceptibility. Behçet's disease is diagnosed worldwide, but the highest prevalence is reported in countries stretching from Japan to the Mediterranean region along the ancient trading route the Silk Road.

Chapter 5, "Malignant Mesothelioma *In Situ*: A Controversial Diagnostic Entity – A Review", examines the aggressiveness of malignant serosal surfaces strongly associated with asbestos exposure. Malignant mesothelioma can be difficult to distinguish from reactive benign hyperplasia. Mutations in BAP-1 and CDKN2a distinguish mesothelioma from reactive hyperplasia. Malignant mesothelioma is a rare malignancy of serosal-lined surfaces and the tumors can potentially invade local tissues and metastasize to distant sites. The World Health Organization's (WHO) newest classification of thoracic malignancies adds malignant mesothelioma in situ as a distinct diagnostic entity.

Chapter 6, "Diagnosis of Dentofacial Anomalies", examines dentofacial anomalies, including clinical features, diagnostic criteria, and investigation protocols. These anomalies involve the dentofacial region and may be related to teeth, maxilla, mandible, and soft tissue. They are syndromic conditions that can spread to various other vital organs. Alterations of craniofacial form, structure, or function are the cardinal features of these conditions. Therefore, clinicians should be knowledgeable about dysmorphological changes in orofacial structures so they can consider certain specific disease entities and rule out the involvement of other tissues and organ systems that may present similarly.

Chapter 7, "Neuropathic Pruritus: An Underrecognized and Often Misdiagnosed and Difficult to Treat Medical Condition", reviews case reports, clinical trials, cohort studies, systematic reviews, and meta-analyses associated with neuropathic pruritus. Statistical estimates suggest that about 8% of chronic pruritic cases are of neuropathic origin. Damage to any part of the peripheral and central somatosensory system can lead to neuropathic pruritus. Common neuropathic pruritic syndromes include different clinical presentations such as postherpetic pruritus, trigeminal trophic syndrome, anogenital pruritus, scalp dysesthesia, nerve compression syndromes (e.g., notalgia paresthetica, brachioradial pruritus), and small-fiber neuropathy (secondary to various metabolic, infectious, autoimmune, and genetic diseases).

Chapter 8, "Lipoatrophia Semicircularis", discusses a rare, benign, and reversible subcutaneous tissue atrophy that mostly affects women. It appears mainly on the anterior and lateral regions of the thighs and consists of unilateral, bilateral transverse, semi-circular, and depressed bands appearing approximately 72 cm from the ground. The cause is not yet known, but an unproven hypothesis suggests circulatory abnormalities, microtraumas, wearing of tight trousers, exposure to electromagnetic fields in the work environment, or electrostatic charges generated from computers or printers as possible causes of bioelectric changes in the skin.

Chapter 9, "Short QT Syndrome: Update on Genetic Basis", describes short QT syndrome (SQTS) as an extremely rare inherited arrhythmogenic entity; it affects less than 200 families worldwide. The prevalence estimate is less than 1/10.000 in adults and about 1/2000 in children and adolescents. SQTS is potentially lethal for children in the first year of life. It leads to cardiac arrest in close to 4% of patients, making it

one of the causes of sudden infant death syndrome (SIDS). SQTS is characterized by a short QT interval when ECG shows asymmetric and sharp T waves in the precordial area. Resting ECG should be performed at a normal heart rate when SQTS is suspected Ventricular and atrial fibrillation are present in most patients and cardiac events usually occur in adrenergic situations (noise or exercise). The most common symptoms are palpitations (30%), syncope (25%), and cardiac arrest (40%).

The editors wish to thank the authors for their hard work, faith in us, and worthy contributions. We are also thankful for the staff at IntechOpen, especially Author Service Manager Ms. Nika Karamatic. Finally, we thank our families for their understanding and support throughout the process of editing this book.

Editor Nduka is grateful to his wife Ogochukwu and his children Chimerem-mma, Onyinye, and Chisom.

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Section 1

Environmental, Technological and Climatic Induced Diseases

Chapter 1

Introductory Chapter: Possible Occupational, Technological and Climatic Contributions to Rare Diseases Occurance

John Kanayochukwu Nduka

1. Introduction

The quest to ensure public health is at the front burner of all government around the world over but these efforts cannot be a reality if Sub-Saharan Africa and less developed countries of the world does not take center stage in health planning of the advanced countries. COVID-19 outbreak has proven that no country is immune to health catastrophe and poor nations face more devastating consequences in major disease outbreak, as a result of poverty and inadequate public health infrastructure and lack of up to date medical record, it implies that many emerging diseases are not well documented and reported, coupling this scenario with devastating effect of noncommunicable diseases that has been ranked highest killer in some African country [1]. As a result, large-scale initiatives, updated medical records, training, and disease outbreak reporting are needed to help support the effort of various governmental and nongovernmental agencies in establishing accessible public health services. Potable water supply in Sub-Sahara Africa is an uphill task due to inadequate policy formulation to cover poverty and disease-laden rural dwellers. A decade ago, Ebonyi State in Nigeria was devastated by guinea worm infestation of water sources that it needed international support for eradication [2, 3], yet, it is possible that in local water source**s,** inorganic and organic chemical pollution was not taken into account by the relevant authorities in the same way that the guinea worm was.

2. Factors that may encourage rare diseases

2.1 Technology and occupation

As knowledge multiplies, it acts synergistically with technology, and recent advances in the field of environmental health are a gateway to health hazards, risks, and susceptibilities. Technological advances have brought more people together, increased production processes but inadvertently led to more consumption, and accompanied wastes (gaseous emission, solid, and liquid waste), which exacerbate human health *via* devastation of aquatic ecosystem, pressure on water resources, deforestation, and increase in agricultural chemicals. Human occupational exposure/contact through inhalation, ingestion, and dermal contact causes enzyme hormonal

distortion, inhibits fetal growth, and activates DNA damage. A hallmark of technology is in industrial emission, transportation such as roads, aviation, radiation from telecommunication, and military armaments activates climate change imprint. Air pollution occasioned by dust particles, vehicular emission, soot, nitrates, NH_3 and nitrogenous gaseous oxides (NOx), oxides of sulfur, aerosols, CH_3, PM2.5, and PM10 activate biomarkers (ceruloplasmin, orosomucoid, C3, and alpha-1-antitrypsin), which may be a pointer to high risk at moderate exposure levels that significantly and positively elevate the risk of cardiovascular disease *via* chronic systemic inflammation [4]. The aforementioned effect also exacerbates and promotes progression of atherosclerosis and ups cardiovascular events, including regularity of noncommunicable respiratory diseases (NCRDs) with asthma, chronic bronchitis, obstructive respiratory disease, and allergic rhinitis [5, 6]. Human ailments such as cancer, renal issues, cognitive impairment, bronchitis, and neurological disorders have been attributed to environmental toxicants such as heavy metals (Cd, Ni, Cr, Pb, Hg, As) [7], which partly correlates with findings of Unachukwu et al. [1], agreeing with several pieces of literature linking heavy metals to noncommunicable diseases. Pb^{+2} and metals like Cd^{+2} activates blood lipids, which undermine cardiovascular ailment (CVD) and atherosclerosis, exacerbating blood pressure (BP) rise and hypertension that triggers stroke, diabetes, pollution keratoconjunctivitis (PKC) [8–10]. Human factors that may exacerbate the occurrence of rare diseases may include low attention emission from pharmaceutical industries, inappropriate government policy, lack of public health advocacy groups, poor coverage, low monitoring, and inadequate reportage by the global health research community. Occupational **e**xposure plays a major role in rare disease occurrence**,** hexavalent chromium (Cr^{+6}) is carcinogenic, corrodes skin, and causes denaturation and precipitation of tissue proteins [11]. Occupational exposure to chromium is mostly by inhalation, but gastrointestinal tract and skin can occur [12], hence respiratory tract is the primary target organ for Cr^{+6} and its compounds. Nickel is absorbed through the lungs [13, 14], gastrointestinal tract [15], and skin [16], but excreted in the urine [17]. Artisanal effect, respiratory abnormalities, and industrial occupation take a huge aspect of rare disease that may be undocumented [18] and show that it may be significant in public health issues through occupational exposure considering the work of Orisakwe et al. [19, 20] and that of Vitayavirasuk et al. [21], which shows that subjects exposed to heavy metal in a paint factory and automobile paint spray may have compromised health status.

3. Climate change and rare disease occurrence

Literature documentation on potential and prevalence of infectious disease as a result of climate variability exist. Infectious disease occurrence history is rooted in geography and prevalent in places with hot and wet weather [22], likewise in global warming episodes, it is expected that diseases will spread further as it play role in the widespread emergence, resurgence, and redistribution of infectious diseases. Most commonly, insects transmitted diseases are highly sensitive to variations in climate alternation. Included in this category are the vector–borne communicable diseases like dengue, malaria, hantavirus, and cholera, others are salmonellosis, cholera, and giardiasis [23]. Temperature variation may likely cause changes in the life cycle of pathogens as it can cause death of pathogens. Again, elevated temperatures have been documented to affect the fertility and sporogony of microorganisms [24]. Changes in climatic parameters such as humidity, amount, volume, and duration of rainfall may

influence distribution of waterborne pathogens that are prevalent in the rainy season. In extremely high-temperature duration that can cause drought, the water resources of the given location tend to decrease and concentrate, and effluent waterborne pathogens rise in amount and effect [25]. Infectious diseases are also influenced by atmospheric water (humidity) vapor, a well-known example is the influenza virus transmission and rate of survival. An important fact about climate change's impact on infectious diseases is that it cannot be generalized, the effect peculiar to a given environment may differ from another as climatic factor change. Microclimate may have profound effect on hosts housing disease pathogens as well as host. Pattern of changes in population and geographical location influences insect vector that is strictly associated with pattern and variation in climates, small scaled environment (microenvironment) may act as a shield to contain disease vector/host, for the fact that microclimate variation is insignificant but on large-scale climate differences over regional influence scenario may differ [26]. A localized environment of extreme heat may have heat rash, heat edema, heat syncope, cramps, exhaustion, life-threatening heatstroke, and other related ailments as major occurrences of diseases among the populace.

The book – Rare Disease is aimed at documenting information about certain diseases that occasionally occur or may be strange, it may have been witnessed before or reemerged, and it will espouse its fatalities, treatment options, and its containment. It will contain information on possible causes or outbreaks, point of its discovery, nature of the disease, infection rate, possible causative agents and life span, and information about conditions enabling its spread. The book will contain information on effect of the disease on age group, color, sex, and occupation. Climate and environmental parameters that aid survival of causative organisms and their transmission will be discussed. The book will also contain information on cultural practices that exacerbate the outbreak, progression, and fatalities of disease. Finally, the book will contain information on drugs, herbal products, and supplements for treatment. Possible patient medical history and genetic makeup in relation to the disease can be important information. Advise on personal and community hygiene for effective prevention and treatment in an emerging scenario. Public health and policymakers' responsibility in prevention and management of outbreaks of rare diseases to ensure minimal fatalities will be highlighted.

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References

[1] Unachukwu CN, Agomuo DD. Pattern of non-communicable diseases among medical admissions in port-Harcourt, Nigeria. Nigerian Journal of Clinical Practice. 2008;**11**(1):14-17

[2] Anosike JC, Azoro VA, Nwoke BEB, Keke RI, Okere AN, Oku EE, et al. Dracunculiasis in the north eastern border of Ebonyi state, south eastern Nigeria. The International Journal of Hygiene and Environmental Health. 2003;**206**(1):45-51. DOI: 10.1078/1438-4639-00176

[3] Nwakor FN, Ekwe KC, Azoro VA. Prevalence and disabilities caused by Guinea-worm disease, (dracunculiasis) infection among rural dwellers in Ebonyi state, Nigeria. Journal of Agriculture and Social Research (JASR). 2008;**8**(2):1-7

[4] Nduka JK, Umeh CT, Kelle HI, Mgbemena MN, Nnamani RA, Okafor PC. Ecological and health risk assessment of heavy metals in roadside soil, dust and water of three economic zones in Enugu urban, Nigeria. Urban Climate. 2023 (In press)

[5] Mehjar A, Yiyi X, Lars B, Bjorn F, Bengt Z, Peter M, et al. Air pollution and biomarkers of cardiovascular disease and inflammation in the Malmö diet and cancer cohort. Environmental Health. 2022;**21**:39. DOI: 10.1186/s12940-022-00851-1

[6] Glenn BE, Espira LM, Larson MC, Larson PS. Ambient air pollution and non- communicable respiratory illness in sub-saharan Africa: A systematic review of the literature. Environmental Health. 2022;**21**:40. DOI: 10.1186/s12940-022-00852-0

[7] Meeker JD, Rossano MG, Protas B, Diamond MP, Puscheck E, Dally D, et al. Cadmium, lead and other metals in relation to semen quality: Human evidence for molybdenum as a male reproductive toxicant. Environmental Health Perspectives. 2008;**116**(11):1473-1479. DOI: 10.1289/ehp.11490

[8] Ademuyiwa O, Ugbaja RO, Idumebor F, Adebawo O. Plasma lipid profiles and risk of cardiovascular disease in occupational lead exposure in Abeokuta, Nigeria. Lipids in Health and Disease. 2005;**4**:19

[9] Asonye CC, Bello ER. The blight of pollution keratoconjunctivitis among children in oil-producing industrial areas of Delta state Nigeria. Ecotoxicology and Environmental Safety. 2004;**59**:244-248. DOI: 10.1016/j.ecoenv.2003.12.011

[10] Orisakwe OE. Lead and cadmium in public health in Nigeria: Physicians neglect and pitfall in patient management. North American Journal of Medical Sciences. 2014;**6**(2):61-70. DOI: 10.4103/1947-2714.127740

[11] Patnaik P. A Handbook of Inorganic Chemical. 1st ed. New York: Mcgraw Hill Publishers; 2003. pp. 140-609

[12] De flora S. Threshold mechanisms and site specificity in chromium (VI). Carcinogenesis. 2000;**2**:533-541

[13] Bernnett BG. Environmental nickel pathways in man. In: Sunderman FW Jr, editor. Nickel in the Human Environment Proceedings of a Joint Symposium, IARC Scientific Publication No. 53. Lyon, France: International Agency for Research on EA Cancer; 1984. pp. 469-485

[14] Sunderman FW Jr, Nickel OA. In: Merjan E, editor. Metals and their

Compounds in the Environment. New York: VCH Verlagsqsse//sahaft; 1991. pp. 1101-1126

[15] Patriarce M, Lyon TD, Fell GS. Nickel metabolism in humans investigated with oral stable isotope. The American Journal of Clinical Nutrition. 1997;**66**:616-621

[16] Fullerton A, Andersen JR, Hoelgaard A, Menne T. Permeation of nickel salts through human skin in vitro. Contact Dermatitis. 1986;**15**:173-177

[17] Angerer J, Lehnert G. Occupational chronic exposure to metals II: Nickel exposure of stainless-steel welders-biological monitoring. International Archives of Occupational and Environmental Health. 1990;**62**:7-10

[18] Nduka JK, Kelle HI, Amuka JO. Health risk assessment of cadmium, chromium and nickel from car paint dust from used automobiles at auto-panel workshops in Nigeria. Toxicology Report. 2019;**6**:449-456. DOI: 10.1016/j.toxrep.2019.05.007

[19] Orisakwe OE, Nwachukwu E, Osadalor HB, Afonne OJ, Okocha CE. Liver and kidney function tests amongst paint factory workers in Nkpor, Nigeria. Toxicology and Industrial Health. 2007;**23**(3):161-165

[20] Orisakwe OE, Dioke CE, Nwobodo EO, Okomkwo VC, Anike IC, Enendu AO. Respiratory abnormalities associated with occupational exposure to particulate insults in "Okada" (motocycle) operators in Nnewi. Nig. Med. Pract. 1996;**32**:36-38

[21] Vitayavirasuk B, Junhom S, Tantisaeranee P. Exposure to lead, cadmium and chromium among spray painters in automobile body repair shops. Journal of Occupational Health. 2005;**47**:518-522

[22] WHO. Malaria Cases (per 100,000) by Country. 2005. Global Health Atlas, Geneva: World Health Organization. Available from: gamapserver.who.int/maplibrary/files/maps/global_cases.jpg

[23] Yu P, Tian H, Ma C, Wei J, Lu X, Wang Z, et al. Hantavirus infection in rodents and the haemorrhagic fever with renal syndrome in Shaaxi province, China. 1984 – 2012. Epidemiology and Infection. 2015;**143**:405-411

[24] Harvell CD, Mitchell CE, Ward JR, Altizer S, Dobson AP, Ostfeld RS, et al. Climate warming and disease risks for terrestrial and marine biota. Science. 2002;**296**:2158-2162

[25] Hofstra N. Quantifying the impact of climate change on enteric waterborne pathogens concentration in surface water. Current Opinion in Environmental Sustainability. 2011;**3**:471-479

[26] Xiaoxu W, Yongmei L, Sen Z, Lifan C, Bing X. Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. Environment International. 2016;**86**:14-23. DOI: 10.1016/j.envint.2015.09.007

Chapter 2

A Short Overview of Behcet's Disease

Karthik Shunmugavelu and Evangeline Cynthia Dhinakaran

Abstract

Behçet's disease is a chronic, relapsing-remitting, occlusive vasculitis affecting multiple organ system. Greek physician Adamantiades had reported the disease as a classic trisymptom complex of hypopyon, iritis, and orogenital aphthosis. Behçet's disease has an undulating course of exacerbations and remissions, and appears to be more severe in young, male, and Middle Eastern or Far Eastern patients. This article describes in brief Behçet's disease in a new perspective.

Keywords: Behçet's disease, immune deregulation, chronic, clinical features of Behçet's disease, etiology of Behçet's disease

1. Introduction

Behçet's disease is a multisystemic, chronic disorder, characterized by oral and genital aphthous ulcers, arthritis, and cutaneous lesions, ocular, gastrointestinal and neurological manifestations. It was discovered by Prof. Hulusi Behçet a Turkish dermatologist in 1937–41 [1].

It is a chronic inflammatory disease of unknown etiology that can affect all body organ systems because of inflammatory effects on arteries and veins of all sizes with worldwide occurrence. The aetiopathological mechanisms of disease development remain unclear. The evidence base for treatment is limited but new knowledge is emerging and current treatment options range from symptomatic treatment, through to non-biological and biological immunosuppressive drugs, to cover the spectrum of clinical manifestations [2, 3].

2. Epidemiology

Traditionally known as the 'silk route' disease, Behçet's disease is seen mainly along the historical Silk Route, which joined the East to the West suggesting that an inherited tendency to develop Behçet's disease was spread by merchants who traveled these trading routes. The highest prevalence was seen in Turkey with 20–420 in 100,000 inhabitants while the lowest was in UK with a prevalence of 0.64. However, due to migration of people from various counties and environmental factors the disease is now prevalent worldwide. Predominant age of occurrence is between 3rd and 4th decades. Disease is more predominant in males with more severe disease manifestations in some Mediterranean areas [4–9].

3. Etiopathogenesis

The etiology of Behçet's disease remains uncertain but various studies suggest an infectious trigger with inflammatory mediators and immune deregulation as the cause in a genetically susceptible host. Studies have shown an association between Behçet's disease and the allele HLA-B*51 (chromosome 6p21), which is relatively common in many ethnic groups [1, 10–12].

HLA-B*52, which differs from HLA-B*51 by only two amino acids in peptide binding groove, is not associated with Behçet's disease in any population, suggesting selective peptide binding. Geographical distribution of HLA-B*51 among healthy subjects roughly corresponds with global disease distribution. But 1/3 of patients, even in countries with a high disease prevalence, do not possess this gene [1, 10–12].

In Japanese series prevalence of HLA-B*51 is only 57%. There is some evidence that HLA B51, as well as B12, B15, B27, B57, DR2, and DR7 may bear a relationship disease. A possible explanation for these data is that HLA-B*51 molecule expresses Bw4 motif, which itself may be causally related to disease [1, 10–12].

MHC class I chain related [MIC] gene locus is situated adjacent to HLA-B domain. MICA is expressed at gastrointestinal epithelial surfaces in response to bacterial infection. γδ T cells and NK cells are upregulated, recognize and kill MICA transfected cells. MICA ligand for NKG2D, also expressed on γδ T cells and NK cells. Association b/w MICA6 and Behçet's disease may be a secondary phenomenon related to HLA-B*51. MEFV gene mutations is seen in persons with Mediterranean fever and is associated with vascular system [13–15].

ERAP1 variant associated with Behçet's disease processes microbial proteins in such a way that they can be loaded onto HLA-B*51 molecule to trigger an abnormal immune response. A significant association of Behçet's disease with variants near CCR1, KLRC4, AND STAT4 gene also found. Single nucleotide polymorphism [SNP] Gene encoding protein tyrosine phosphatase type 22 [PTPN22 620 W] has an inverse relationship with Behçet's disease [13–15].

Environmental factors such as organophosphates, heavy metal intoxication, organochlorides and allergens may trigger initiation or exacerbate Behçet's disease [16, 17].

Streptococcus sanguis and *Streptococcus oralis* may be found in the oral microbiome of Behçet's disease patients. Hepatitis virus, parvovirus B19, mycobacteria, *Escherichia coli Borrelia burgdorferi*, *Saccharomyces cerevisiae* fungus can be elevated in Behçet's disease [16, 17].

4. Clinical features

Signs and symptoms can be recurring and may precede the onset of mucosal membrane ulcerations by 6 months to 5 years. Prior to onset of disease, patients may exhibit a symptoms including malaise, anorexia, generalized weakness, cachexia, decreased or elevated temperature headache, perspiration, lymphadenopathy, substernal and temporal pain. A history of repeated tonsillitis, sore throats, tonsillitis, myalgias, and migratory erythralgias without overt arthritis is common [18–21].

Diagnostic criteria from Behçet syndrome research committee of Japan [1987 revision].

a. Complete – Four major features.

b. Incomplete – 3 major features, 2 major and 2 minor features, Typical ocular symptoms and 1 major or 2 minor features.

c. Possible – 2 major features, 1 major and 2 minor features.

Major features

- Recurrent aphthous ulceration of oral mucous membrane,
- Skin lesions -Erythema nodosum—like lesions, subcutaneous thrombophlebitis, cutaneous hypersensitivity and folliculitis.
- Eye lesions—Iridocyclitis, retinouveitis, chorioretinitis definite history of chorioretinitis or retinouveitis.

Minor features

- Arthritis without deformity,
- Ankylosis,
- Gastrointestinal lesions characterized by ileocecal ulcers,
- Vascular lesions epididymitis, and
- Central nervous system symptoms.

Recurrent oral ulcers occur in >90% of cases. They recur at least 3 episodes in a year. Grossly & histologically similar to common oral ulcers, but are more extensive and multiple ulcers. Lesions are multiple, painful,1–3 cm in diameter & sharply margined with fibrin coated base and surrounding erythema. They heal without scarring in 4–30 days [18–21].

Genital ulcers [90%, M > F] resemble their oral counterparts but cause greater scarring. In males ulcers usually occur on scrotum, penis, and groin. In females they occur on vulva, vagina, groin, and cervix. Ulcers may also be found in urethral orifice and perianal area. Sometimes epididymitis may arise [18–21].

Ocular manifestaions include anterior uveitis and posterior uveitis. Retinal vasculitis can lead to blindness.

Secondary complications such as cataract, glaucoma, tractional retinal detachment, chronic cystoid macular edema, vision loss & neovascular lesions can also occur. Blindness occurs within 4–5 years from onset of ocular symptoms [18–21].

Arthralgia, thrombophlebitis, and central nervous involvement, cardiac and pulmonary manifestations are occasional complications of the disease [18–21].

5. Histopathological features

The intraoral ulcers are nonspecific, and are similar to recurrent aphthous ulcers according to Lehner. Endothelial proliferation has been observed in the lesions of Behçet's disease but not in the recurrent aphthous ulcer [1, 22, 23].

Perivascular infiltrate of mononuclear cells; mast cell infiltrate and neutrophilic vasculitis may be found. Papulopustular lesions with spongiosis, basal keratinocyte vacuolization, intraepidermal pustules and suppurative folliculitis are seen [1, 22, 23].

Vasculitis also appears to be an essential lesion in Behçet's disease, thrombi in vessel lumens, perivascular inflammatory infiltrate are also observed [1, 22, 23].

6. Management

Type of management depends on the organ affected and its severity. Therapeutic options according to the disease type, severity, age, and sex of each patient must be categorized. Investigations are mainly nonspecific indices of inflammation that include leukocytosis, elevated ESR and CRP [24–26].

The severity of the syndrome usually abates with time. Ocular, vascular, and neurologic disease, require more aggressive treatment. Corticosteroids, colchicine, azathioprine, cyclosporine, thalidomide, cyclophosphamide, Interferon-α and tumor necrosis factor-α inhibitors can be prescribed [24–26].

Apart from patients with central nervous system- Behçet's disease and major vessel disease, the life expectancy is normal. The only other serious complication is blindness [24–26].

7. Conclusion

Although the exact cause of Behçet's disease is unknown, genes, environmental triggers, and an abnormal immune response may be possible causes. In severe cases, there's a risk of serious and potentially life-threatening manifestations, such as blindness and strokes.

Majority of the people exhibit episodes where their symptoms are severe (flare-ups or relapses), followed by periods where the symptoms disappear (remission). Therefore, the importance of close scrutiny for lesions in Behçet's disease cannot be overstated.

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References

[1] Shafer WG, Hine MK, Levy BM. A Textbook of Oral Pathology. Philadelphia: Saunders; 2009

[2] Nair JR, Moots RJ. Behcet's disease. Clinical Medicine [Lond]. 2017;**17**(1):71-77

[3] Yurdakul S, Gunaydin I, Tuzun Y, et al. The prevalence of Behcet's syndrome in a rural area in northern Turkey. The Journal of Rheumatology. 1988;**15**:820-822

[4] Davatchi F, Chams-Davatchi C, Shams H, et al. Behcet's disease: Epidemiology, clinical manifestations, and diagnosis. Expert Review of Clinical Immunology. 2017;**13**(1):57-65

[5] Cakir N, Dervis E, Benian O, et al. Prevalence of Behcet's disease in rural western Turkey: A preliminary report. Clinical and Experimental Rheumatology. 2004;**22**:S53-S55

[6] Azizlerli G, Kose AA, Sarica R, et al. Prevalence of Behcet's disease in Istanbul, Turkey. International Journal of Dermatology. 2003;**42**:803-806

[7] Seaman G, Pearce RA. Behcet's disease manifestation in a population drawn from the UK Behcet's syndrome society. In: Hamza M, editor. Behcet's Disease. Tunisia: Pub Adhoua; 1997. pp. 196-199

[8] Chen Y, Lai Y, Yen Y, et al. Uveitis as a potential predictor of acute myocardial infarction in patients with Behcet's disease: A population-based cohort study. BMJ Open. 2021;**11**:e042201

[9] Alpsoy E, Bozca BC, Bilgic A. Behçet disease: An update for dermatologists. American Journal of Clinical Dermatology. 2021;**22**:477-502

[10] Mizuki N, Inoko H, Ohno S. Molecular genetics [HLA] of Behçet's disease. Yonsei Medical Journal. 1997;**38**(6):333-349

[11] Nishiyama M, Takahashi M, Manaka K, Suzuki S, Saito M, Nakae K. Microsatellite polymorphisms of the MICA gene among Japanese patients with Behçet's disease. Canadian Journal of Ophthalmology. 2006;**41**(2):210-215

[12] Mizuki N, Inoko H, Ohno S. Pathogenic gene responsible for the predisposition of Behçet's disease. International Reviews of Immunology. 1997;**14**(1):33-48

[13] Arber N, Klein T, Meiner Z, Pras E, Weinberger A. Close association of HLA-B51 and B52 in Israeli patients with Behçet's syndrome. Annals of the Rheumatic Diseases. 1991;**50**(6):351-353

[14] de Menthon M, Lavalley MP, Maldini C, Guillevin L, Mahr A. HLA-B51/B5 and the risk of Behçet's disease: A systematic review and meta-analysis of case–control genetic association studies. Arthritis and Rheumatism. 2009;**61**(10):1287-1296

[15] Mizuki N, Ota M, Kimura M, et al. Triplet repeat polymorphism in the transmembrane region of the MICA gene: A strong association of six GCT repetitions with Behçet disease. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**(4):1298-1303

[16] Galeone M, Colucci R, D'Erme AM, Moretti S, Lotti T. Potential infectious etiology of Behçet's disease. Pathology Research International. 2012;**2012**:595380

[17] Türsen U. Pathophysiology of the Behçet's disease. Pathology Research International. 2012;**2012**:493015

[18] Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: Disease manifestations, management, and advances in treatment. Nature Clinical Practice. Rheumatology. 2007;**3**:148

[19] Calamia KT, Wilson FC, Icen M, et al. Epidemiology and clinical characteristics of Behçet's disease in the US: A population-based study. Arthritis and Rheumatism. 2009;**61**:600

[20] Karincaoglu Y, Borlu M, Toker SC, et al. Demographic and clinical properties of juvenile-onset Behçet's disease: A controlled multicenter study. Journal of the American Academy of Dermatology. 2008;**58**:579

[21] Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. The New England Journal of Medicine. 1999;**341**:1284

[22] Gündüz O. Histopathological evaluation of Behçet's disease and identification of new skin lesions. Pathology Research International. 2012;**2012**:209316

[23] Kokturk A. Clinical and pathological manifestations with differential diagnosis in Behçet's disease. Pathology Research International. 2012;**2012**:690390

[24] Rokutanda R, Kishimoto M, Okada M. Update on the diagnosis and management of Behçet's disease. Open Access Rheumatology: Research and Reviews. 2014;**7**:1-8

[25] Leiba M, Ehrenfeld M. Behcet's disease: Current therapeutic perspectives. Current Treatment Options in Cardiovascular Medicine. 2005;**7**(2):139-148

[26] Taylor J, Glenny AM, Walsh T, et al. Interventions for the management of oral ulcers in Behçet's disease. Cochrane Database of Systematic Reviews. 2014;(9):1-54

Chapter 3

Entero-Behcet: A Challenging Aspect of Behçet's Disease

Abire Allaoui, Fatima Belabbess, Rajaa Jabbouri, Fatim-Zahra Alaoui and Abdelhamid Naitelhou

Abstract

Behcet disease is a proteiform vasculitis, and it can have multiple presentations. One of these presentations is digestive involvement commonly known as entero-Behcet. It is a challenging presentation of Behcet disease, because of its similarity with other inflammatory digestive diseases, especially Crohn disease, which makes its diagnosis difficult and uncertain in many cases. It is also challenging to treat, and its treatment can go from corticosteroids and immunosuppressive therapy to biologics. The absence of a standardized protocol to treat patients can be confusing for practitioners treating entero-Behcet. This incites doctors treating entero-Behcet to have multidisciplinary meetings to discuss patients' cases. This review will give an insight into pathophysiology, diagnosis, and management of entero-Behcet to help practitioners taking care of this challenging aspect of entero-Behcet.

Keywords: behcet, entero-Behcet, diagnosis, treatment, Behcet disease

1. Introduction

Behcet disease (BD) is a primitive vasculitis from unknown origin, characterized by recurrent oral and/or genital aphthosis, ocular manifestations, and arthritis. Intestinal presentation of BD is rare, its prevalence is up to 5–10% [1], but can be very severe and difficult to diagnose and to differentiate from an inflammatory bowel disease, especially when it is the initial manifestation. East Asian countries have a higher frequency of intestinal manifestation in BD compared with Western or Middle Eastern countries [2]. Intestinal involvement in BD is known as entero-Behcet (EB), and it is defined when a patient presenting with BD has intestinal symptoms associated to aphthous ulceration confirmed by endoscopic exploration [3] and unexplained by infectious or toxic causes or another inflammatory disease. Intestinal involvement in BD usually occurs 4–6 years after the onset of oral ulcers [4]. Intestinal manifestations as well as vascular involvement are more common after the age of 40 [5]. The digestive symptoms are essentially abdominal pain, nausea, vomiting, and diarrhea. Ulcers can even lead to gastrointestinal bleeding and to intestinal perforation. In equivalence with BD, the pathophysiology of EB is not fully understood; it is also a multifactorial disease, implying genetic, environmental, and immune factors.

Similar to Crohn disease (CD), EB is characterized by a prevalence for the ileocecal area; however, every segment of the digestive tract can be affected [3, 6]; they present with some similarities concerning the genetic basis and pathophysiology; therefore, the treatment for EB is modeled on the CD one, such as corticosteroids, immunosuppressors, and biologics. But there is still no consensus for management of intestinal Behcet's disease to date.

It is essential that every specialist caring for patients with BD should know every aspect of the clinical manifestations, the diagnostic work-up, and the up-to-date management strategies available for EB. This review will give an insight into pathophysiology, diagnosis, and management of EB to help practitioners taking care of this challenging aspect of BD.

2. Pathophysiology

Human leukocyte antigen (HLA)-B51 allele, ERAP 1, and MHC class I-related gene A (MICA) are the classical genetic factors of BD, which have not been identified in CD [1, 7]. The interleukin (IL) 10 and the IL23R-IL12RB2 loci that were recently identified, on the contrary, are associated with both BD and CD [1]. On the immune level, Th1, Th17, CD4+, and CD8+ T cell, and γδ + T cell activities, as well as IL-12, IL-23, IL-27 and tumor necrosis factor alpha (TNF-α) levels, were increased in patients with BD as well as in CD [1]. A study has recently reported that the IL-12B levels correlated with the clinical and endoscopic disease activities of EB and CD [8].

Genetic factors cannot completely explain the emergence of BD; therefore, additional factors are essential for the pathogenesis of BD/EB. Among these factors, environmental triggers have been suspected to be associated with BD, especially microbiological agents such as streptococcal antigens and herpes simplex virus (HSV) [7]. A molecule mimicry between those microbial agents and human peptides such as the heat shock proteins (HSPs) can be also a triggering factor [7, 9]. The role of microbiota has been emphasized in recent studies, where an unbalanced gut microbiome with reduced intestinal microbial diversity has been found in BD patients, marked by a decreased butyrate production, which has been suggested to induce inflammation [7].

On the nosological level, there are two forms of EB: neutrophilic phlebitis that leads to mucosal inflammation and ulcer formation and large vessel disease (i.e., mesenteric arteries) that results in intestinal ischemia and infarction [6]. A recent study has demonstrated that thrombophlebitis in the mesenteric veins and not arteries plays a central role in the perforation in EB, suggesting that there might be distinct mechanisms of pathogenesis for EB, including mucosal inflammation and infarction due to venous obstruction [10].

3. Diagnosis

Esophageal involvement is unusual [11]. The clinical presentations are essentially ulcers, stenosis, perforation, varices, and decreased motility. The patient will present with retrosternal chest pain, dysphagia, odynophagia, hematochezia, and melena [6, 11].

The stomach is presumably the least involved gastrointestinal organ in EB. Commonly, patients present with dyspepsia and epigastric pain. Bleeding can occur on ulcers that can be found in the stomach or the duodenum [6].

Intestinal ulcerations are the main pathological features of EB [12]. Most common complication of intestinal BD was found to be perforation (12.7%), followed by fistula (7.6%), stricture (7.2%), and abscess (3.3%) [13]. The most common location of perforation is reported to be terminal ileum, ileoceocal valve, and ascending colon [6].

Pancreas, liver, and biliary system are rarely involved, the underlying phenomenon is usually vasculitis. The most prominent complication of the hepatobiliary system in BD is Budd-Chiari syndrome [6].

There are no pathognomonic tests for EB. Recently, novel diagnostic criteria and a disease activity index have been proposed in the diagnosis of intestinal BD [14, 15]. These criteria are based on endoscopic features and clinical patterns. Similar to CD, a diagnosis of EB combines clinical, endoscopic, pathological, and radiological criteria [1]. The disease activity index for intestinal Behcet's disease (DAIBD) is categorized as quiescent, mild, moderate, and severe disease based on the total score ($\leq$19, 20 $\sim$ 39, 40 $\sim$ 74, and $\geq$ 75, respectively), DAIBD includes clinical features that have been present over the preceding 7 days such as the general condition of patient, extraintestinal manifestations, intestinal complications, abdominal symptoms, fever, and stool frequency not requiring laboratory data or endoscopic findings [15]. Future studies are needed to confirm its interest in different populations and ethnics.

4. Diagnostic modalities

Studies have found that the levels of fecal calprotectin and serum anti-α-enolase antibody were significantly correlated with the disease activity of EB [16]. The rate of anti-Saccharomyces cerevisiae antibodies (ASCA) detection is remarkably higher in patients with BD, especially in patients with gastrointestinal involvement, than in controls [2]. But these biological parameters are not commonly used to assess EB in daily practice to date.

Capsule endoscopy has a major role in detecting small bowel lesions including reddened lesions, erosions, and ulcers, especially when conventional exploration remains negative [17]. Endoscopic exploration remains the gold standard in exploring EB. The typical endoscopic features found are oval-shaped large intestinal ulcerations in the ileoceocal area with deep and discrete borders. These features can vary from aphthous to deep penetrating volcano-shaped ulcerations and ulcerations with a more frequent focal to less frequently diffuse distribution, in contrast with CD [1, 6]. In this regard, a valuable diagnostic algorithm using a classification analysis of the lesions has been proposed in order to differentiate between EB and CD [18].

There are no pathognomonic histologic findings for EB. Vasculitis, which is the main characteristic of BD, can affect small veins and venules in intestinal mucosa. But histology often shows nonspecific inflammation (lymphocytic or neutrophilic infiltrations) rather than vasculitis [2]. The absence of granuloma is in favor of EB rather than CD. Nevertheless, granulomas can be absent in CD. Transmural inflammation, chronicity, and focality are not discriminatory because they are observed in both EB and CD. Normal circumferential mucosa surrounding a large ulceration is one of the characteristic histologies of intestinal BD [2, 18].

5. Differential diagnosis

EB and CD share the majority of extraintestinal manifestations, essentially oral aphthous ulcers, arthritis, uveitis, cutaneous symptoms such as erythema nodosum

and pyoderma gangrenosum, and thromboembolic events. But these features have some specificities when happening in BD, which can help to differentiate EB from CD, especially on the initial setting. So, in BD, uveitis is more severe and recurrent, and it is often characterized by chronic posterior uveitis or panuveitis with necrotizing retinal vasculitis and can frequently lead to cecity if it is not correctly treated. Articular manifestations in BD commonly include arthralgia, oligoarthritis, and polyarthritis, in contrast with CD, where the most common joint features are spondyloarthritis. Genital ulcers, neurologic and vascular involvement are more common in BD [2, 13, 15]. On the intestinal level, both diseases affect the ileoceocal region with predilection. Anal complications (stricture, fistula, and abscess formation), which are frequently observed in CD, are rare in EB [15].

The endoscopic findings in EB include round/oval ulcers, punched-out lesions with discrete margins (>1 cm), focal distribution (<5 ulcers), in contrast with CD, where the ulcers are more longitudinal with cobblestone appearance. A classification score was suggested in a Korean study to help distinguish EB from CD, where it was stated that irregular/geographic-shaped ulcers and focal distributions are suggestive of EB, while segmental/diffuse lesions suggest more CD [18]. Similarly, the pathological features are slightly different between both diseases. Thus, in EB, it comprises vasculitis of the small veins and venules with deep ulcerations, without granulomas or cobblestoning, ischemic perforation, and thrombosis. In CD, transmural mucosal inflammation is noted with inflammatory cell infiltrate (lymphocytes, plasma cells) with focal crypt irregularity and granulomas [12, 15].

In addition to CD, intestinal tuberculosis is also commonly cited on the differential diagnosis, but practitioners should be aware of the existence of other less commonly cited diagnoses such as NSAID-induced ulcers of the gastrointestinal tract, which can be widely used in BD [6].

6. Management

Concerning the management of EB, there is a lack of randomized controlled studies. Knowing that EB and CD share a considerable number of genetic backgrounds, pathogenesis, and clinical features, current therapeutic strategies for EB are molded on those proposed for CD.

7. Medical management

Studies found that 5-ASA and sul-fasalazine should only be used in patients with mild to moderate disease, as the risk of relapse on ASA or sulfasalazine monotherapy increased significantly at higher disease activity levels [19]. In moderate to severe cases, corticosteroids are generally recommended as the first-line treatment for EB [20]. Treatment response to steroids generally induces remission in almost half of cases and lowers the risk of surgery [6]. Azathioprine and methotrexate are recommended in third-line treatment in patients with moderate to severe EB, who are resistant to both corticosteroids and TNF-inhibitors. The use of thiopurines after surgery has an interest in preventing recurrence in intestinal BD patients [6, 21]. The use of thalidomide, mycophenolate, and tacrolimus was reported in some case reports/series, but these are not included in current consensus statements for medical management [1, 6].

8. Anti-TNF-alpha agents

Many reports confirmed the efficacy of anti-TNF-α antibody (infliximab/adalimumab) in the treatment of EB, where the remission rate can reach 80–89% [22–24]. There are also reports on the long-term efficacy of anti-TNF-α antibodies in treating EB [22]. Anti-TNF-α antibodies were also effective in preventing postoperative recurrence with a recurrence-free state for 2–3 years. Studies have reported that infliximab at 5 mg/kg is effective in improving ulcers and subsequently maintaining remission in patients with ulcers occurring at the anastomotic site within 2 weeks after ileoceocal resection who fail to respond to conventional therapy with prednisolone, azathioprine, mesalamine, and colchicine [25].

In a recent study, authors administered anti-TNF-α antibody to 49 patients with refractory EB and demonstrated its high efficacy based on both endoscopy results and a quantitative disease activity index, with a beneficial effect on sparing corticosteroids. Besides, anti-TNF-α antibodies demonstrated sufficient efficacy to control disease activity without concomitant corticosteroids in some patients [26].

9. Tocilizumab

In a recent review, that has included 20 publications about 47 BS patients with different organ involvements refractory to previous treatment with conventional immunosuppressives and biologic agents, tocilizumab failed to improve patients with gastrointestinal involvement, with even exacerbation of symptoms in some patients [27].

10. Secukinumab

In a multicenter, retrospective study of 15 BS patients with refractory manifestations secukinumab led to a complete or partial response in 90% during a follow-up of 18 months [23]. Interestingly, 60% of these patients had intestinal involvement, and they responded completely to secukinumab, an agent that paradoxically may induce or aggravate Crohn's disease. Thus, more research is necessary to understand the role of IL-17 in the pathogenesis of BD [5].

11. Tofacitinib

A retrospective study from China looked at the efficacy of tofacitinib 5 mg twice daily in 13 BD patients with refractory vascular, gastrointestinal, or articular involvement. In this study, tofacitinib had no effect on intestinal involvement. This was attributed to the resemblance of pathophysiology between EB and CD for which tofacitinib is already known to be ineffective [28].

12. Apremilast

This treatment led to rapid improvement of oral and genital ulcers and reduction of glucocorticoid dose with no difference between monotherapy and combination

therapy. Other BS manifestations such as intestinal symptoms also improved [29], but apremilast can frequently present with severe gastrointestinal adverse effects [30], which can be limiting of its use in EB in the future.

13. Surgery

Surgical management in EB is required in cases complicated with perforation and massive bleeding and can be salutary in some cases of abdominal abscess, fistula, and stricture. Additionally, patients who are refractory to medical treatment will benefit from surgical treatment [31]. Surgery in EB will be less and less used with the rising usage of biologics.

14. Prognosis and follow-up

Clinical remission has been a long-standing goal of therapy in patients with EB, but recently, with analogy to CD, researchers are paying increasing attention to endoscopic remission, which is also termed as mucosal healing [16], which would be in the future a major therapeutic target, especially with the advent of biologics. Mucosal healing is defined as the complete absence of inflammatory and ulcerative lesions in all segments of the gut on endoscopic examination [16].

The occurrence of intestinal involvement is generally considered an indicator of poor prognosis with increased morbidity and mortality, due the important prevalence of digestive bleeding, intestinal perforation, fistulas, which will often require surgery. Risk factors for developing intestinal manifestations were found to be male gender, elevated ESR, CRP, IL-6 and decreased hemoglobin [6]. The relapses were also studied and were more likely to occur in patients with intestinal ulcers in the ileoceocal and colorectal regions or in patients with poor compliance [32]. To date, there are no established guidelines for surveillance.

15. Conclusion

Entero-Behcet can be a challenging aspect of Behcet's disease to diagnose and to treat. It can also bear a poor prognosis. Many efforts were made to help the diagnosis, especially to distinguish it from Crohn disease, by developing classification scores and severity disease index. Treatment strategies have also benefited from the rise of biologics use with advantageous results, which has permitted to target not only clinical remission but also mucosal healing. But there is a need to provide more robust evidence-based therapeutic protocols and to establish guidelines for endoscopic surveillance.

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References

[1] Cheon JH. Advances in management of intestinal Behçet's disease: A perspective from gastroenterologists. Journal of Rheumatic Diseases. 2021;**28**:4-16

[2] Kim DH, Cheon JH. Intestinal Behçet's disease: A true inflammatory bowel disease or merely an intestinal complication of systemic vasculitis? Yonsei Medical Journal. 2016;**57**(1):22-32

[3] Kobayashi K, Ueno F, Bito S, Iwao Y, Fukushima T, Hiwatashi N, et al. Development of consensus statements for the diagnosis and management of intestinal Behçet's disease using a modified Delphi approach. Journal of Gastroenterology. 2007;**42**(9):737-745

[4] Skef W, Hamilton MJ, Arayssi T. Gastrointestinal Behçet's disease: A review. World Journal of Gastroenterology. 2015;**21**(13):3801-3812

[5] Hatemi G, Seyahi E, Fresko I, Talarico R, Uçar D, Hamuryudan V. One year in review 2021: Behçet's syndrome. Clinical and Experimental Rheumatology. 2021;**39**(5):3-13

[6] Nguyen A, Upadhyay S, Javaid MA, Qureshi AM, Haseeb S, Javed N, et al. Behcet's disease: An in-depth review about pathogenesis, gastrointestinal manifestations, and management. Inflammatory Intestinal Diseases. 2021;**6**(4):175-185

[7] van der Houwen TB, van Hagen PM, van Laar JAM. Immunopathogenesis of Behçet's disease and treatment modalities. Seminars in Arthritis and Rheumatism. 2022;**52**:151956

[8] Lee HW, Chung SH, Moon CM, Che X, Kim SW, Park SJ, et al. The correlation of serum IL-12B expression with disease activity in patients with inflammatory bowel disease. Medicine (Baltimore). 2016;**95**(23):e3772

[9] Lehner T. The role of heat shock protein, microbial and autoimmune agents in the aetiology of Behcet's disease. International Reviews of Immunology. 1997;**14**(1):21-32

[10] Hirohata S, Kikuchi H, Ueda M, Kyogoku M. Histopathology of perforated gastrointestinal tracts in Behçet's disease: Evidence for the critical role of thrombophilia. Clinical and Experimental Rheumatology. 2021;**39**(5):137-138

[11] Houman MH, Ben Ghorbel I, Lamloum M, Khanfir M, Braham A, Haouet S, et al. Esophageal involvement in Behcet's disease. Yonsei Medical Journal. 2002;**43**(4):457-460

[12] Lopalco G, Rigante D, Venerito V, Fabiani C, Franceschini R, Barone M, et al. Update on the medical management of gastrointestinal Behçet's disease. Mediators of Inflammation. 2017;**2017**:1460491

[13] Jung YS, Cheon JH, Park SJ, Hong SP, Kim TI, Kim WH. Long-term clinical outcomes of Crohn's disease and intestinal Behcet's disease. Inflammatory Bowel Diseases. 2013;**19**(1):99-105

[14] Cheon JH, Han DS, Park JY, Ye BD, Jung SA, Park YS, et al. Development, validation, and responsiveness of a novel disease activity index for intestinal Behçet's disease. Inflammatory Bowel Diseases. 2011;**17**(2):605-613

[15] Valenti S, Gallizzi R, De Vivo D, Romano C. Intestinal Behçet and Crohn's

disease: Two sides of the same coin. Pediatric Rheumatology Online Journal. 2017;**15**(1):33

[16] Gong L, Zhang YL, Sun LX, Chen GR, Wu D. Mucosal healing in intestinal Behçet's disease: A systematic review and meta-analysis. Journal of Digestive Diseases. 2021;**22**(2):83-90

[17] Hamdulay SS, Cheent K, Ghosh C, Stocks J, Ghosh S, Haskard DO. Wireless capsule endoscopy in the investigation of intestinal Behçet's syndrome. Rheumatology. 2008;**47**(8):1231-1234

[18] Lee S, Kim B, Kim T, Kim W. Differential diagnosis of intestinal Behçet's disease and Crohn's disease by colonoscopic findings. Endoscopy. 2009;**41**(1):9-16

[19] Kinoshita H, Nishioka H, Ikeda A, Ikoma K, Sameshima Y, Ohi H, et al. Remission induction, maintenance, and endoscopic outcome with oral 5-aminosalicylic acid in intestinal Behçet's disease. Journal of Gastroenterology and Hepatology. 2019;**34**(11):1929-1939

[20] Watanabe K, Tanida S, Inoue N, Kunisaki R, Kobayashi K, Nagahori M, et al. Evidence-based diagnosis and clinical practice guidelines for intestinal Behçet's disease 2020 edited by Intractable Diseases, the Health and Labour Sciences Research Grants. Journal of Gastroenterology. 2020;**55**(7):679-700

[21] Lee HW, Cheon JH, Lee HJ, Park SJ, Hong SP, Kim TI, et al. Postoperative effects of thiopurines in patients with intestinal Behçet's disease. Digestive Diseases and Sciences. 2015;**60**(12):3721-3727

[22] Kambayashi H, Omori T, Saito S, Murasugi S, Kashiwagi H, Ito A, et al. The efficacy of medium- to long-term anti-TNF-α antibody-based maintenance therapy in Behçet's disease patients with intestinal lesions. Internal Medicine. 2020;**59**(19):2343-2351

[23] Park YE, Cheon JH. Updated treatment strategies for intestinal Behçet's disease. The Korean Journal of Internal Medicine. 2018;**33**(1):1-19

[24] Kinoshita H, Kunisaki R, Yamamoto H, Matsuda R, Sasaki T, Kimura H, et al. Efficacy of infliximab in patients with intestinal Behçet's disease refractory to conventional medication. Internal Medicine. 2013;**52**(17):1855-1862

[25] Kashima H, Matsumoto S, Kojima S, Koito Y, Miura T, Ishii T, et al. Efficacy of anti-tumor necrosis factor-α therapy against intestinal Behçet's disease complicated by recurrent enterocutaneous fistulae. Biologics: Targets and Therapy. 2022;**16**:1-6

[26] Miyagawa I, Nakano K, Iwata S, Nakayamada S, Saito K, Hanami K, et al. Comparative study of corticosteroid monotherapy, and TNF inhibitors with or without corticosteroid in patients with refractory entero-Behcet's disease. Arthritis Research & Therapy. 2019;**21**(1):151

[27] Akiyama M, Kaneko Y, Takeuchi T. Effectiveness of tocilizumab in Behcet's disease: A systematic literature review. Seminars in Arthritis and Rheumatism. 2020;**50**(4):797-804

[28] Liu J, Hou Y, Sun L, Li C, Li L, Zhao Y, et al. A pilot study of tofacitinib for refractory Behçet's syndrome. Annals of the Rheumatic Diseases. 2020;**79**(11):1517-1520

[29] Atienza-Mateo B, Martín-Varillas JL, Graña J, Espinosa G, Moriano C, Pérez-Sandoval T,

et al. Spanish Collaborative Group of Refractory Behçet's Disease. Apremilast in refractory orogenital ulcers and other manifestations of Behçet's disease. A national multicentre study of 51 cases in clinical practice. Clinical and Experimental Rheumatology. 2020;**38**(5):69-75

[30] Vieira M, Buffier S, Vautier M, Le Joncour A, Jamilloux Y, Gerfaud-Valentin M, et al. Apremilast in refractory Behçet's syndrome: A multicenter observational study. Frontiers in Immunology. 2021;**11**:626792

[31] Hisamatsu T, Hayashida M. Treatment and outcomes: Medical and surgical treatment for intestinal Behçet's disease. Intestinal Research. 2017;**15**(3):318-327

[32] Zhang L, Tian Y, Ye JF, Lin CH, Guan JL. Poor prognostic factors in patients with newly diagnosed intestinal Adamantiades-Behçet's disease in the Shanghai Adamantiades-Behçet's disease database: A prospective cohort study. Orphanet Journal of Rare Diseases. 2019;**14**(1):274

Chapter 4

Genetics of Behçet's Disease

Ayca Kocaaga

Abstract

Behçet's disease (BD; MIM 109650) is an autoinflammatory disease characterized by with recurrent oral aphthae, genital ulcers and vasculitis involving the skin, joints, eyes, veins, arteries, nervous and gastrointestinal systems. Although the pathogenesis remains uncertain, genome-wide and validation studies have demonstrated that genetic predisposition is a major factor in disease susceptibility. Several gene polymorphisms that are involved in the response to pathogens and modulate inflammation have been associated with the pathophysiology of BD. Understanding the genetic association with BD may ensure insight into the pathogenesis and for development of targeted therapies for this autoinflammatory disease. This chapter will deal the role of genetic and epigenetic factors as contributing factors in the pathogenesis of BD.

Keywords: autoinflammation, Behçet's disease, epigenetics, genetics, pathogenesis

1. Introduction

Behçet's disease (BD; MIM 109650) is an autoinflammatory disease characterized by with recurrent oral aphthae, genital ulcers and vasculitis involving the skin, joints, eyes, veins, arteries, nervous and gastrointestinal systems [1]. BD is diagnosed worldwide, although its highest prevalence coincides with the countries stretching from Japan to the Mediterranean region along the ancient trading route "Silk Route". Among the affected countries, the prevalence of BD varies between Western (0.12–7.5 per 100,000) and Eastern countries (6.3–14 per 100,000) [2]. The prevalence of BD is the highest in Turkey (80–420 cases per 100,000) [3]. Although the pathogenesis remains uncertain, it is thought that both genetic and environmental factors contribute to the onset and progression of the BD [4]. The first reported susceptibility genetic region for BD was found in the human leukocyte antigen (HLA) region, or the major histocompatibility complex (MHC) on chromosome [5]. HLA-B51 antigen was recognized as the strongest evidence of a BD genetic background [6]. Multiple other putative genes outside the HLA region have also been identified.

2. HLA and HLA-related genes

2.1 HLA

The MHC, also known in humans as the human leukocyte antigen (HLA) region encodes several molecules that play key roles in the immune system [7]. A strong

association was established between the HLA regions and autoimmune disorders. Among them, HLA-B51 has been shown to be the strongest risk allele for BD in multiple studies and in different ethnic populations [6, 8–11]. Several other HLA class I and class II alleles including HLA-A26, HLA-B15, HLA-B5701, HLA-B2702, HLA-B3901, HLA-B52, HLA-B56, HLA-DRB104, and HLA-DRB107 have been also associated with BD in different populations [12–15]. The several HLA alleles including HLA-A03, -B15, -B35, -B49, -B58 were reported BD-protective [1, 16, 17]. In addition to susceptibility, HLA alleles were also associated with reflect clinical outcomes of BD. The HLA-A26:01 was associated with poor visual prognosis and high incidence of posterior uveitis in previous studies [15, 18]. There were significant associations found between clinical manifestations of BD and some HLA alleles such as HLA-A26:01 with uveitis, HLA-A*02:07 with skin lesions and arthritis, and HLA-A*30:04 with vascular lesions, genital ulcers, and positive pathergy test [17]. These findings indicate that HLA alleles may be associated clinical manifestations and prognosis and the specific HLA alleles are can be used as genetic markers for diagnostic or prognostic classification of BD patients.

2.2 CIITA

The HLA class II transactivator gene (CIITA), encodes an important transcription factor that regulates the MHC class II genes, IL-4, IL-10 and other immune-mediating genes [19]. CIITA is implicated in various autoimmune and autoinflammatory diseases [20]. In a recent study of a Chinese Han population, the GG genotype and G allele of the CIITA gene (rs12932187) were correlated with risk factor for BD, and the GG carriers had a higher expression of the CIITA gene [21].

2.3 ERAP1

Endoplasmic reticulum aminopeptidase 1 (ERAP1) is an essential enzyme to optimizing the length of peptides to bind with MHC-class I molecules by trimming their N-terminal in the ER [22]. The association between ERAP1 and BD was first reported in a Turkish population. The rs10050860 and rs17482078 SNPs of the ERAP1 gene were found to confer risk to BD in Turkish population [23]. Zhang et al. reported the rs1065407 and rs10050860 polymorphisms might be associated with increased risk of BD in a Chinese cohort [24]. Sousa et al. studied in an Iranian cohort and reported that rs10050860 and rs13154629 of ERAP1 might contribute to the genetic susceptibility of BD [25]. A functional study indicated that the expression of ERAP1 was found to be significantly lower in active BD patients. The patients carrying AA genotype of rs1065407 and CC genotype of the rs10050860, respectively, were found a higher expression level of the ERAP1 gene than the patients carrying AC or CC and CT or TT genotypes of the SNPs, respectively, in response to lipopolysaccharide stimulation [24, 26].

2.4 MICA

The major histocompatibility complex class I chain related gene A (MICA) is a gene that functions in immune activation under cellular stress conditions, such as infections, tissue injury, pro-inflammatory signals, and malignant transformation [27]. MICA*009 and *019 alleles were found strongly associated with BD in a Spanish population [28]. The MICA-A6 allele has been reported to increase the risk of BD in

Japanese and Korean populations. In a recent study, the MICA*049 allele was found to be significantly higher in BD patients than in controls in a Chinese cohort [29]. On the other hand, Eyerci et al. reported the MICA*006 (MICA-A6) and MICA*009 alleles were associated with BD susceptibility in the HLA-B*51 positive Turkish population. [30]. MICA-A5.1 was indicated a negative correlation with ocular lesions and iridocyclitis in BD patients [31].

3. Interleukin (IL) family genes

3.1 IL-1 gene family

IL-1 gene family is composed of IL-1α, IL-1β, and IL-1Ra [32]. Interleukin-1α and -1β, are pleiotropic cytokines with primarily proinflammatory effects, which induce acute phase responses, activate endothelial cells, and lead to expression of adhesion molecules and coagulation factors [33]. IL-1Ra acts as an antagonist of IL-1 by blocking the IL-1 receptor [34]. Previous studies have shown that the IL-1α (-889) C allele is significantly associated with BD risk [35, 36]. Alayli et al. also reported that the frequency of IL-1β (−511) CC genotype is significantly higher in BD patients compared to controls [35]. In another study showed that IL-1Ra mspa1l 1100 CT and IL-1Ra mspa1l 1100 TT promoter polymorphisms could be confer susceptibility to BD in Turkish population [37]. Barış et al. found IL-1RN2 gene polymorphism was correlated with the presence of articular involvement and the IL-1β gene polymorphism was correlated with the presence of an ocular lesion [38].

3.2 IL-4

Interleukin-4 (IL-4) is a key cytokine secreted by Th2 lymphocytes. It has cytotoxic, anti-tumor effects, inhibits induction of nitric oxide synthase, and also has role in chemotaxis, formation of endothelial cell adhesion molecules and hematopoiesis [39]. IL-4 gene 70 bp VNTR polymorphism was first reported to be associated with BD in the Turkey. The P1 allele of the IL-4 gene 70 bp VNTR polymorphism was found to constitute a risk for developing BD in a Turkish population. In the same study, P2P2 genotype was associated deep venous thrombosis and ocular involvement in the BD patients [40]. The IL-4 -1098 G, IL-4 -590 T alleles and IL-4 TTC haplotypes were showed more common in the patients with BD when compared with healthy controls in an another Turkish cohort. They also demonstrated that IL-4Rα (+1902) gene polymorphism was associated with the Pathergy test positivity in BD patients [41].

3.3 IL-10

IL-10 is an anti-inflammatory cytokine, which is secreted by T lymphocytes (mainly Th2 subsets), B lymphocytes, NK cells, monocytes, and macrophages, plays critical roles in modulating immune response and preventing inflammatory and autoimmune pathologies [42]. IL-10 may inhibit the antigen-presenting process by downregulating the expression of HLA molecules on the surface of a cell and suppressing the expression of multiple proinflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-8 [43]. The first reported SNP of the IL10 gene was rs1800871 that found to be an association with BD in the UK and Middle Eastern cohorts [44].

The -1082A > G (rs1800896), −819 T > C (rs1800871), and -592A > C (rs1800872) SNPs of IL-10 gene were found to be association with BD susceptibility in different populations including Chinese, Japanese, Korean and Iranian [45–48].

3.4 IL-12A, IL12B and IL-12RB2/ IL-23R

IL-12A is a gene which encodes for IL-35 that is a subunit of the heterodimeric cytokines IL-12 (encoded by IL-12B) and IL-35 [49]. It binds to a heterodimeric IL-12 receptor (IL-12R) which consists of IL-12Rβ1 (encoded by IL-12 RB1) and IL-12Rβ2 (encoded by IL-12RB2) [50]. IL-12A gene variants (rs1780546 and rs17810458) were revealed to be associated with BD susceptibility in a Turkish cohort [23]. In a study with a Chinese cohort rs3212227/IL-12B genotype CC and C allele was found involved in the susceptibility to BD [51]. IL-23 is a member of the IL-12 cytokine family that plays important roles in the development process of the Th17 cells [52, 53]. The IL-23 receptor consists of two subunits encoded by the IL-23R and IL-12RB1 genes [54]. A meta-analysis of the association data (including a total of 2430 BD cases and 2660 controls) provided strong evidence for associations of the IL23R/IL12RB2 loci with BD [55]. The IL-23R/IL-12RB2 genes were associated with BD, in multiple reports with different populations including Japanese, Chinese, and Korean [56–58].

3.5 IL-17 and IL-18

IL-17 is a pleiotropic inflammatory cytokine that plays a pivotal role in a variety of pathologic conditions by inducing numerous inflammatory molecules and the recruitment of neutrophils [59]. This cytokine is produced by CD + T helper, hematopoietic cells, Th17 cells and neutrophils and consists of a family of cytokines from IL-17A to IL-17F [60]. Jang et al. reported the allele and genotype frequencies of A126G SNP of IL-17 were significant differences between BD and controls [61]. The another genetic study in a Korean population, the IL17A rs8193036C > T variant was associated with the risk of intestinal BD [62]. In another study, the IL-17A gene rs2275913 polymorphism has been showed it might be associated with intestinal involvement in patients with BD [63]. IL-18 is a proinflammatory cytokine that mediates T-helper (Th)-1-polarized immune responses. Lee et al. found that IL-18 − 607 C/A promoter polymorphism was significantly associated with BD and also age at disease onset [64]. IL-18 gene −607 promoter site polymorphism was associated with patients with BD in Egyptian patients. Moreover, they found GG genotype at position −137 had a higher risk of developing ocular manifestations in patients with BD [65].

3.6 IL-28 and IL-29

IL-29, IL-28A and IL-28B are subgroups of Type III IFNs known as IFN-λs that induce activation of the Jak/STAT signaling pathway and modulating the Th1/Th2 response [66, 67]. The first relationship between IL-28 and IL-29 and BD was investigated in a study from Turkey. Genc et al. showed that the GG genotype of rs8099917 (IL28 G/T) might be a protective factor against BD. They also found a significant difference between patients with and without central nervous system (CNS) involvement in rs12979860 (IL28 C/T) polymorphism [68].

3.7 IL-33

IL-33 is a member of the IL-1 cytokine family that expressed by various types of immune cells such as mast cells, macrophages and dendritic cells, that drives production of Th2-associated cytokines [69, 70]. The rs7044343 and rs11792633 variants of IL-33 gene were associated with the decreased risk of BD in Turkish patients [71]. Talei et al. showed that a significantly higher prevalence of the IL-33 SNP rs1342326 T/G in BD patients. They showed also this genotype was also associated with increased IL-33 expression in patients with BD compared to healthy controls [72].

4. Genes involved in autoinflammation and autoimmunity

4.1 CCR1 and CCR3

C–C chemokine receptor type 1 (CCR1) and C–C chemokine receptor type 3 (CCR3) encode the chemokine receptor belonging to the G protein-coupled receptor super family. These receptors play an important role in the accumulation and activation of inflammatory cells [73, 74]. The rs7616215 SNP located in the CCR1-CCR3 locus was showed to be associated with BD in a Turkish population [25]. The CCR1 gene was associated to susceptibility with BD in multiple cohorts including Turkish, Japanese, and Iranian cohorts [23, 25]. Hou et al. reported that the CCR1-CCR3 (rs13084057 in the 30 UTR of CCR1; rs13075270 and rs13092160 in the intergenic region between CCR1 and CCR3) polymorphisms also associated with BD in a Chinese population [75].

4.2 FCRL3

The Fc receptor-like (FCRL) family is a recently recognized potential immunoregulatory cell surface molecule. FCRL3 is predominantly expressed in germinal centers of lymphoid organs and has been linked to B cell maturation [76]. FCRL3 may be involved in the mechanisms regulating Treg dysfunction, which may in turn contribute to the loss of self-tolerance and development of autoimmunity [77]. The -110 G allele and CGCG haplotype of FCRL3 were found to be associated with BD, while the ATCG haplotype was found to be protective for BD in a Chinese population [78]. In a study with Iranian BD patients, there was a significant difference demonstrated between groups at position -169 (rs7528684) of FCRL3 gene [79].

4.3 MEFV

The Mediterranean fever (MEFV) protein also named pyrin is an is an significant regulator of innate immunity and the inflammatory response to IL-1β and IFN-γ. Some clinical findings and geographic distribution of FMF and BD seem to be similar [80]. Touitou et al. who first suggested a possible implication of MEFV mutations in BD, reported higher frequencies of four mutations such as M694V, V726A, E148Q, and L110P mutations [81]. The MEFV SNPs rs61752717 Met694Val, rs28940580 Met680Ile, and rs3743930 Glu148Gln were reported conferred risk to both of FMF and BD [80, 82–84].

4.4 IRF1 and IRF8

IRF-1 is originally identified to be a regulator of the interferon (IFN)–β gene family. It plays an important role in various biologic functions such as innate immunity to viral infection, lymphocyte development, macrophage cytotoxicity, induction of apoptosis and tumor suppression [85, 86]. A study by Lee et al. showed that a significant association between BD and IRF-1 gene polymorphisms (-415 C/A, -410 A/G, and -300 A/G, and 3'-untranslated region (UTR) A/G) [87]. Interferon Regulatory Factor (IRF) 8 is a transcription factor of a member of Interferon (IFN) Regulatory Factor (IRF) family that it regulates expression of type I IFN stimulated genes and the development and function of a variety of immune cells [88, 89]. The rs17445836 and rs11642873 polymorphisms of the IRF8 gene were associated with BD and these SNPs appeared to regulate IRF8 expression and cytokine production in a Chinese cohort [90]. The other SNPs (rs11117433, rs142105922 and rs7203487) of the IRF8 gene were reported BD-associated in multiple cohorts including Turkish, Iranian, and Japanese populations [91].

4.5 TNFAIP3

TNFAIP3 gene encodes A20 protein, which is a key regulator of the nuclear factor (NF)-κB signaling pathway, toll-like receptor (TLR), interleukin 1 receptor (IL1R), and nucleotide-binding oligomerization domain containing 2 (NOD2) [92]. A genetic linked between the TNFAIP3 gene SNPs (rs9494885, rs10499194 and rs7753873) and BD was reported in Chinese BD patients [93].

4.6 Toll-like receptors

Toll-like receptor (TLR) proteins are a family receptors that recognize pathogen molecules and have a critical role in both innate and adaptive immune systems [94]. TLRs are thought to be one of the links between infection and autoinflammatory or autoimmune disease [95]. The TLR2 rs2289318 CC genotype and rs3804099 CT genotype were significantly associated with ocular BD in a Chinese population [96]. The associations of the TLR4 gene with BD have been found to be contradictory in different studies. It was not found an association between TLR4 gene polymorphisms and BD in Italian and Chinese patients [97, 98]. Horie et al. showed that the TAGCGGTAA haplotype of TLR4 gene was significantly associated with BD susceptibility and BD arthritis in a Korean cohort [99]. A Japanese study indicated that the TLR4 gene may confer susceptibility to BD [100]. Fernández et al. revealed the rs2407992 and the rs5744067 of TLR8 were associated with susceptibility to BD in Spanish patients [101]. An Asian study revealed a significant association between the TLR7 rs5743733 and rs3853839 and BD and it showed also an association of TLR9 rs352140 with BD [102].

4.7 GIMAP

The GIMAP (GTPase of the immune associated nucleotide binding protein) gene family have been suggested as being involved in different aspects of the immune system in different species. These events appear to be associated with cell regeneration and proliferation and apoptosis [103]. The SNPs in GIMAP1 (rs2286900), GIMAP2 (rs10266069 and rs10256482), and GIMAP4 (rs1916012, rs1522596, and rs1608157) were associated with BD in a study of Korean and Japanese populations, but they were not found to be associated in a study with European cohort [104].

4.8 NOD1 and NOD2

Nod-like receptors (NLRs) are a member of pattern-recognition receptor molecules (PRRs) can capable to sense several pathogens or endogenous danger signals [105]. In a Chinese study, the C allele (major) of the NOD1 SNP rs2075818 was associated with BD susceptibility [21]. In a recent study indicated that the CC genotype of rs2075818 (NOD1 G/C) increased the risk of BD by 3.780-fold and the AA genotype of rs2075820 (NOD1 G/A) was increased the risk of cardiovascular involvement in BD 4.286-fold. In addition, they did not find the NOD2 gene variants (R334Q and R334W) in nor the BD patients and neither control groups [106]. Multiple reports have demonstrated that a Crohn's disease-associated polymorphism, Arg702Trp of the NOD2 rs2066844 was protective to BD [107, 108].

5. Other genes

5.1 STAT4

Signal transducer and activator of transcription-4 (STAT4) is a transcription factor that activates gene expression involved in differentiation of naïve T cells into Th1 and Th17 cells, natural killer (NK) cells, mast cells, and dendritic cells [109–111]. The association between the BD and STAT4 gene appears to be consistent in many independent reports including Korean, Turkish, and Iranians [23, 25]. The functional studies have shown that risk allele A of STAT4 rs897200 correlates clinically with BD disease score due to increased mRNA level of STAT4 gene and expression of IL-17 [112].

5.2 FOXP3

FOXP3 is a key transcription factor in the development and function of T(reg) cells. Recent reports have shown the FOXP3 SNPs contribute to the susceptibility to some autoimmune and autoinflammatory disorders. The FOXP3 SNP rs3761548 (-3279 C/A) was significantly associated with BD in the Iranian patients [113]. The FOXP3 (-3279 C/A) A allele has been reported to be associated with neural involvement in BD in Egyptian patients [114]. A low copy number variant of the FOXP3 gene was shown to increase risk in female BD patients in a Chinese cohort [115].

5.3 FUT2

FUT3 (Fucosyltransferase) gene is responsible for the formation of histo-blood group antigens, it might affect the intestinal microbiota composition and modulate innate immune responses [116]. Recent studies indicated that the association between the FUT2 gene variants (rs632111, rs601338, rs602662, rs492602, rs681343, and rs281377) and BD was reported in Iranian and Turkish populations [117].

5.4 ACE and VEGF

The renin-angiotensin system (RAS) is important in vascular tone and inflammatory processes. It has been suggested that DD genotype of ACE gene I/D polymorphism might be a genetic marker for BD in Turkish populations [118, 119]. In the other hand, the ACE gene I/D polymorphism was not associated with BD patients in

a Iranian cohort and in an another Turkish population [120, 121]. VEGF is a potent angiogenic factor exhibiting various endothelial cell effects, including endothelial cell survival, proliferation, migration and tube formation, and also acts as a proinflammatory cytokine [122, 123]. The carriers of the -634C (3'untranslated region UTR) and I (insertion/deletion) alleles of VEGF gene were associated with a susceptibility to BD in Italian patients [124].

5.5 UBAC2 and LACC1

Ubiquitin-associated domain containing 2 (UBAC2) encodes an ubiquitination-related structural domain that is implicated in ubiquitination and proteasomal degradation. The association of the UBAC2 gene polymorphisms (rs9513584, rs9517723, rs7999348) with BD were found in multiple cohorts found including Turkish, Chinese Han, Italian, and Japanese populations [125–128]. The LACC1 (Laccase domain-containing 1), also known as multicopper oxidoreductases, encodes an oxidoreductase that promotes fatty-acid oxidation. It known functions in activation of inflammasome, bactericidal activity of macrophages, and production of mitochondrial and NADPH-oxidase-dependent reactive oxygen species. SNP rs9316059 of the LACC1 was associated with BD in all the populations tested including Chinese Han, Turkish, Iranian and Japanese [91, 129].

5.6 SUMO4

Small ubiquitin-like modifier 4 (SUMO4) has been shown to have the potential to down-regulate NF-kappaB signal, leading to decreased transcription of pro-inflammatory cytokines [130, 131]. The association between the SUMO4 gene (rs237024 and rs237026) polymorphisms and BD was first reported in a Chinese cohort, and they showed the GGAC haplotype was protectively associated with BD in HLA-B51 positive patients [132]. The association was replicated in Tunisian and Korean cohorts for the rs237024 and rs237026 polymorphisms of SUMO4 gene. This study also showed this polymorphisms were associated with disease severity and also some clinical manifestations such as skin lesions, and vascular involvement [133, 134].

5.7 ROCK1 and ROCK2

The Rho-kinase (ROCK) family members, consisting of ROCK1 and ROCK2, play significant roles in the actin cytoskeleton organization and regulate a wide range of fundamental cellular functions, such as adhesion, migration, motility, cell proliferation, apoptosis, and multiple inflammatory responses [135, 136]. Oguz et al. showed the SNPs rs73963110, rs112130712, rs111874856, rs112108028 might increase the susceptibility to Behçet's disease, but they failed for the other SNPs such as rs35996865, rs111312709 and rs2271255 [137]. In addition, the ROCK2 gene rs35768389 (Asp601Val) polymorphism was showed to be associated with BD and the C allele was significantly higher in BD patients compared to controls [138].

5.8 VDR gene

The proven role of vitamin D in innate and adaptive immune responses has led to an increase in studies on the relationship between vitamin D and autoinflammatory diseases. The VDR gene encodes the VDR protein, a member of the nuclear receptor

superfamily, that is essential for the biological functions of vitamin D [139, 140]. Karray et al. found that the VDR gene (rs1544410 and rs2228570) polymorphism were associated with BD in Tunisian patients [141]. In a study with a Turkish cohort, the VDR gene rs1544410 A allele and rs2228570 C allele were reported to be a risk factor for BD susceptibility [142]. In a meta-analysis, the role of the four common VDR polymorphisms has been investigated and it was suggested that rs731236 polymorphism might be a risk factor for BD [143].

6. Epigenetic factors

Epigenetics is the study of stable and heritable changes in the function of genes which occur without altering the DNA sequence and include DNA methylation, histone modification, and microRNAs [144]. MicroRNAs (miRNAs) are short noncoding RNAs are crucial in regulating multiple cellular processes, such as development, proliferation and apoptosis [145]. Several miRNAs have been associated with the susceptibility of BD disease, which includes many different inflammatory pathways [146]. Zhou et al. revealed miR155 expression was significantly decreased in dendritic cells from patients with BD with active compared to inactive uveitis [147]. In addition, the many SNPs in miRNA have been showed to be a risk for BD in association studies. Both of the TT genotype and T allele of rs11614913 located at pre-miR196a2 were found had increased frequency in patients with BD [148]. The microRNA-146a rs2910164 was associated with decreased frequency of CC genotype and C allele in patients with BD, whereas GG genotype was significantly increased in an Egyptian cohort [149]. Also, TT genotypes and T allele of rs3746444 miRNA-499 exhibited a significantly higher risk in patients with BD in a study of Turkish population [150]. In a Spanish cohort, the relative promoter methylation level of the IL-6 mRNA was found significantly lower in BD patients compared to controls [151]. The variant in the pre-miRNA region of miR-196a2, rs11614913, was associated with BD susceptibility, as well as BD arthritis [148]. In an Epigenome-wide association study with Chinese BD patients, the genetic variants of 10 CpG-SNPs were not associated with BD susceptibility [152].

7. Conclusion

From a genetic perspective, several molecules involved in the response to pathogens and multiple genes that activate or regulate inflammation appear to be critical in the etiopathogenesis of BD. However, the precise pathogenic mechanisms of these genes on BD are still unclear. In addition, it is unknown how genetic components as well as other associated risk factors such as bacterial and viral pathogens affect the developmental process of BD. Genome-wide association studies (GWAS) have become a very important step in understanding BD pathogenesis. GWASs with satisfactory numbers of subjects in regions where BD is prevalent revealed a strong association between BD and inflammatory cytokines such as IL-1, IL-4, IL-6, IL-10, IL-17, and IL-23–IL-12RB2. Some association studies, for example TNFAIP3, TLRs and miRNAs, appear to be conflict in different study groups and/or populations. The conflicting results of these genes associated with BD suggest that they may be ethnically specific or have occurred due to sample selection bias. In the future, similar studies in different populations with a higher number of patients will provide

significant advances in the etiopathology of BD. We proposed that genetic factors located at loci outside the MHC region (IL1A-IL1R, IL10, CCR1-CCR3, ERAP1, IRF8, RIPK2, FUT2, IL-28, IL-29, NOD1, NOD2, VEGF and etc....) contributed to BD susceptibility by playing a role in host defense and immune responses to pathogens in inflammation pathways. Moreover, specific gene polymorphisms have been linked with clinical presentation of BD such as ocular lesions, neurological and intestinal and cardiovascular involvement. The future direction will guide possible therapeutic approaches by understanding the functional significance of BD-associated gene polymorphisms, as well as insights into the pathogenesis of the disease.

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References

[1] Tursen U et al. Pathological and immunological developments in Behcet's disease. Pathology Research International. 2012;**2012**:305780

[2] Ortiz-Fernández L, Sawalha AH. Genetics of Behçet's disease: Functional genetic analysis and estimating disease heritability. Front Med (Lausanne). 2021;**8**:625710

[3] Cakir N et al. Prevalence of Behçet's disease in rural western Turkey: A preliminary report. Clinical and Experimental Rheumatology. 2004;**22**(4 Suppl 34):S53-S55

[4] Zeidan MJ et al. Behçet's disease physiopathology: A contemporary review. Autoimmunity Highlights. 2016;**7**(1):4

[5] Takeuchi M, Kastner DL, Remmers EF. The immunogenetics of Behçet's disease: A comprehensive review. Journal of Autoimmunity. 2015;**64**:137-148

[6] Demirseren DD et al. HLA-B51 subtypes in Turkish patients with Behçet's disease and their correlation with clinical manifestations. Genetics and Molecular Research. 2014;**13**(3):4788-4796

[7] Wieczorek M et al. Major histocompatibility complex (MHC) class I and MHC class II proteins: Conformational plasticity in antigen presentation. Frontiers in Immunology. 2017;**8**:292

[8] Gough SC, Simmonds MJ. The HLA region and autoimmune disease: Associations and mechanisms of action. Current Genomics. 2007;**8**(7):453-465

[9] Salvarani C et al. Association of MICA alleles and HLA-B51 in Italian patients with Behçet's disease. The Journal of Rheumatology. 2001;**28**(8):1867-1870

[10] Paul M et al. Allelic distribution of HLA-B*5 in HLA-B5-positive Israeli patients with Behçet's disease. Tissue Antigens. 2001;**58**(3):185-186

[11] Mizuki N et al. Sequencing-based typing of HLA-B*51 alleles and the significant association of HLA-B*5101 and -B*5108 with Behçet's disease in Greek patients. Tissue Antigens. 2002;**59**(2):118-121

[12] Ortiz-Fernández L, Carmona FD, Montes-Cano MA, García-Lozano JR, Conde-Jaldón M, Ortego-Centeno N, et al. Genetic Analysis with the Immunochip Platform in Behçet Disease. Identification of Residues Associated in the HLA Class I Region and New Susceptibility Loci. PLoS One. 2016;**11**(8):e0161305

[13] Montes-Cano MA et al. HLA and non-HLA genes in Behçet's disease: A multicentric study in the Spanish population. Arthritis Research & Therapy. 2013;**15**(5):R145

[14] Pekiner FN et al. HLA-A, B (class I) and HLA-DR, DQ (class II) antigens in Turkish patients with recurrent aphthous ulceration and Behçet's disease. Medical Principles and Practice. 2013;**22**(5):464-468

[15] Kaburaki T et al. Genetic association of HLA-A*2601 with ocular Behçet's disease in Japanese patients. Clinical and Experimental Rheumatology. 2010; **28**(4 Suppl 60):S39-S44

[16] Ting JP, Trowsdale J. Genetic control of MHC class II expression. Cell. 2002;**109**(Suppl):S21-S33

[17] Kang EH et al. Associations between the HLA-A polymorphism and the clinical manifestations of Behcet's disease. Arthritis Research & Therapy. 2011;**13**(2):R49

[18] Kang EH et al. Genetic and non-genetic factors affecting the visual outcome of ocular Behcet's disease. Human Immunology. 2013;**74**(10):1363-1367

[19] León Machado JA, Steimle V. The MHC Class II Transactivator CIITA: Not (Quite) the Odd-One-Out Anymore among NLR Proteins. International Journal of Molecular Science. 2021;**22**(3)

[20] Nakamura MC. CIITA: A master regulator of adaptive immunity shows its innate side in the bone. Journal of Bone and Mineral Research. 2014;**29**(2):287-289

[21] Li L et al. Genetic variations of NLR family genes in Behcet's disease. Scientific Reports. 2016;**6**:20098

[22] Li L, Batliwala M, Bouvier M. ERAP1 enzyme-mediated trimming and structural analyses of MHC I-bound precursor peptides yield novel insights into antigen processing and presentation. The Journal of Biological Chemistry. 2019;**294**(49):18534-18544

[23] Kirino Y et al. Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1. Nature Genetics. 2013;**45**(2):202-207

[24] Zhang L et al. Association of ERAP1 gene polymorphisms with Behçet's disease in Han Chinese. Investigative Ophthalmology & Visual Science. 2015;**56**(10):6029-6035

[25] Sousa I et al. Brief report: Association of CCR1, KLRC4, IL12A-AS1, STAT4, and ERAP1 With Behçet's disease in Iranians. Arthritis & Rhematology. 2015;**67**(10):2742-2748

[26] Conde-Jaldón M, Montes-Cano MA, García-Lozano JR, Ortiz-Fernández L, Ortego-Centeno N, González-León R, et al. Epistatic interaction of ERAP1 and HLA-B in Behçet disease: A replication study in the Spanish population. PLoS One. 2014;**9**(7):e102100

[27] Baranwal AK, Mehra NK. Major histocompatibility complex class I chain-related a (MICA) molecules: Relevance in solid organ transplantation. Frontiers in Immunology. 2017;**8**:182

[28] Muñoz-Saá I et al. Allelic diversity and affinity variants of MICA are imbalanced in Spanish patients with Behçet's disease. Scandinavian Journal of Immunology. 2006;**64**(1):77-82

[29] Zhu W et al. MICA*049, not MICA*009, is associated with Behçet's disease in a Chinese population. Scientific Reports. 2019;**9**(1):10856

[30] Eyerci N et al. Association of MICA alleles and human leukocyte antigen B in Turkish patients diagnosed with Behçet's disease. Archives of Rheumatology. 2018;**33**(3):352-357

[31] Wallace GR et al. IL-10 genotype analysis in patients with Behçet's disease. Human Immunology. 2007;**68**(2):122-127

[32] Migliorini P et al. The IL-1 family cytokines and receptors in autoimmune diseases. Autoimmunity Reviews. 2020;**19**(9):102617

[33] Zarrouk-Mahjoub S et al. Pro- and anti-inflammatory cytokines in post-infarction left ventricular remodeling. International Journal of Cardiology. 2016;**221**:632-636

[34] Dayer JM, Oliviero F, Punzi L. A brief history of IL-1 and IL-1 Ra in

rheumatology. Frontiers in Pharmacology. 2017;**8**:293

[35] Alayli G et al. T helper 1 type cytokines polymorphisms: Association with susceptibility to Behçet's disease. Clinical Rheumatology. 2007;**26**(8):1299-1305

[36] Akman A et al. Relationship between periodontal findings and specific polymorphisms of interleukin-1alpha and -1beta in Turkish patients with Behçet's disease. Archives of Dermatological Research. 2008;**300**(1):19-26

[37] Zou J, Guan JL. Interleukin-1-related genes polymorphisms in Turkish patients with Behçet disease: A meta-analysis. Modern Rheumatology. 2014;**24**(2):321-326

[38] Barış S et al. The impact of the IL-1β, IL-1Ra, IL-2, IL-6 and IL-10 gene polymorphisms on the development of Behcet's disease and their association with the phenotype. Medicina Clínica (Barcelona). 2016;**146**(9):379-383

[39] Mitchell RE et al. IL-4 enhances IL-10 production in Th1 cells: Implications for Th1 and Th2 regulation. Scientific Reports. 2017;7(1):11315

[40] Inanir A et al. Association of IL-4 gene VNTR variant with deep venous thrombosis in Behçet's disease and its effect on ocular involvement. Molecular Vision. 2013;**19**:675-683

[41] Oral HB et al. Interleukin-4 gene polymorphisms confer Behçet's disease in Turkish population. Scandinavian Journal of Immunology. 2011;**73**(6):594-601

[42] Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Critical Reviews in Immunology. 2012;**32**(1):23-63

[43] Trifunović J et al. Pathologic patterns of interleukin 10 expression—A review. Biochem Med (Zagreb). 2015;**25**(1):36-48

[44] Akdis M, Burgler S, Crameri R, Eiwegger T, Fujita H, Gomez E, et al. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. Journal of Allergy and Clinical Immunology. 2011;**127**(3):701-21.e1-70

[45] Chang JT, Shevach EM, Segal BM. Regulation of interleukin (IL)-12 receptor beta2 subunit expression by endogenous IL-12: A critical step in the differentiation of pathogenic autoreactive T cells. The Journal of Experimental Medicine. 1999;**189**(6):969-978

[46] Kappen JH et al. Genome-wide association study in an admixed case series reveals IL12A as a new candidate in Behçet disease. PLoS One. 2015;**10**(3):e0119085

[47] Afkari B et al. Molecular analysis of interleukin-10 gene polymorphisms in patients with Behçet's disease. Immunology Letters. 2018;**194**:56-61

[48] Yu H et al. Identification of susceptibility SNPs in IL10 and IL23R-IL12RB2 for Behçet's disease in Han Chinese. The Journal of Allergy and Clinical Immunology. 2017;**139**(2):621-627

[49] Jones LL et al. Distinct subunit pairing criteria within the heterodimeric IL-12 cytokine family. Molecular Immunology. 2012;**51**(2):234-244

[50] van de Vosse E et al. IL-12Rβ1 deficiency: Mutation update and description of the IL12RB1 variation database. Human Mutation. 2013;**34**(10):1329-1339

[51] Li X et al. Genetic variations of IL-12B, IL-12Rβ1, IL-12Rβ2 in Behcet's

disease and VKH syndrome. PLoS One. 2014;**9**(5):e98373

[52] Tang C et al. Interleukin-23: As a drug target for autoimmune inflammatory diseases. Immunology. 2012;**135**(2):112-124

[53] Yang J et al. Targeting Th17 cells in autoimmune diseases. Trends in Pharmacological Sciences. 2014;**35**(10): 493-500

[54] Parham C et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. Journal of Immunology. 2002;**168**(11):5699-5708

[55] Remmers EF et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet's disease. Nature Genetics. 2010;**42**(8):698-702

[56] Mizuki N et al. Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behçet's disease susceptibility loci. Nature Genetics. 2010;**42**(8):703-706

[57] Qin X et al. Association study of rs924080 and rs11209032 polymorphisms of IL23R-IL12RB2 in a Northern Chinese Han population with Behcet's disease. Human Immunology. 2016;**77**(12):1284-1290

[58] Kang EH et al. Behçet's disease risk association fine-mapped on the IL23R-IL12RB2 intergenic region in Koreans. Arthritis Research & Therapy. 2017;**19**(1):227

[59] Monin L, Gaffen SL. Interleukin 17 Family Cytokines: Signaling Mechanisms, Biological Activities, and Therapeutic Implications. Cold Spring Harb Perspect Biol. 2018;**10**(4).

[60] Kuwabara T et al. The role of IL-17 and related cytokines in inflammatory autoimmune diseases. Mediators of Inflammation. 2017;**2017**:3908061

[61] Jang WC et al. Interleukin-17F gene polymorphisms in Korean patients with Behçet's disease. Rheumatology International. 2008;**29**(2):173-178

[62] Kim ES et al. Interactions between IL17A, IL23R, and STAT4 polymorphisms confer susceptibility to intestinal Behcet's disease in Korean population. Life Sciences. 2012;**90**(19-20):740-746

[63] Nakamura K et al. Interleukin-17A gene polymorphism with the susceptibility of intestinal symptoms in patients with Behçet's disease. The Journal of Dermatology. 2016;**43**(6):708-709

[64] Lee YJ et al. Interleukin-18 promoter polymorphisms in patients with Behçet's disease. Human Immunology. 2006;**67**(10):812-818

[65] Hazzaa HH, Rashwan WA, Attia EA. IL-18 gene polymorphisms in aphthous stomatitis vs. Behçet's disease in a cohort of Egyptian patients. Journal of Oral Pathology & Medicine. 2014;**43**(10):746-753

[66] Chyuan IT, Tzeng HT, Chen JY. Signaling Pathways of Type I and Type III Interferons and Targeted Therapies in Systemic Lupus Erythematosus. Cells. 2019;**8**(9)

[67] Goel RR, Kotenko SV, Kaplan MJ. Interferon lambda in inflammation and autoimmune rheumatic diseases. Nature Reviews Rheumatology. 2021;**17**(6):349-362

[68] Cakmak Genc G, Karakas Celık S, Kocaaga A, Koca R, Dursun A. Association Between IL28B, IL29 Gene Polymorphisms and Clinical

Manifestations of Behçet's Disease. Immunol Invest. 2021;**50**(8):906-913

[69] Chan BCL et al. IL33: Roles in allergic inflammation and therapeutic perspectives. Frontiers in Immunology. 2019;**10**:364

[70] Liew FY, Girard JP, Turnquist HR. Interleukin-33 in health and disease. Nature Reviews Immunology. 2016; **16**(11):676-689

[71] Koca SS et al. Serum IL-33 level and IL-33 gene polymorphisms in Behçet's disease. Rheumatology International. 2015;**35**(3):471-477

[72] Talei M et al. Interleukin-33 gene expression and rs1342326 polymorphism in Behçet's disease. Immunology Letters. 2019;**212**:120-124

[73] Elemam NM, Hannawi S, Maghazachi AA. Role of chemokines and chemokine receptors in rheumatoid arthritis. ImmunoTargets and Therapy. 2020;**9**:43-56

[74] Chang TT, Chen JW. The Role of Chemokines and Chemokine Receptors in Diabetic Nephropathy. Int J Mol Sci. 2020;**21**(9)

[75] Hou S et al. Two-stage association study in Chinese Han identifies two independent associations in CCR1/ CCR3 locus as candidate for Behçet's disease susceptibility. Human Genetics. 2012;**131**(12):1841-1850

[76] Swainson LA et al. Expression of the autoimmune susceptibility gene FcRL3 on human regulatory T cells is associated with dysfunction and high levels of programmed cell death-1. Journal of Immunology. 2010;**184**(7):3639-3647

[77] Sakaguchi S et al. Regulatory T cells and immune tolerance. Cell. 2008;**133**(5):775-787

[78] Li K et al. Association between polymorphisms of FCRL3, a non-HLA gene, and Behçet's disease in a Chinese population with ophthalmic manifestations. Molecular Vision. 2008;**14**:2136-2142

[79] Shahram F et al. Single nucleotide polymorphisms of FCRL3 in Iranian patients with Behcet's disease. Iranian Journal of Public Health. 2019;**48**(6):1133-1139

[80] Wu Z, Zhang S, Li J, Chen S, Li P, Sun F, et al. Association between MEFV Mutations M694V and M680I and Behçet's Disease: A Meta-Analysis. PLoS One. 2015;**10**(7):e0132704

[81] Touitou I et al. MEFV mutations in Behçet's disease. Human Mutation. 2000;**16**(3):271-272

[82] Kirino Y et al. Targeted resequencing implicates the familial Mediterranean fever gene MEFV and the toll-like receptor 4 gene TLR4 in Behçet disease. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**(20):8134-8139

[83] Esmaeili M et al. Common MEFV mutations in Iranian Azeri Turkish patients with Behçet's disease. Scandinavian Journal of Rheumatology. 2011;**40**(5):383-386

[84] Tasliyurt T et al. Common MEFV gene mutations in Turkish patients with Behcet's disease. Gene. 2013;**530**(1):100-103

[85] Wietzke-Braun P et al. Interferon regulatory factor-1 promoter polymorphism and the outcome of hepatitis C virus infection. European Journal of Gastroenterology & Hepatology. 2006;**18**(9):991-997

[86] Yang Y et al. Association study between the IL4, IL13, IRF1 and UGRP1

genes in chromosomal 5q31 region and Chinese Graves' disease. Journal of Human Genetics. 2005;**50**(11):574-582

[87] Lee YJ et al. Associations between interferon regulatory factor-1 polymorphisms and Behçet's disease. Human Immunology. 2007;**68**(9):770-778

[88] Holtschke T et al. Immunodeficiency and chronic myelogenous leukemia-like syndrome in mice with a targeted mutation of the ICSBP gene. Cell. 1996;**87**(2):307-317

[89] Ouyang X et al. Transcription factor IRF8 directs a silencing programme for TH17 cell differentiation. Nature Communications. 2011;**2**:314

[90] Jiang Y et al. Two genetic variations in the IRF8 region are associated with Behçet's disease in Han Chinese. Scientific Reports. 2016;**6**:19651

[91] Takeuchi M et al. Dense genotyping of immune-related loci implicates host responses to microbial exposure in Behçet's disease susceptibility. Nature Genetics. 2017;**49**(3):438-443

[92] Boone DL et al. The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses. Nature Immunology. 2004;**5**(10):1052-1060

[93] Li H et al. TNFAIP3 gene polymorphisms confer risk for Behcet's disease in a Chinese Han population. Human Genetics. 2013;**132**(3):293-300

[94] Akira S, Takeda K, Kaisho T. Toll-like receptors: Critical proteins linking innate and acquired immunity. Nature Immunology. 2001;**2**(8):675-680

[95] Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature. 1997;**388**(6640):394-397

[96] Fang J et al. Association of TLR2 gene polymorphisms with ocular Behcet's disease in a Chinese Han population. Investigative Ophthalmology & Visual Science. 2013;**54**(13):8384-8392

[97] Boiardi L et al. Toll-like receptor 4 (TLR4) gene polymorphisms in Italian patients with Behçet's disease. Clinical and Experimental Rheumatology. 2009;**27**(2 Suppl 53):S43-S47

[98] Du L et al. No association of CTLA-4 polymorphisms with susceptibility to Behçet disease. The British Journal of Ophthalmology. 2009;**93**(10):1378-1381

[99] Horie Y et al. Association of TLR4 polymorphisms with Behcet's disease in a Korean population. Rheumatology (Oxford). 2009;**48**(6):638-642

[100] Meguro A et al. Association of the toll-like receptor 4 gene polymorphisms with Behcet's disease. Annals of the Rheumatic Diseases. 2008;**67**(5):725-727

[101] Ortiz-Fernández L et al. Association of haplotypes of the TLR8 locus with susceptibility to Crohn's and Behçet's diseases. Clinical and Experimental Rheumatology. 2015;**33**(6 Suppl 94): S117-S122

[102] Song GG et al. Toll-like receptor polymorphisms and vasculitis susceptibility: Meta-analysis and systematic review. Molecular Biology Reports. 2013;**40**(2):1315-1323

[103] Hellquist A et al. The human GIMAP5 gene has a common polyadenylation polymorphism increasing risk to systemic lupus erythematosus. Journal of Medical Genetics. 2007;**44**(5):314-321

[104] Ortiz-Fernández L et al. GIMAP and Behçet disease: No association in the European population. Annals of the Rheumatic Diseases. 2014;**73**(7):1433-1434

[105] Strober W et al. Signalling pathways and molecular interactions of NOD1 and NOD2. Nature Reviews Immunology. 2006;**6**(1):9-20

[106] Kocaaga A, Cakmak Genc G, Karakas Celık S, Koca R, Dursun A. Association of NOD1, NOD2, PYDC1 and PYDC2 genes with Behcet's disease susceptibility and clinical manifestations. Ophthalmic Genet. 2021:1-7

[107] Kappen JH et al. Low prevalence of NOD2 SNPs in Behçet's disease suggests protective association in Caucasians. Rheumatology (Oxford). 2009;**48**(11):1375-1377

[108] Burillo-Sanz S et al. Mutational profile of rare variants in inflammasome-related genes in Behçet disease: A next generation sequencing approach. Scientific Reports. 2017;**7**(1):8453

[109] Kim J et al. Imbalance of Th17 to Th1 cells in Behçet's disease. Clinical and Experimental Rheumatology. 2010; **28**(4 Suppl 60):S16-S19

[110] Watford WT et al. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. Immunological Reviews. 2004;**202**: 139-156

[111] Morinobu A et al. STAT4 serine phosphorylation is critical for IL-12-induced IFN-gamma production but not for cell proliferation. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**(19):12281-12286

[112] Hou S et al. Identification of a susceptibility locus in STAT4 for Behçet's disease in Han Chinese in a genome-wide association study. Arthritis and Rheumatism. 2012;**64**(12):4104-4113

[113] Hosseini A et al. A single nucleotide polymorphism in the FOXP3 gene associated with Behçet's disease in an Iranian population. Clinical Laboratory. 2015;**61**(12):1897-1903

[114] Abdelmoktader A, Bassyoun RH, Wegdan AA, Talaat RM, Bassyouni IM. Genetic Association of Promoter FOXP3 Gene Polymorphism with Behcet's Disease in Egyptians Patients. Virology & Immunology Journal; 2018;**2**(2):000147

[115] Liao D et al. Copy number variants and genetic polymorphisms in TBX21, GATA3, Rorc, Foxp3 and susceptibility to Behcet's disease and Vogt-Koyanagi-Harada syndrome. Scientific Reports. 2015;**5**:9511

[116] Ferrer-Admetlla A et al. A natural history of FUT2 polymorphism in humans. Molecular Biology and Evolution. 2009;**26**(9):1993-2003

[117] Xavier JM et al. FUT2: Filling the gap between genes and environment in Behçet's disease? Annals of the Rheumatic Diseases. 2015;**74**(3):618-624

[118] Yigit S et al. DD genotype of ACE gene I/D polymorphism is associated with Behcet disease in a Turkish population. Molecular Biology Reports. 2013;**40**(1):365-368

[119] Turgut S et al. Angiotensin-converting enzyme I/D polymorphism in Behçet's disease. Medical Principles and Practice. 2005;**14**(4):213-216

[120] Jabbarpoor Bonyadi MH, Yaseri M, Soheilian M. Tumor necrosis factor (TNF)-308, −1031, and angiotensin-converting enzyme (ACE) DD/II polymorphisms' role in Behcet's

disease with and without uveitis: A meta-analysis. Ophthalmic Genetics. 2020;**41**(3):235-239

[121] Dursun A et al. Angiotensin-converting enzyme gene and endothelial nitric oxide synthase gene polymorphisms in Behçet's disease with or without ocular involvement. Inflammation Research. 2009;**58**(7):401-405

[122] Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. Clinical Science (London, England). 2005;**109**(3):227-241

[123] Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocrine Reviews. 2004;**25**(4):581-611

[124] Salvarani C et al. Vascular endothelial growth factor gene polymorphisms in Behçet's disease. The Journal of Rheumatology. 2004;**31**(9):1785-1789

[125] Fei Y et al. Identification of novel genetic susceptibility loci for Behçet's disease using a genome-wide association study. Arthritis Research & Therapy. 2009;**11**(3):R66

[126] Sawalha AH et al. A putative functional variant within the UBAC2 gene is associated with increased risk of Behçet's disease. Arthritis and Rheumatism. 2011;**63**(11):3607-3612

[127] Hou S et al. Replication study confirms the association between UBAC2 and Behçet's disease in two independent Chinese sets of patients and controls. Arthritis Research & Therapy. 2012;**14**(2):R70

[128] Yamazoe K et al. Comprehensive analysis of the association between UBAC2 polymorphisms and Behçet's disease in a Japanese population. Scientific Reports. 2017;**7**(1):742

[129] Wu P et al. Association of LACC1, CEBPB-PTPN1, RIPK2 and ADO-EGR2 with ocular Behcet's disease in a Chinese Han population. The British Journal of Ophthalmology. 2018;**102**(9):1308-1314

[130] Rallabhandi P et al. Sumoylation of topoisomerase I is involved in its partitioning between nucleoli and nucleoplasm and its clearing from nucleoli in response to camptothecin. The Journal of Biological Chemistry. 2002;**277**(42):40020-40026

[131] Guo D et al. A functional variant of SUMO4, a new I kappa B alpha modifier, is associated with type 1 diabetes. Nature Genetics. 2004;**36**(8):837-841

[132] Hou S et al. SUMO4 gene polymorphisms in Chinese Han patients with Behcet's disease. Clinical Immunology. 2008;**129**(1):170-175

[133] Kamoun M et al. Association of small ubiquitin-like modifier 4 (SUMO4) polymorphisms in a Tunisian population with Behçet's disease. Clinical and Experimental Rheumatology. 2010; **28**(4 Suppl 60):S45-S49

[134] Park G et al. SUMO4 C438T polymorphism is associated with papulopustular skin lesion in Korean patients with Behçet's disease. Rheumatology International. 2012;**32**(10):3031-3037

[135] Amano M, Nakayama M, Kaibuchi K. Rho-kinase/ROCK: A key regulator of the cytoskeleton and cell polarity. Cytoskeleton (Hoboken). 2010;**67**(9):545-554

[136] Yao L et al. The role of RhoA/Rho kinase pathway in endothelial dysfunction. Journal of Cardiovascular Disease Research. 2010;**1**(4):165-170

[137] Oguz E et al. Association of Rho-kinase 1 (ROCK1) gene polymorphisms with Behçet's disease. Molecular Diagnosis & Therapy. 2014;**18**(4):419-426

[138] Oguz E et al. Association between Rho-kinase (ROCK2) gene polymorphisms and Behçet's disease. Translational Research. 2012;**160**(6):428-434

[139] Kaleta B et al. Vitamin D receptor gene BsmI polymorphism in polish patients with systemic lupus erythematosus. ISRN Endocrinology. 2013;**2013**:427818

[140] Joshi S et al. 1,25-dihydroxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A. Molecular and Cellular Biology. 2011;**31**(17):3653-3669

[141] Karray EF et al. Associations of vitamin D receptor gene polymorphisms FokI and BsmI with susceptibility to rheumatoid arthritis and Behçet's disease in Tunisians. Joint, Bone, Spine. 2012;**79**(2):144-148

[142] Dal NE et al. The role of vitamin D receptor gene polymorphisms in the pathogenesis of Behçet's disease: A case-control study in Turkish population. Annals of Human Genetics. 2019;**83**(3):177-186

[143] Mirfeizi Z et al. Associations between vitamin D receptor polymorphisms and susceptibility to Behcet's disease: A meta-analysis. Immunological Investigations. 2018; **47**(4):389-402

[144] Renauer PA, Coit P, Sawalha AH. The DNA methylation signature of human TCRαβ+CD4-CD8- double negative T cells reveals CG demethylation and a unique epigenetic architecture permissive to a broad stimulatory immune response. Clinical Immunology. 2015;**156**(1):19-27

[145] Xu SJ, Hu HT, Li HL, Chang S. The Role of miRNAs in Immune Cell Development, Immune Cell Activation, and Tumor Immunity: With a Focus on Macrophages and Natural Killer Cells. Cells. 2019;**8**(10)

[146] Puccetti A et al. MicroRNA expression profiling in Behçet's disease. Journal of Immunology Research. 2018;**2018**:2405150

[147] Zhou Q et al. Decreased microRNA-155 expression in ocular Behcet's disease but not in Vogt Koyanagi Harada syndrome. Investigative Ophthalmology & Visual Science. 2012;**53**(9):5665-5674

[148] Qi J et al. A functional variant of pre-miRNA-196a2 confers risk for Behcet's disease but not for Vogt-Koyanagi-Harada syndrome or AAU in ankylosing spondylitis. Human Genetics. 2013;**132**(12):1395-1404

[149] Ibrahim W et al. MicroRNA-146a expression and microRNA-146a rs2910164 polymorphism in Behcet's disease patients. Clinical Rheumatology. 2019;**38**(2):397-402

[150] Oner T et al. Association of Pre-miRNA-499 rs3746444 and Pre-miRNA-146a rs2910164 polymorphisms and susceptibility to Behcet's disease. Genetic Testing and Molecular Biomarkers. 2015;**19**(8):424-430

[151] Alipour S et al. Methylation status of interleukin-6 gene promoter in patients with Behçet's disease. Reumatologia Clinica (Engl Ed). 2020;**16**(3):229-234

[152] Huang Y et al. Different methylation of CpG-SNPs in Behcet's disease. BioMed Research International. 2019;**2019**:3489305

Section 2

Hormonal, Physiological, Inflamatory and Unknown Origin Induced Rare Disease

Chapter 5

Malignant Mesothelioma *In Situ*: A Controversial Diagnostic Entity – A Review

Richard Kradin

Abstract

Malignant mesothelioma is a rare aggressive malignancy of serosal surfaces that is strongly associated with exposure to asbestos. The pathological diagnosis of malignant mesothelioma can be difficult to distinguish from reactive benign hyperplasia. Mutations in *BAP-1 and CDKN2a* distinguish mesothelioma from reactive hyperplasia. An *in situ* growth phase of mesothelioma until recently was difficult to ascertain due to limits of histological assessment and because mesothelioma tends to spread diffusely along serosal surfaces making sampling for invasion impossible without extensive resection. The current WHO classification of thoracic tumors recognizes mesothelioma *in situ* as a distinct entity based on histological, genetic, and clinical features. This chapter reviews the topic and concludes that the diagnosis of malignant mesothelioma *in situ* should be limited to patients eligible for radical resection to confirm the putative diagnosis.

Keywords: mesothelioma, in situ, invasion, *BAP-1*, *CDKN2A*

1. Introduction

Malignant tumors result from dysregulated clonal cell proliferations. Malignant tumors can potentially invade local tissues and metastasize to distant sites. There are many pathways leading to malignant transformation and the spread of tumor. Most solid epithelial tumors pass through a stage of *in situ* neoplasia, in which disordered cellular proliferation occurs locally, and in the absence of invasion of underlying tissues. Pathologists are trained to recognize *in situ* malignant neoplasia based on its histological features, including non-disruption of the cell basement membrane. The clinical importance of distinguishing *in situ* malignancy is that it may be cured by surgical resection in a high percentage of cases.

Malignant mesothelioma is a rare malignancy of serosal-lined surfaces [1]. Most mesotheliomas occur in the pleura (85%), with the remainder in peritoneum (~10%), pericardium and tunica vaginalis (each less than 2.5%). Mesothelioma was rarely described in the medical literature prior to 1960, when Wagner described a large cohort of cases in South African asbestos miners and those living in proximity to the mines. Subsequently, a large percentage of mesotheliomas have been demonstrated to be causally linked to prior exposure to asbestos, the latter a naturally occurring

fibrous magnesium silicate that was used extensively as an insulating material in the construction and other trades in the twentieth century. There is a prolonged latency for the development of malignant mesothelioma, on average greater than 30 years following first exposures to asbestos. Other recognized causes of mesothelioma are rare and include therapeutic radiation and the mineral erionite that was used in the construction of homes in the Cappadocia region of Turkey [2].

Mesothelial cells line normal serosal surfaces. They secrete acid mucins and regulate cavitary fluid accumulation of lubricant fluid. In response to inflammation, normal mesothelial cells proliferate and show enhanced fluid secretion, leading to exudative effusions that bring patients to clinical attention. Reactive mesothelial proliferation can be difficult to differentiate histologically from mesothelial malignancy. Mesothelial cells are pluripotential cells; and under neoplastic conditions, they may give rise to tumors with epithelioid, sarcomatoid, or mixed (biphasic) histologies. Until recently, unequivocal evidence of soft tissue invasion was required to distinguish malignancy from benign reactive mesothelial proliferations. Unfortunately, the propensity of malignant mesothelioma to spread diffusely along serosal surfaces and to invade adjacent structures makes curative surgical excision virtually impossible. Consequently, nearly all patients with malignant mesothelioma die from their disease.

2. Genetics of mesothelial malignancy

Malignant mesothelioma are heterogeneous with complex genetic, chromosomal, and epigenetic changes. Mesotheliomas are often polyclonal neoplasms, likely reflecting a "field effect" induced by asbestos. They also display relatively low mutation burdens, compared to most adult solid tumors [3].

The Cancer Genome Atlas program studied 74 mesotheliomas for genetic alterations using next-generation sequencing (NGS), whole-exome sequencing (WES), messenger RNA expression, methylation analysis, microRNA expression, exomes, reverse-phase protein array, and transcription factor analyses. They observed frequent characteristic mutations in *BAP-1, CDKN2A*, *NF2*, *TP53*, *LATS2*, and *SETD2* [4]. Bueno et al. using NGS [5] and by Hmeljak et al. by WES [6] confirmed this mutation profile, suggesting that the development of mesothelioma may be due to mutations in a limited number of genes [1]. In this regard, Badhai et al. demonstrated that concomitant deletions of *BAP1, NF2,* and *CDKN2A* genes in mice resulted in malignant mesothelioma in all animals, and that the knockout of both *CDKN2a* and *NF2* genes yielded mesothelioma in 75% [7]. However, knockout of each of these three genes individually failed to yield malignancy. Currently, there is no evidence that neoplastic mutations capable of causing mesothelioma occur spontaneously in nature in the absence of an additional environmental stimulus, e.g. asbestos. In this regard, Yoshikawa et al. found that chromothripsis, i.e. chromosome shattering followed by random chromosomal rearrangement, may be the cause of multiple genetic alterations observed in mesotheliomas caused by asbestos [8].

Roughly, half of all cases of malignant mesothelioma show biallelic mutations in *BAP-1* (*BRACA-associated protein-1*), and 60–80% of mesothelial malignancies show biallelic deletions in the *CDKN2A* gene. *BAP-1* codes for a ubiquitin carboxy-terminal hydrolase and is a member of the deubiquitylase family of proteins. The gene maps primarily to the 3p21.3 chromosome and its encoded protein can be localized to both the nucleus and cytoplasm of mesothelial cells. *BAP-1* acts as a tumor cell

suppressor via several pathways, and its functional loss drives tumor cell proliferation [5]. Families showing characteristic autosomal *BAP-1* germline mutations show an increased incidence of a variety of malignancies, most characteristically uveal melanoma, malignant mesothelioma, and renal cell carcinoma [1]. However, there is no compelling evidence to suggest that germline mutations alone, in the absence of environmental carcinogen, can give rise spontaneously to mesothelioma.

Biallelic acquired deletions of *CDKN2A* (cyclin-dependent kinase inhibitor 2A) are associated with mesothelioma. Suppression of *CDKN2A* transcription is a common feature of a variety of tumors and is currently the most common genetic defect observed in malignant mesothelioma [9].

3. Invasion and metastasis

Malignant transformation can occur without tumor invasion and metastasis and may precede it in many cases. The steps leading to tumor invasion and spread are complex and include both genetic and epigenetic changes. The mammalian organism is divided into tissue compartments separated by extracellular matrix, i.e. basement membrane, and interstitial stroma [10]. Basal epithelial cells normally attach to basement membrane, or as in the case of mesothelial cells, directly to subjacent interstitial matrix. In normal tissues, these cell populations do not intermix.

On the "other" side of the basement membrane, the interstitial stroma includes an array of cells, including fibroblasts, myofibroblasts, and their secreted matrix. Like epithelium, nerve cells, muscle cells, and blood vessels are surrounded by a continuous extracellular matrix. During tissue remodeling, benign proliferative disorders, and carcinoma *in situ,* the cell populations on either side of this cell/matrix boundary do not intermix. But in malignant invasive tumors, a neoplastic cell, or group of cells, will penetrate the local stroma. It can then enter lymphatic or vascular circulations and subsequently migrate to distant sites, extravasate, and then proliferate as a secondary colony. Invasive tumor cells disobey the normal order of tissue/matrix boundaries and proliferate where they normally do not belong.

Tumor invasion by malignant cells is an active process [10]. Interactions of the tumor cell with basement membrane and interstitial matrix require initial attachment, the dissolution of matrix, and cellular migration. In this regard, tumor cells secrete lytic enzymes or induce the host to elaborate proteinases that degrade matrix adhesion molecules. Locomotion propels the tumor cell across the basement membrane and stroma through a zone of proteolyzed matrix. Directional movement is regulated by cell surface ligand binding and mobilization of cytoskeletal elements that interact with the cell membrane surface. Tumor cell motility is modulated by cytokines, and direction of movement is influenced by local chemoattractants.

Little is known about the specific pathways that promote tissue invasion and metastasis in malignant mesothelioma. Malignant mesothelioma cells produce collagens, and the prognosis of mesothelioma may be related to the expression of matrix metalloproteinases. Malignant mesothelioma tumors also induce immune responses from their hosts. Chronic inflammation is manifested by the presence of tumor inflammatory cells and the local release of cytokines. Mesothelioma cell growth also requires neoangiogenesis to provide nutrients to proliferating cells and supportive matrix. Growth signals and loss of tumor-suppressor genes may provide the growth advantage that leads to tumor cell proliferation.

4. Distinguishing malignant mesothelioma *in situ*

The existence of an *in situ* phase of malignant mesothelioma has long been postulated but difficult to prove. But as a consequence of tumor genetic analysis, it is now possible to identify mesothelial cells that harbor characteristic genetic mutations that are only seen in malignant cells and not seen in "atypical" but benign mesothelial proliferations. These include loss of *BAP-1* expression and *CDKN2A* (p16) deletions. The loss of *BAP-1* is most commonly present as an acquired somatic mutation (~50% of epithelioid mesotheliomas) but can occur rarely as a germ-line defect within families [11]. Distinguishing benign from malignant mesothelial cells via genetic analysis in cytology and tissue biopsy specimens currently allows distinguishing mesothelioma *in situ* from benign mesothelial proliferations. Recent studies suggest that immunostaining for MTAP (metalloadenosylphosphorylase) is a reliable substitute marker for loss of expression of *CDKN2A/p16* by FISH, and absence of MTAP expression by immunostaining in cytology and biopsy specimens strongly suggests malignant transformation [10]. In a similar vein, loss of nuclear BAP-1 protein expression by immunostaining correlates with loss of *BAP-1* gene and is a reliable marker of neoplastic transformation (see **Figure 1**).

In 2018, Churg et al. described 10 patients with mesothelioma *in situ,* which they defined as (1) a single layer of surface mesothelial cells (2) showing loss of BAP1 nuclear immunostaining, with (3) no evidence of tumor invasion by radiographic imaging for at least 1 year [12]. Nine of their cases were pleural mesotheliomas, with one peritoneal mesothelioma. Most patients were biopsied for repeated pleural effusions of uncertain etiology. In two patients, mesothelioma *in situ* was an incidental finding in lungs that had been resected for pulmonary carcinoma. *CDKN2A* showed deletions by FISH analysis in only one of eight cases. Invasive malignant mesothelioma developed in seven patients at 12 to 92 months following the diagnosis of *in situ* mesothelial neoplasia, and there was no clinical evidence of invasive mesothelioma in three patients at 12, 57, and 120 months of follow-up. The authors concluded that mesothelioma *in situ* has a high risk of becoming invasive over time, but that curable interventions might in theory be possible in such cases.

Elliott et al. [13] reported a case of malignant peritoneal mesothelioma that had apparently progressed from mesothelioma *in situ* over a 10-month period in a 24-year-old woman with advanced endometriosis. Initial surgery showed deeply infiltrative endometriosis with progestin effect. Postoperatively, the patient had intractable pelvic pain and vaginal discharge. Imaging studies were negative, but laparoscopy 10 months later revealed vesicular lesions on the omentum and pinpoint white lesions studding the small bowel, appendix, and pelvic peritoneum. A diagnosis of epithelioid mesothelioma was established based on biopsy of the omentum and was confirmed by immunohistochemical loss of BAP1 expression. Upon genetic testing, the patient was found to have a germline mutation in *BAP1.*

5. The WHO classification of mesothelioma in situ

The most recent WHO classification of thoracic malignancies includes malignant mesothelioma *in situ* as a distinct diagnostic entity. According to the new criteria "mesothelioma is clinically suspected in patients presenting with non-resolving pleural effusions in the setting of heavy asbestos exposure with or without pleural plaques

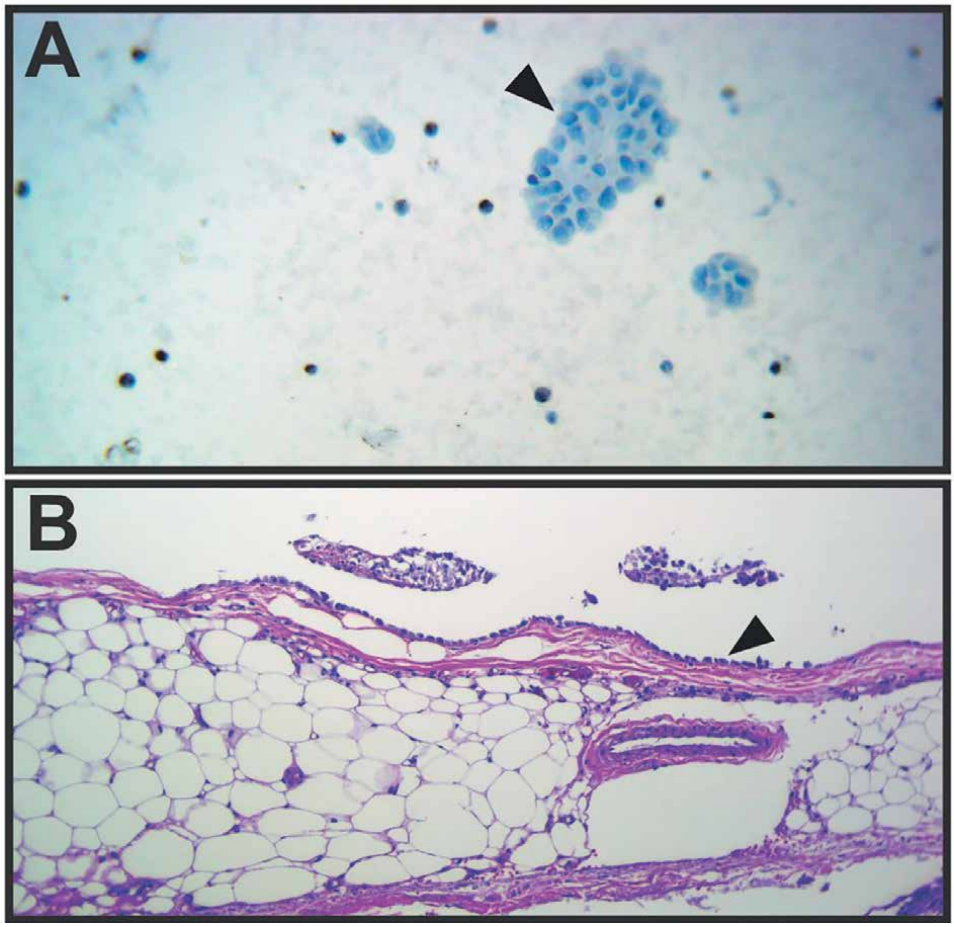

Figure 1.
A 74-year-old man presented with recurrent right pleural effusions. Cytological analysis of the fluid showed (A) clusters of atypical mesothelial cells with loss of BAP-1 nuclear expression (arrow) by immunohistochemistry consistent with malignancy. Retention of BAP-1 immunostaining (brown nuclear pigment) is seen exudate inflammatory cells. Pleurectomy/decortication revealed (B) a single layer of mesothelial cells with loss of BAP-1 expression (not shown) lining the pleural surfaces with no evidence of invasion. The patient has been clinically free of tumor for 18 months.

and in patient with familial predisposition. The diagnosis is based on a combination of clinical imaging and pathological features." It should be noted that this differs from the standard criteria for most *in situ* malignancies, which are ascertained exclusively by the absence of pathological evidence of tissue invasion. According to the WHO, the diagnosis of mesothelioma *in situ* requires "extensive" thoracoscopic sampling of tumor, and small biopsies or cytological sampling are judged insufficient to establish this diagnosis.

Although the diagnosis of mesothelioma *in situ* cannot be made by histological examination alone, any histological evidence of invasion excludes the diagnosis. Loss of *BAP-1* expression immunohistochemically (or alternatively loss of *CDKN2A* either by *FISH* or loss of MTAP expression by immunostaining must be present) as loss of these genetic markers reliably distinguish mesothelial malignancy from benign hyperplasia.

To date, only a handful of cases of malignant mesothelioma *in situ* have been reported. These have been predominantly in the pleura and in men in the seventh decade. Apparently, demographics will not distinguish *in situ* mesothelioma from invasive malignancy. Klebe et al. [14] noted that an international survey of 34 pulmonary pathologists, with an interest in malignant mesothelioma diagnosis, exhibited marked inconsistencies in establishing the diagnosis of *in situ* mesothelioma, despite the published WHO guidelines.

Serious problems apparently persist with respect to the confidence in which this diagnosis is made, as well as in with how to approach this "entity" therapeutically. It may be premature to accept mesothelioma *in situ* as a discrete entity in (1) the absence of clearly defined criteria with respect to what constitutes adequate sampling and (2) the lack of consensus as to how best to approach it therapeutically. The current WHO criteria apply to mesotheliomas of the pleura, presumably because it may be too difficult to establish this diagnosis with confidence in the larger peritoneal cavity.

Accurate sampling to exclude microscopic foci of invasion is virtually impossible to achieve in the absence of complete tumor excision with detailed pathological examination. The WHO criteria do not include validated criteria for how extensively to sample serosal surfaces, although it recognizes that limited sampling will lead to overdiagnosis of this entity.

Although having molecular markers of mesothelial malignancy is a substantial scientific advance, enthusiasm should be balanced by consideration of the clinical implications of the diagnosis of mesothelioma *in situ*. As previously noted, for most localized solid epithelial tumors, diagnosing an *in situ* carcinoma will trigger surgical excision with high cure rates. The question is whether malignant mesothelioma *in situ* is equally amenable to such an approach. Unfortunately, many patients with malignant mesothelioma, both invasive and *in situ*, are elderly with significant co-morbidities so that the extensive surgical resections necessary to extirpate all areas of *in situ* mesothelioma may be precluded. Considering the high rate of developing invasive disease within five years, the clinical value of making a diagnosis of mesothelioma *in situ* is questionable, unless the patient is a candidate for radical surgery. When curative therapeutic intervention is not possible, the diagnosis of mesothelioma *in situ* has no demonstrated clinical implication.

For this reason, it is argued that a diagnosis of mesothelioma *in situ* should be reserved for cases for whom curative excision is feasible. Only then the diagnosis can be pathologically confirmed and the potential value of the diagnosis confirmed by long-term tumor-free survival. Despite understandable enthusiasm for designating a new category of mesothelial neoplasia based primarily on genetic evidence, cases meeting the current criteria who are not surgical candidates might best be diagnosed as "malignant mesothelial neoplasia," with the expectation that their tumor will likely become frankly invasive at some future point in time in the absence of curative treatment. Patients meeting the current WHO criteria for mesothelioma *in situ* but who are not surgical candidates should be assigned to experimental chemotherapy or immunotherapy protocols to determine whether sustained responses can possibly be achieved. Unfortunately, intercurrent mortality from other causes may complicate the evaluation of this "entity."

6. Conclusion

Malignant mesothelioma is a rare and deadly malignancy. Five-year survival rates are negligible, even following surgical and chemo/immunotherapeutic interventions.

For this reason, the possibility of defining a preinvasive stage of malignant mesothelioma theoretically offers the possibility of therapeutic cure. However, the diffuse nature of the disease and the advanced age of most patients with mesothelioma *in situ* represent obstacles to accurate diagnosis and curative treatment. Patients who meet current WHO criteria for this diagnosis should be carefully selected and treated on protocols to determine whether surgery and/or chemo/immunotherapies can yield long-term survival. Identifying confirmed cases of *in situ* mesothelioma may also allow researchers to determine molecular/genetic pathways responsible for the invasive behaviors of malignant mesothelioma and potentially provide new molecular targets for therapeutic intervention.

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Conflict of interest

Dr. Kradin has testified as an expert witness in cases of mesothelioma attributed to asbestos.

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References

[1] Carbone M, Adusumilli PS, Alexander HR Jr, Baas P, Bardelli F, Bononi A, et al. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. CA: A Cancer Journal for Clinicians. 2019;**69**(5):402-429

[2] Nicholson A, Dacic S, Znaor A. Tumors of the pleura and pericardium. In: Thoracic Tumors. WHOI Classification of Tumor Series: Lyons; 2021

[3] Severson D, DeRienzo A, Bueno R. Mesothelioma in the age of "Omics": Before and after The Cancer Genome Atlas. Journal of Thoracic Cardiovascular Surgery. 2020;**160**:1078-1083

[4] Blanquart C, Jaurand M-C, Jean D. Biology of malignant mesothelioma and relevance of pre-clinical models. Frontiers in Oncology. 2020;**10**:388-399

[5] Bueno R, Stawiski E, Goldstein L, Durinck S, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nature Genetics. 2016;**48**:407-416

[6] Hmeljak J, Sanchez-Vega F, Hoadley K, Shih J, et al. Integrative Molecular Characterization of Malignant Pleural Mesothelioma. Cancer Discovery. Vol. 82018. pp. 1548-1565

[7] Badhai J, Pandey G, Song J. Combined deletion of Bap1, Nf2, and Cdkn2ab causes rapid onset of malignant mesothelioma in mice. Journal of Experimental Medicine. 2020;**217**:1-11

[8] Yoshikawa Y, Kuribayashi K, Minami T, Ohmuraya M, Kijima T. Epigenetic alterations and biomarkers for immune checkpoint inhibitors-current standards and future perspectives in malignant pleural mesothelioma treatment. Frontiers in Oncology. 2020;**10**:554-570

[9] Ilei P, Ladanyi M, Rusch V, Zakowski M. The use of CDKN2A deletion as a diagnostic marker for malignant mesothelioma in body cavity effusions. Cancer. 2003;**25**:51-56

[10] Liotta L. Tumor invasion and metastases-role of the extracellular matrix: Rhoads memorial award lecture. Cancer Research. 1986;**49**:636-649

[11] Pilarski R, Carlo MI, Cebulla C, Abdel-Rahman M. BAP1 tumor predisposition syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2022

[12] Churg A, Hwang H, Tan L, Qing, Taher A, et al. Malignant mesothelioma in situ. Histopathology. 2018;**72**:1033-1038

[13] Elliot D, Trvieso J, As-Sanie S, Hrycaj S, Lieberman R, Myers J, et al. Progression of peritoneal mesothelioma in situ to invasive mesothelioma arising in the setting of endometriosis with germline BAP1 mutation: A case report. International Journal of Gynecological Pathology. 2021;on line ahead of print

[14] Klebe S, Nakatani Y, Dobra K, Butnor K, Roden A. The concept of mesothelioma in situ, with consideration of its potential impact on cytology diagnosis. Pathology. 2021;**53**:446-453

Chapter 6

Diagnosis of Dentofacial Anomalies

Mahesh Kaggere Puttaraju, Prasanna Srinivasa Despandae and Viveka S

Abstract

It is very challenging to understand and analyse anomalies of dentofacial region. Diagnosis plays a very important role in the further treatment of any condition related to orofacial anomalies. Diagnosis includes taking complete history and required investigations and conclusion. History gives more information towards clinical path, and investigation will lay more emphasis on conclusion. Anomalies involving dentofacial region may be related to tooth, maxilla, mandible, soft tissue anomalies and syndromic conditions. Dentofacial anomalies not only involve the dentofascial region but can spread to various other vital organs, so sometimes correlating the systemic problem will be of prime importance. When the other body is involved, the varied presentation will be a challenge in diagnosis. Multiple organs should be investigated for an diagnostic conclusion. Brining diagnostic information of anomalies is the aim of the chapter. Here, we cover various clinical features, diagnostic criteria, and investigation protocols of dentofacial anomalies.

Keywords: dentofacial anomalies, tooth, syndrome, diagnosis, disturbances in structure of teeth

1. Introduction

Societal forces define norms for an acceptable physical appearance and equate to a good smile. Significant aesthetic and functional issues in both jaws are included in dental abnormalities. It has been discovered that certain syndromes and systemic disturbances are connected with changes in craniofacial form, structure or function to the point where these changes can be categorised as the essential characteristics of such illnesses. It is crucial that the clinician is aware of any dysmorphologic alterations to the orofacial structures in order to consider specific disease entities and rule out the participation of any other tissues or organ systems that might be syndromically connected. Dental appearance with success in life plays an important role. An increased concern for dental appearance has been observed during adolescence and early adulthood. One among them is malocclusion that is described as an irregularity of the teeth or a poor relationship of the dental arches beyond the range of what is accepted as normal. Malocclusion can impact quality of life causing psychosocial limitations (awkwardness in the social context or reduced career opportunities) and functional disturbances (affecting mastication, swallowing and speech; increasing susceptibility to trauma; and increasing prevalence of dental caries, periodontal disease and temporomandibular joint disorders). Even though the malocclusion is not a dentofacial anomalies, it is a part of various dentofacial anomalies.

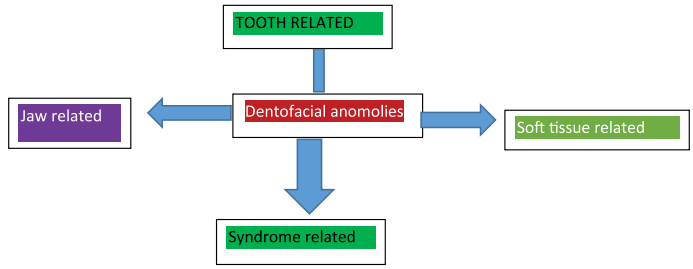

Figure 1.
Distribution of dentofacial anomalies.

For any individual defect, there may be variation in phenotype, associated anomalies and cause. To help organise these various disorders, dysmorphologists have grouped them into 'syndromes', 'sequences' and 'associations' based on our level of understanding of their aetiologies as shown in **Figure 1**.

2. Developmental anomalies of teeth

In the course of their lifetime, humans produce two sets of teeth: the primary dentition and the permanent dentition. By the age of 12, the primary dentition is fully replaced by permanent teeth that last for lifetime, as opposed to many animals, which have numerous sets of teeth that erupt depending on how and when a functional tooth is used and exfoliated.

Human teeth begin to develop during foetal development and continue growing until 10 years after birth. Teeth abnormalities develop for a number of reasons, such as poor nutrition, systemic illnesses, genetic problems, that influence a person throughout this time.

The developmental disturbances of teeth can be classified as anomalies affecting the following features:

- size
- shape
- number
- surface disturbances

2.1 Microdontia

When teeth are physically smaller than usual, the term 'microdontia' should be used. As one or more developing lobes of a tooth germ fail, resulting in microdonts, the condition can also cause aberrant form.

Both generalised and localised microdontia exist. Generalised microdontia is typically linked to a growth hormone or pituitary dysfunction-related developmental disorder. A single tooth in the arch is typically affected by localised microdontia. The maxillary lateral incisors (peg laterals) and third molars are the most commonly afflicted teeth. Usually, a size comparison between the neighbouring and opposing teeth makes the diagnosis simple.

2.2 Macrodontia

Megadontia or megalodontia are other names for macrodontia. The phrase is used when one or more teeth stand out as being larger than they should be. When present in a normal person, macrodontia causes crowding and malocclusion. However, the entire dentition may be impacted without occlusal inconsistencies in cases of growth of hormone-related gigantism [1, 2]. True-generalised macrodontia, as this condition is known, is incredibly uncommon. Relative macrodontia is a condition that is frequently observed in which the teeth may be slightly larger in size or may appear huge because of a smaller jaw size. A single tooth's macrodontia may be caused *via* fusion or gemination.

Patients with macrodontia frequently have aesthetic concerns, and the diagnosis is aided by clinically bigger teeth and malocclusion. Normal internal tooth structures are visible on radiographs**.**

3. Developmental disturbances in shape of teeth

3.1 Gemination

Gemination is an aberration that develops when a single tooth germ tries to divide by invaginating, which results in the partial creation of two teeth. The tooth typically has one or two crowns, which may be totally or partially separated, but only one root and one root canal [1].

Clinically, a single root has a bifid crown with complete segregation or minor grooving between two big crowns. The total number of teeth stays the same during gemination because only a single tooth bud can be partially split to change the number of teeth. The most often impacted teeth in both dentitions are the incisors and canines.

These are common pulp canals and either a single or partially divided pulp chamber, according to radiology, which are greater than usual crown width with a shallow groove (**Figure 2**).

3.2 Fusion

Fusion is the joining of two distinct tooth germs, which can be seen radiographically as two different pulp chambers and root canals [2]. The action of pressure or mechanical physical force that produces close contact between two erupting teeth

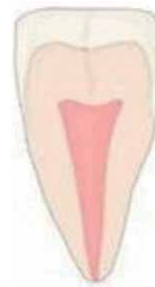

Figure 2.
Features of gemination.

Figure 3.
Courtesy: JSS Dental College, figure showing fusion of lateral incisor with supernumerary tooth.

was identified as a possible explanation, although the exact cause of fusion is still unknown. It occurs more frequently in teeth at the front. In contrast to permanent teeth, it occurs more frequently in deciduous teeth [3].

Clinical: With or without a bifid crown, the tooth is about twice as large as it should be. Root canals in a tooth may be single or combined. Fusion may happen between a normal and a supernumerary tooth or result in fewer teeth [3, 4]. The union's true character and scope will become increasingly clear (**Figure 3**).

3.3 Concrescence

Concrescence is two fully formed teeth, joined along the root surfaces by cementum. The process is noted more frequently in the posterior and maxillary regions. Lack of adequate space and crowding of teeth are the most accepted elucidated aetiology.

Diagnosis is made commonly with the help of radiographs. It is not always possible to distinguish among concrescence, teeth in close contact and superimposed teeth. Radiograph will show union of two teeth with the help of cementum.

3.4 Talon's Cusp

The talon cusp, an aberrant structure that resembles an eagle's talon, is produced by the cingulum regions of a maxillary or mandibular permanent incisor [4], commonly observed on the lateral or central maxillary incisor.

Clinical: A T-shaped elevation on the tooth makes Talon's cusp an easy diagnosis.

Radiological: Where it occurs, overlaid on the incisors, there is a coating of enamel that appears to be normal, and the outline is smooth.

3.5 Dilaceration

The term 'dilaceration' refers to an angulation, or a sharp bend or curve, in the root or crown of a formed tooth.

Clinical diagnosis is not possible.

Radiological: Curve or bending occurs anywhere along the length of tooth, sometimes at cervical portion or midway along the root or even just at the apex of root.

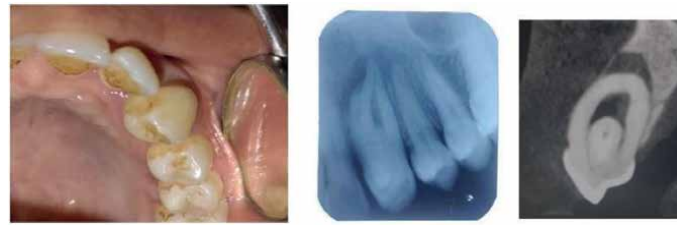

Figure 4.
Clinical and intra-oral radiographic presentation of the condition. Courtesy. JSS Dental College.

3.6 Dens in dente (dens invaginatus)

The 'dens in dente' is a developmental variant that is believed to come from an invagination in the tooth crown's surface prior to calcification. Prior to the calcification of the dental tissues, there is histologically observed deepening or invagination of the enamel organ into the dental papilla [5].

Clinical: The tooth's labial face is frequently bulbous. Conical or asymmetrical crown shapes are both possible. Dental infolding is a rare clinical occurrence. Rarely, primary teeth may be impacted.

Radiological: It can be identified as a pear-shaped invagination of enamel and dentin that has a close resemblance to the pulp in depth and a tight constriction at the aperture on the surface of the tooth. The tooth appears to be 'inverted' (**Figure 4**).

3.7 Dens evaginatus

The dens evaginatus is a developmental condition that appears clinically as an accessory cusp or a globule of enamel on the occlusal surface between the buccal and lingual cusps of premolars, unilaterally or bilaterally, although it has been reported to occur rarely on molars, cuspids and incisors.

Schulze [6] distinguished the following five types of DE for posterior teeth by the location of the tubercle.

1. A cone-like enlargement of the lingual cusp.

2. A tubercle on the inclined plane of the lingual cusp.

3. A cone-like enlargement of the buccal cusp.

4. A tubercle on the inclined plane of the buccal cusp.

5. A tubercle arising from the occlusal surface obliterating the central groove.

Clinical: It appears as a tubercle of enamel on occlusal surface of the affected tooth. Polyp-like protuberance in central groove on lingual ridge of buccal cusp is seen.

Radiological: Occlusal surface has tuberculated appearance.

3.8 Enamel pearl

Heterotopic presence of enamel in the form of a globule is called enamel pearl. It is usually found on the root surface.

Clinical: It appears as a yellowish white, spherical structure adherent to the furcation area of the root surface. The diameter ranges from 1 mm to 3 mm.

Radiological: It appears as smooth, round and well-defined radiopacity present along the root surface. Radiodensity is same as that of the enamel.

3.9 Taurodontism

It is characterised by clinical and anatomical crown of normal shape and size, an elongated body and short roots with longitudinally enlarged pulp chambers [7].

Clinical: Affected teeth tend to be rectangular and exhibit pulp chambers with a dramatically increased apico-occlusal height and a bifurcation close to the apex [7, 8].

Radiological: Pulp chamber is extremely large with much greater apico-occlusal height than normal. Extensions of rectangular pulp chamber occur into elongated body of the tooth [7]. Pulp lacks the usual constriction at the cervix of tooth. The root and root canals are exceedingly short. There is also increased dimension between cementoenamel junction and furcation.

3.10 Supernumerary roots

Teeth that are normally single-rooted exhibit two roots.

Clinical: They develop as slender outgrowths at the centre of furcation area of molar teeth.

Radiological: If the bifurcation produces two distinct apices and these are arranged as one mesial to the other, then it will be seen on the radiographs. If the two apices are on the labial and lingual side, they may get superimposed on each other appearing as a bulbous root, which may mimic hypercementosis.

4. Developmental disturbances in structure of teeth

Amelogenesis imperfect: A complex collection of diseases known as amelogenesis imperfecta shows developmental changes in the enamel's structure when no underlying systemic problem is present.

Inaccuracies in hypoplastic amelogenesis.

Pits that range in size from a pinhead to a pea are dispersed around the teeth's surface. The pits can be placed in rows or columns and are more noticeable on the buccal surfaces of the teeth.

Localised pattern: Linear depressions and horizontal rows of pits can be seen on the affected teeth. The affected region is typically found in the middle third of the buccal surfaces of the teeth. Typically, neither the incisal edge nor the occlusal surface is impacted.

All teeth have an enamel that is thin, firm, shiny, and has an autosomal dominant smooth pattern. There is lack of the proper enamel thickness.

Radiographs exhibit a thin peripheral outline of radiodense enamel. Unerupted teeth, often undergoing resorption, may be seen.

Enamel agenesis: A total lack of enamel formation. The teeth are the shape and colour of the dentin, with a yellow-brown hue, open contact points and crowns that taper towards the incisal-occlusal surface. The surface of the dentin is rough, and an anterior open bite is seen frequently.

Radiographs demonstrate no peripheral enamel overlying the dentin.

4.1 Hypomaturation amelogenesis imperfecta

Pigmented pattern: The surface enamel is mottled and agar brown. The enamel often fractures from the underlying dentin and is soft enough to be punctured by a dental explorer.

X-linked pattern: The deciduous teeth are opaque white with a translucent mottling; the permanent teeth are opaque yellow-white and may darken with age. Focal areas of brown discoloration may develop within the white opaque enamel [9].

Snow-capped patterns: A zone of white opaque enamel on the incisal or occlusal one quarter to one-third of the crown.

4.2 Hypocalcified amelogenesis imperfecta

On radiographs, the teeth show a thin radiopaque enamel outline around the periphery. Unruptured teeth showing signs of resorption are common.

Both dentitions have diffuse thin, smooth and glossy enamel in an X-linked pattern. Open contact points and crown preparation shapes are common in teeth. Brown to golden brown is the range of colour.

An outline of radiopaque enamel can be seen on radiographs.

Rough surface: The enamel is thin and firm and has a rough pattern. Similar to the smooth forms, the teeth have open contact sites and taper towards the incisal-occlusal surface. From white to bright white, the colour varies.

Clinical: On eruption, the enamel is yellow-brown or orange, but it often becomes stained brown to black and exhibits rapid calculus apposition.

A thin radiopaque enamel outline around the teeth's periphery can be seen on radiographs. Unruptured teeth that are showing resorption are common.

Thin, shiny, smooth enamel is diffused in both dentitions with an X-linked pattern. There are exposed contact sites and the teeth frequently resemble crown preparations. Brown to yellow-brown are the different shades.

Enamel that is radiopaque can be seen around the edges on radiographs.

The enamel has a rough surface and is thin and firm. The teeth display open contact points and taper towards the incisal-occlusal surface just like in the smooth forms. White to yellow-white can be seen throughout the spectrum.

Radiological: the density of the enamel and dentin are similar. Before eruption the teeth are normal in shape; however, after a period of function much of the cuspal enamel is lost, with the occlusal surface becoming the most irregular (**Figure 5**) [10].

4.3 Dentinogenesis imperfecta

Both deciduous and permanent teeth are affected by the autosomal dominant syndrome known as dentinegenesis imperfecta [11, 12].

Clinical: Affected teeth have large crowns, grey to yellowish brown colour, and constricted cervical areas give them a 'tulip' form.

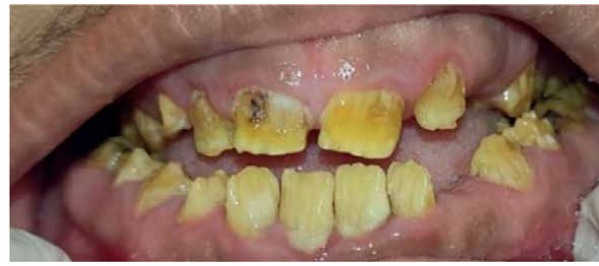

Figure 5.
Courtesy: JSS Dental College, clinical picture of amelogenesis imperfecta.

Radiologically, the teeth appear to be solid and devoid of root canals and pulp chambers. Because enamel is easily fractured, exposed dentin has rapid attrition. The teeth feature narrow roots, bulbous crowns, cervical constriction, and early pulp chamber and root canal obliteration.

Dentition with enamel that is normal in thickness, dentin that is incredibly thin and pulps that are noticeably enlarged is dentin dysplasia.

It is a rare disturbance of dentin formation, characterised by normal but atypical dentin formation, with abnormal pulp morphology.

Clinical:

Type I (radicular). Both dentitions are affected, although the teeth appear clinically normal in morphologic appearance and colour. Occasionally, there may be a slight amber translucency. However, the teeth characteristically exhibit extreme mobility and are commonly exfoliated prematurely or after only minor trauma as a result of their abnormally short roots.

Type II (coronal): The deciduous teeth have the same yellow, brown or bluish-grey opalescent appearance as seen in dentinogenesis imperfect [12].

Radiological:

Type I (radicular): In both dentitions, the roots are short, blunt, conical or similarly malformed. In the deciduous teeth, the pulp chambers and root canals are usually completely obliterated, while in the permanent dentition, a crescent-shaped pulpal remnant may still be seen in the pulp chamber.

Type II (coronal): Bulbous crowns, cervical constriction, thin roots, and early obliteration of the pulp. The permanent teeth demonstrate normal clinical coloration; however, radiographically, the pulp chambers exhibit significant enlargement and apical extension. This altered pulpal anatomy has been described as thistle tube shaped or flame shaped (**Figure 6**).

4.4 Regional odontodysplasia

Regional odontodysplasia is a specific, non-hereditary anomaly of tooth development that has severe negative effects on the growth of enamel, dentin and pulp [13].

Clinical

Asymmetrical in shape appears yellow to brownish and is often tiny. They either indicate a delay in eruption or a complete failure [12.14]. They have a noticeably different shape, are typically quite uneven in appearance and frequently show signs of poor mineralisation.

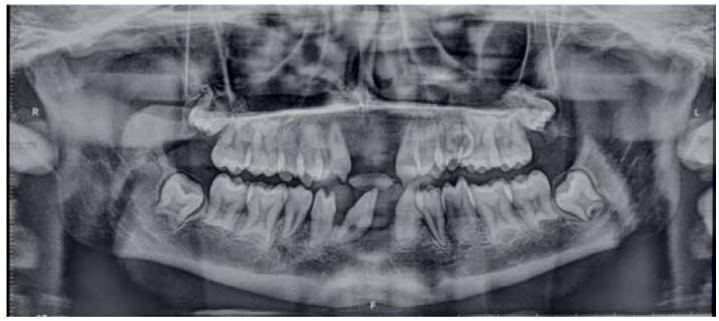

Figure 6.
Courtesy: JSS Dental College. Radiograph showing malformed tooth with short roots in Type I dentin dysplasia.

Radiological

The nickname 'ghost teeth' refers to the changed teeth's light, wispy appearance caused by the presence of radiolucent pulp surrounded by extremely thin enamel and dentin. There is little contrast between the dentin and the enamel, and the coronal silhouette is blurry or unclear. There may be visible short roots and open apices. The thickened pulps frequently show one [14].

5. CT image of cleft palate, courtesy JSS Medical College, Mysore

5.1 Soft tissue anomalies

5.1.1 Cleft lip and palate

Birth deformities such as cleft lip and palate can cause a person to have a number of orofacial malformations. One of the most prevalent birth defects, orofacial clefts can occur alone or in combination with other congenital malformations. Both syndromic and non-syndromic clefts with accompanying abnormalities make up a sizable portion of these clefts [15, 16].

Openings or cracks in the upper lip, the palate or both are known as cleft lip and cleft palate, respectively. When a developing baby's facial tissues do not fully seal, it can lead to cleft lip and cleft palate. The most prevalent birth malformations are cleft lip and cleft palate. Although they most frequently manifest as solitary birth abnormalities, they are also linked to a variety of inherited genetic diseases or syndromes (**Figure 7**).

Diagnostic features:

Typically, a split (cleft) in the lip or palate is obvious from birth. Cleft lip and palate can manifest as follows:

a facial split that affects one or both sides of the lip and palate (roof of the mouth).

a break in the lip that is only visible as a tiny notch or that extends through the upper gum and palate and into the base of the nose. A crack in the roof of the mouth that has no impact on how the face looks. Less frequently, a cleft only affects the soft palate muscles in the rear of the mouth, where the lining of the mouth covers them (submucous cleft palate). This kind of cleft is common [16].

Figure 7.
Baby with cleft lip and palate deformity, showing corrected cleft palate and lip (photos courtesy JSS Dental College, cleft centre).

Signs and symptoms of submucous cleft palate may include the following:

1. Difficulty with feedings.

2. Difficulty swallowing, with potential for liquids or foods to come out the nose.

3. Nasal-speaking voice.

4. Chronic ear infections Diagnosis.

Most cases of cleft lip and cleft palate are noticed right away at birth and do not require special tests for diagnosis. Increasingly, cleft lip and cleft palate are seen on ultrasound before the baby is born (**Figures 8** and **9**).

Ultrasound before birth

During a prenatal ultrasound, sound waves are used to produce images of the growing foetus. A doctor may notice a variation in the face structures after reviewing the images.

Beginning about the 13th week of pregnancy, ultrasonography can identify cleft lip. Accurately diagnosing a cleft lip may get simpler as the foetus continues to

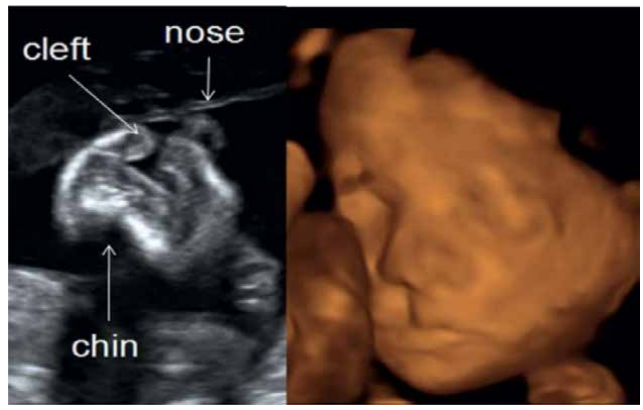

Figure 8.
OPG showing the bony defect in the upper anterior with irregularly arrenged to tooth. Courtesy JSS Dental College, Mysore.

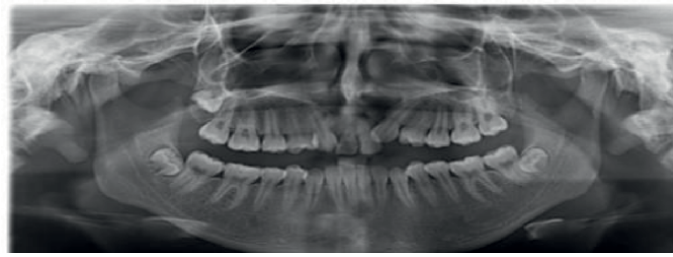

Figure 9.
CT image of cleft palate, courtesy JSS Medical College, Mysore.

develop. When a cleft palate develops on its own, ultrasonography imaging is more challenging (**Figure 10**).

Your doctor might suggest a treatment to remove a sample of amniotic fluid from your uterus if a prenatal ultrasound reveals a cleft (amniocentesis). The fluid test could reveal a genetic condition that could lead to other birth abnormalities in the foetus. But the most common reason for cleft lip and cleft palate is shown **Table 1**.

5.2 Syndromes

5.2.1 Downs syndrome

A second whole or partial copy of chromosome 21 is produced as a result of faulty cell division, which results in the genetic condition known as Downs syndrome. Downs syndrome's physical characteristics and developmental abnormalities are brought on by this excess genetic material.

Individuals with Downs syndrome may have varying degrees of intellectual disability and developmental delays. It is the most prevalent genetic chromosomal defect and the root of children's learning problems. It frequently results in other medical

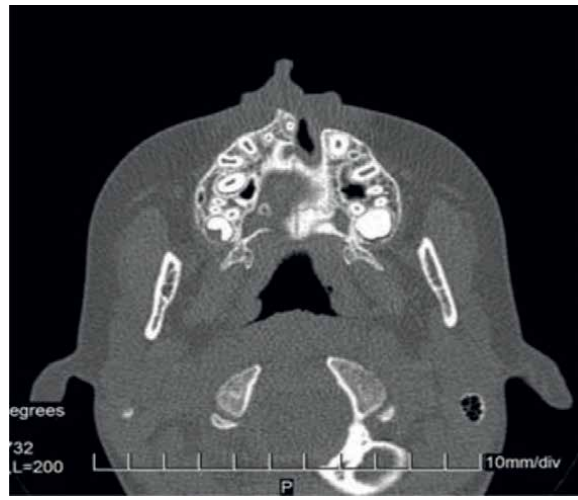

Figure 10.
Fetoscopic image of cleft lip—courtesy: JSS MEDICAL COLLEGE, MYSORE.

Associated syndromes with cleft lip and palate
Autosomal dominant syndromes
Apert
Cleidocranial dysostosis
Hay-Wells
Treacher Collins
Vander Woude
Oculodentodigital
Autosomal recessive syndromes
Cerebro-costo-mandibular
Dubowitz
Mohr
Robert
X-linked inheritance
Oro-facial-digital
Oto-palato-digital
Chromosomal disorders
Mutation in 3p arm, 5p arm, 9p arm and 18q arm
Trisomy 4p, 9p
Trisomy 13
Trisomy 18

Table 1.
Syndrome associated with cleft lip and palate.

issues as well, such as cardiac and gastrointestinal problems. With Downs syndrome, both children and adults have distinctive face features (**Figure 11**) [17].

Though not all people with Downs syndrome have the same features, some of the more common features include the following:

Flattened face
Small head
Short neck
Protruding tongue
Upward slanting eye lids (palpebral fissures)
Unusually shaped or small ears
Poor muscle tone
Broad, short hands with a single crease in the palm
Relatively short fingers and small hands and feet
Excessive flexibility
Tiny white spots on the coloured part (iris) of the eye called Brushfield's spots.
Short height

This extra genetic material is responsible for the characteristic features and developmental problems of Downs syndrome. Any one of three genetic variations can cause Downs syndrome:

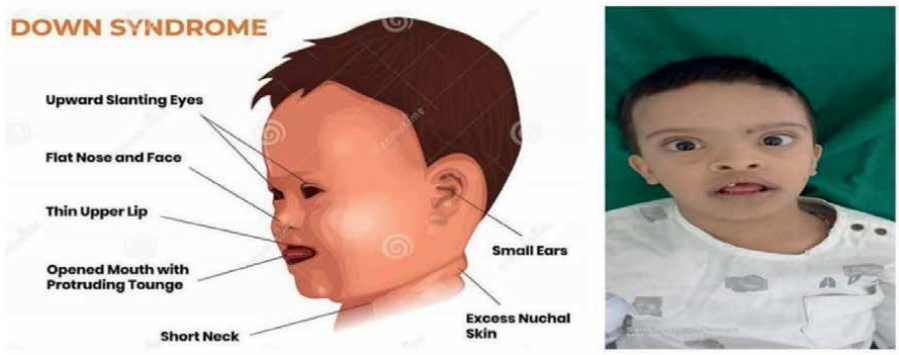

Figure 11.
Salient features of Downs syndrome.

Trisomy 21. About 95 percent of the time, Downs syndrome is caused by trisomy 21—the person has three copies of chromosome 21, instead of the usual two copies, in all cells [18]. This is caused by abnormal cell division during the development of the sperm cell or the egg cell.

Mosaic Downs syndrome. In this rare form of Downs syndrome, a person has only some cells with an extra copy of chromosome 21. This mosaic of normal and abnormal cells is caused by abnormal cell division after fertilisation.

Screening tests during pregnancy

Screening for Downs syndrome is offered as a routine part of prenatal care. Although screening tests can only identify your risk of carrying a baby with Downs syndrome, they can help you make decisions about more-specific diagnostic tests.

Screening tests include the first trimester combined test and the integrated screening test.

The first trimester combined test, which is done in two steps, includes the following:

Blood test. This blood test measures the levels of pregnancy-associated plasma protein-A (PAPP-A) and the pregnancy hormone known as human chorionic gonadotropin (HCG). Abnormal levels of PAPP-A and HCG may indicate a problem with the baby [19].

Nuchal translucency test. During this test, an ultrasound is used to measure a specific area on the back of your baby's neck. This is known as a nuchal translucency screening test. When abnormalities are present, more fluid than usual tends to collect in this neck tissue.

Using your age and the results of the blood test and the ultrasound, your doctor or genetic counsellor can estimate your risk of having a baby with Downs syndrome.

Integrated screening test

During the first and second trimesters of pregnancy, the integrated screening test is administered in two parts. To calculate the likelihood that your child has Downs syndrome, the findings are pooled.

Initial trimester. An ultrasound is used in part one to measure nuchal translucency and a blood test to measure PAPP-A.

First trimester. Alpha fetoprotein, estriol, HCG, and inhibin A are the four pregnancy-related chemicals that are measured by the quad screen in your blood.

Pregnant women's diagnostic procedures

Consider additional testing to confirm the diagnosis if your screening test results are positive or concerning, or if you have a high risk of having a baby with Downs syndrome. You can balance the benefits and drawbacks of these tests with the aid of your healthcare provider.

Diagnostic tests that can identify Downs syndrome include the following:

Sample chorionic villus (CVS). Cells from the placenta are utilised in CVS to examine the foetal chromosomes. Between 10 and 13 weeks of pregnancy, the first trimester is the traditional time for this test to be carried out. A CVS carries a very minimal chance of pregnancy loss (miscarriage).

Amniocentesis. A needle is introduced into the mother's uterus to remove a sample of the amniotic fluid around the foetus. The chromosomes of the foetus are then examined using this sample. After 15 weeks of pregnancy, doctors typically administer this test in the second trimester. A very small risk of miscarriage is also associated with this test.

For couples undergoing *in vitro* fertilisation who are at heightened risk of passing along specific genetic traits, preimplantation genetic diagnosis is a possibility.

Diagnostic tests for newborns

Initial Downs syndrome diagnoses are frequently made based on a baby's looks after delivery. However, babies without Downs syndrome can also have the characteristics linked with the condition, so your doctor will likely request a test called a chromosomal karyotype to confirm the diagnosis. This test examines your child's chromosomes using a blood sample. Downs syndrome is the result of an extra copy of chromosome 21 in all or some cells.

Translocating the Downs syndrome. Additionally, Downs syndrome can develop before or during conception if a piece of chromosome 21 translocates (attaches to another chromosome). These kids have two copies of chromosome 21 as usual, but they also contain additional chromosome 21 genetic material linked to another chromosome.

5.3 Crouzon Syndrome

Synonyms include the following:
craniofacial dysostosis,
craniostenosis, Crouzon type,
Crouzon craniofacial dysostosis.

Crouzon syndrome is a rare genetic disorder. It is a form of craniosynostosis, a condition in which there is premature fusion of the fibrous joints (sutures) between certain bones of the skull. Symptoms primarily include abnormalities of the face and head [20].

Signs and symptoms

The primary features of Crouzon syndrome, also known as craniofacial dysostosis, are pronounced facial deformities and premature closure of the fibrous joints (cranial sutures) connecting some of the skull's bones. Malformations of the cranium and face can range from minor to potentially severe, even in members of the same family who are typically unaffected [21]. Crouzon syndrome is inherited autosomally dominantly and is brought on by changes (mutations) in one of the FGFR genes, typically FGFR2.

The bony cavities of the skull that house the eyeballs or the orbits in the majority of people are unusually shallow. The consequence is a protrusion or bulge forward of the eyeballs, known as proptosis [22]. About 30% of those with Crouzon syndrome go on to develop hydrocephalus, a disorder marked by reduced flow.

Diagnosis

Based on a thorough clinical evaluation, the recognition of recognisable physical characteristics and a battery of specialised testing, Crouzon syndrome is typically diagnosed at birth or during infancy. Advanced imaging methods, such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning, may be used during such testing.

Clinical evaluation and testing

MRIs and CT scans are utilised to identify or detect some abnormalities that may be connected to the illness (e.g. craniosynostosis, other skeletal abnormalities). X-rays and a computer are used in CT scanning to produce a film that shows cross-sectional images of inside structures. A magnetic field and radio waves are used in MRI to produce finely detailed cross-sectional images of certain organs and tissues.

A Crouzon syndrome diagnosis can be confirmed by molecular genetic testing (**Figures 12** and **13**).

5.4 Foetal alcohol syndrome

This is the most severe foetal alcohol spectrum disorder. These are a group of birth defects that can happen when a pregnant woman drinks alcohol (**Figure 14**). Other foetal alcohol syndrome disorders (FASDs) include the following [22, 23]:

partial foetal alcohol syndrome,
alcohol-related birth defects,
alcohol-related neurodevelopment disorder,
neurobehavioural disorder associated with prenatal alcohol exposure.

They can include the following:

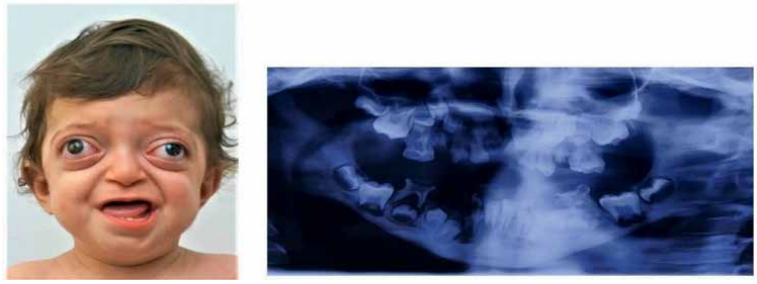

Figure 12.
Salient features of Crouzon syndrome and panoramic image to show bone density and affected teeth.

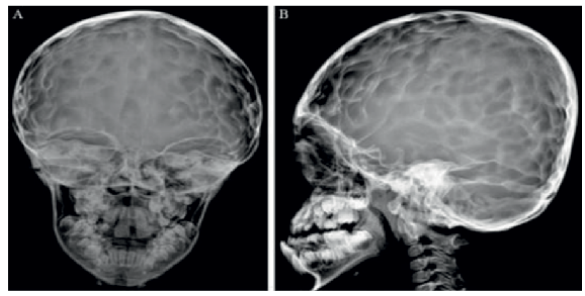

Figure 13.
Skull radiograph A, anterior-posterior and B, lateral views showing prominent convolutional markings appearing as a copper beaten skull. Courtesy: JSS Medical College, Mysore.

Figure 14.
Salient featues of foetal alcohol syndrome.

problems with the heart, kidney and bones,
learning disabilities and low IQ,
trouble with memory, coordination and attention,
hyperactivity.

Problems with sleep and suckling as an infant. Foetal alcohol syndrome can have many symptoms, including the following:

Physical defects:
small head and brain size,
vision or hearing problems,
joint, limb and finger deformities,
distinctive facial features such as small eyes, thin upper lip and a ridge between the nose and upper lip.

Neurological problems:
learning problems,
coordination and balance problems,
trouble reasoning,
hyperactivity,
moodiness.

Behavioural issues:
poor social skills,
difficulty in school,
poor impulse control.

5.5 Goldenhar syndrome (GS)

Oculoauriculovertebral dysplasia, also referred to as hemifacial microsomia, manifests clinically in a variety of ways, including abnormalities of the craniofacial, vertebral, cardiac, renal, and central nervous systems1. Epibulbar dermoids, microtia, mandibular hypoplasia, and spinal abnormalities are among the symptoms of GS that are frequently present. Hemifacial microsomia, the term used to characterise the typical facial feature of GS patients, as well as the other anomalies associated with this disease, are most likely the result of first and second brachial

arch development problems. These developmental abnormalities appear to have a variety of causes [24, 25].

However, the absence of evident features or the unknowledge of GS characteristics makes the diagnosis difficult and late. The classical features of GS patients involve ocular anomalies, including microphthalmia, anophthalmia, epibulbar dermoid (or lipodermoid) tumours, and eyelid colobomas, aural defects, such as preauricular tags, anotia, microtia and hearing loss, vertebral abnormalities, such as scoliosis, hemivertebrae and cervical fusion, and mandibular hypoplasia 8–12. Facial involvement is usually unilateral, resulting in a marked asymmetry. In the series presented here, the patients were affected unilaterally, and all showed mandibular hypoplasia and vertebral anomaly [26].

Syndromes derived from aberrations in the development of the first and second branchial arches are in the spectrum of GS, including Treacher-Collins syndrome (TCS). The presence of facial asymmetry and far less hypoplasia of the malar bones in GS are the important features to differentiate it from TCS. The TCS-affected patients presented downward slating palpebral fissures, colobomas, zygomatic and mandibular hypoplasia, partial absence of the lower eyelid cilia, and abnormalities of the ears (**Figure 15**).

5.6 Van der Woude syndrome

The disease has an impact on how the face develops. A cleft lip, a cleft palate (an opening in the roof of the mouth) or both are common birth defects in those who have this condition. Affected people frequently have depressions (pits) close to the centre of the lower lip, which may appear moist since salivary and mucous glands are

Figure 15.
Skeletal and facial phenotypes of patient #2 of this study. (A) Anterior standing photograph of the patient, demonstrating severe lordoscoliosis. (B) Frontal view of the face showing marked facial asymmetry, malocclusion and eye involvement characterised by microphthalmia and eyelid coloboma of the left eye. (C) Lateral view of the face showing ear malformations, including microtia and preauricular tags (the parents signed informed consent authorising the publication of these pictures).

located there. Also possible are little tissue lumps on the lower lip. Van der Woude syndrome patients can have tooth loss [27].

Like other people with these facial disorders, those who have cleft lip and/or palate also have a greater risk of delayed language development, learning impairments or other modest cognitive issues [28]. The average IQ of individuals with van der Woude syndrome is not significantly different from that of the general population.

5.7 van der Woude syndrome (VWS)

Lip pits* in combination with wiIRF6-related illnesses often fall on a spectrum, ranging from popliteal pterygium syndrome (PPS) at the more severe end to isolated cleft lip and palate and Van der Woude syndrome (VWS) at the moderate end. Rarely, IRF6 pathogenic mutations have also been identified in people with spina bifida (2/192) and nonsyndromic orofacial clefts (18/3811; 0.47 percent). People who have VWS exhibit one or more of the oddities listed below: congenital paramedian lower-lip fistulae (pits), which are typically bilateral, or occasionally tiny mounds with a sinus tract emerging from a mucous gland of the lip, uneven lip (CL) and missing palate (CP). It should be noted that cleft lip with or without cleft palate (CLP) is seen almost twice as frequently as CP alone. Submucous palate cleft (SMCP) has one of the following:

cleft lip with or without cleft palate (CL ± P)
cleft palate (CP)
submucous cleft palate (SMCP)
lip pits* alone and a first-degree relative with CL ± P, CP, or SMCP
CL ± P, CP or SMCP and a first-degree relative with lip pits*
CL or CL + P and CP in the same family
* Lip pits are most often paramedian on the lower lip and can include mounds with a sinus tract leading from a mucous gland of the lip.

5.8 Popliteal pterygium syndrome (PPS)

This syndrome includes the following condition:
popliteal pterygia,
syndactyly,
abnormal external genitalia,
ankyloblepharon,
pyramidal skin on the hallux,
a spectrum of intraoral adhesions, the most severe of which is complete syngnathia.

Musculoskeletal anomalies are rarely reported (e.g. talipes equinovarus, digital reduction, spina bifida occulta, bifid ribs, short sternum).

IRF6-related neural tube defect. Two individuals with an IRF6 pathogenic variant and spina bifida have been reported. Neural tube defects due to an IRF6 pathogenic variant cannot be clinically distinguished from the neural tube defects of other aetiologies. Orofacial cleft was brought on by IRF6. There have been reports of 18 people who had either an orofacial cleft or an IRF6 pathogenic mutation. Clinically, orofacial clefts caused by IRF6 pathogenic variants cannot be discriminated from those caused by other causes.

A proband is diagnosed with an IRF6-related illness based on suggestive evidence, and molecular genetic testing identifies a heterozygous pathogenic mutation in IRF6 [28].

A word is frequently used in clinical genetics to refer to the various methods utilised to pinpoint the molecular causes of genetic illness. Examples of molecular genetic tests include genotyping to identify particular pathogenic variants, gene sequencing to identify pathogenic variations, and amplification or hybridisation techniques to identify copy number variants affecting one or more genes (e.g. qPCR, array CGH, MLPA). Epigenetic alterations are detected using methylation-specific methods.

5.9 Apert syndrome

A hereditary condition known as Apert syndrome is characterised by skeletal deformities. The premature closing of the skull's bones is a major aspect of Apert syndrome (craniosynostosis). Early fusion alters the contour of the head and face and stops the skull from developing normally. The number of fingers and toes that are fused together (syndactyly) varies as well [20].

Many of the distinctive facial characteristics of Apert syndrome are caused by craniosynostosis. Midface hypoplasia, a beaked nose, a wrinkled forehead and a hole in the roof of the mouth are all results of premature skull bone fusion, which prevents the head from growing normally (a cleft palate). Dental problems can result from an underdeveloped upper jaw in people with Apert syndrome.

Many people with Apert syndrome experience vision issues as a result of eye abnormalities, which can include bulging eyes (exophthalmos), wide-set eyes (hypertelorism), outward-facing eyes (downslanting palpebral fissures), eyes that do not look in the same direction (strabismus) and shallow eye sockets (ocular proptosis). Apert syndrome patients with deformed ear structures may experience hearing loss or recurrent ear infections.

People with Apert syndrome who have abnormal facial and cranial structure may also experience breathing issues due to partial airway obstruction. The brain's development is also impacted by craniosynostosis, which may impair intellectual growth. Cognitive abilities range from normal to mild-to-moderate intellectual disability in those with Apert syndrome [29].

Apert syndrome patients exhibit syndactyly of the fingers and toes. Although the severity of the fusion varies, the hands are typically worse off than the feet. Three fingers on each hand and foot are most frequently fused together. The fingers and toes are merged in the most extreme cases. Apert syndrome patients very rarely have extra fingers or toes (polydactyly). Some Apert syndrome sufferers have anomalies in their shoulder or elbow bones. These bone issues might make it difficult to walk around and interfere with daily tasks. While some persons only experience anomalies on one side of the body, others experience abnormalities on both sides.

Hyperhidrosis, oily skin and additional signs and symptoms of Apert syndrome can be present (**Figure 16**).

5.10 Orofacial digital syndrome

The oral-facial-digital syndrome has been linked to the OFD1 gene. Oral-facial-digital syndrome type I is caused by mutations in this gene. Affected family members with a type VII condition were also found to have mutations in the OFD1 gene; nevertheless, experts currently think that type VII and type I disorders are identical [30].

The development of the oral cavity (the mouth and teeth), facial features and digits are all impacted by the oral-facial-digital syndrome, a collection of connected diseases (fingers and toes).

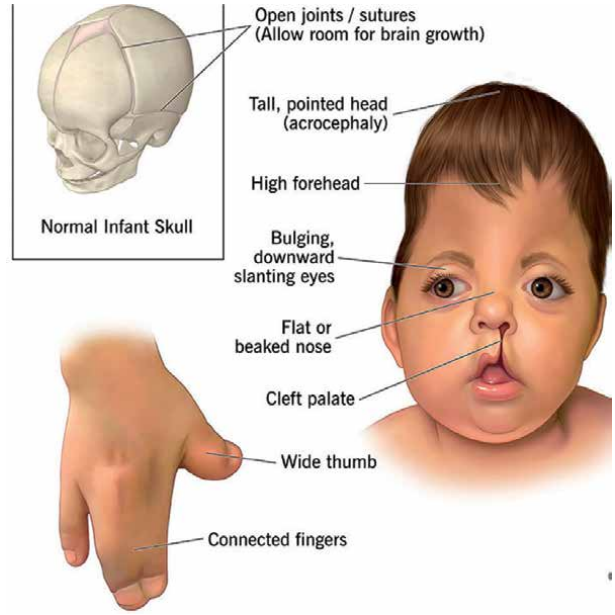

Figure 16.
Salient features of Apert syndrome.

There are at least 13 different possible types of oral-facial-digital syndrome, according to researchers. By their patterns of symptoms and indications, the various categories are categorised. However, there are a lot of overlaps in the characteristics of the different categories, and some types are not clearly defined. The signs and symptoms of oral-facial-digital syndrome vary widely. However, most forms of this disorder involve problems with the development of the oral cavity, facial features and digits [31]. Most forms are also associated with brain abnormalities and some degree of intellectual disability.

A split (cleft) in the tongue, a tongue with an odd-lobed form and the development of noncancerous tumours or nodules on the tongue are among the abnormalities of the oral cavity that occurs in many types of oral-facial-digital syndrome. Additionally, those who are affected might have additional, missing or broken teeth. An aperture in the roof of the mouth is another typical characteristic (a cleft palate). The lip may be abnormally attached to the gums in certain persons with oral-facial-digital syndrome due to bands of excess tissue known as hyperplastic frenula.

Cleft lips, large noses with flat nasal bridges and widely separated eyes are distinctive facial characteristics that are frequently linked to oral-facial-digital syndrome (hypertelorism).

Abnormalities of the digits can affect both the fingers and the toes in people with oral-facial-digital syndrome. These abnormalities include fusion of certain fingers or toes (syndactyly), digits that are shorter than usual (brachydactyly) or digits that are unusually curved (clinodactyly). The presence of extra digits (polydactyly) is also seen in most forms of oral-facial-digital syndrome [31].

Other features occur in only one or a few types of oral-facial digital syndrome. These features help distinguish the different forms of the disorder. For example, the most common form of oral-facial-digital syndrome, type I, is associated with polycystic kidney disease. This kidney disease is characterised by the growth of fluid-filled sacs (cysts) that interfere with the kidneys' ability to filter waste products from the

blood. Other forms of oral-facial-digital syndrome are characterised by neurological problems, particular changes in the structure of the brain, bone abnormalities, vision loss and heart defects.

5.11 Treacher Collins syndrome

SYNONYMUS.
Franceschetti-Zwalen-Klein syndrome.
mandibulofacial dysostosis.
Treacher Collins-Franceschetti syndrome.

Treacher Collins syndrome (TCS), a rare genetic condition, is distinguished by recognisable deformities of the head and face. The zygomatic complex, cheekbones, jaws, palate and mouth are typically underdeveloped in cranial anomalies, which can cause breathing and feeding issues [32]

TCS is mainly brought on by modifications (mutations) in the TCOF1 gene, but it is also linked to changes in the POLR1B, POLR1C or POLR1D genes. While autosomal dominant inheritance is the situation for TCOF1 and POLR1B, autosomal recessive inheritance is the case for POLR1C. On the other hand, POLR1D mutations that are both autosomal dominant and recessive have been linked to TCS. The major characteristic features of TCS encompass certain bones of the face, ears and soft tissues around the eyes. Affected individuals present with distinctive facial features and potentially develop hearing and vision problems. The abnormalities of TCS are typically symmetric (almost identical on both sides of the face) and are present at birth (congenital). Speech and language development can be compromised by hearing loss, cleft palate or jaw and airway problems.

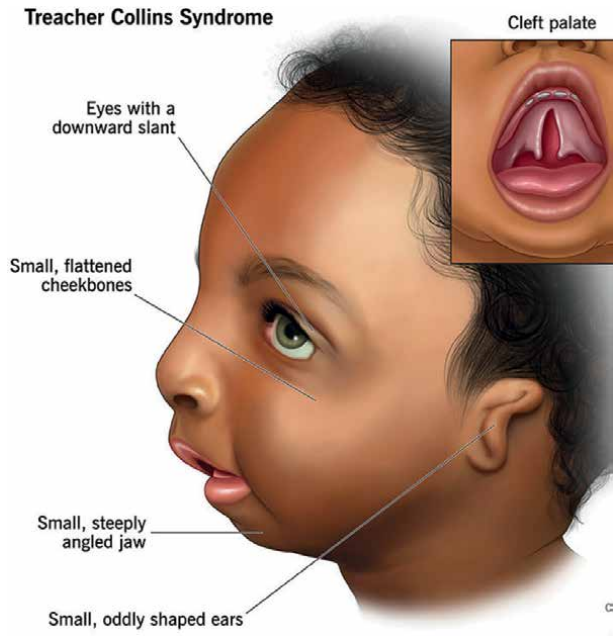

Figure 17.
Salient features of Treacher Collins syndrome.

In children with TCS, the cheekbones are hypoplastic or missing, giving the area of the face a sunken or flat appearance. Due to inadequate development of the lower jaw's (mandible) bone (mandibular hypoplasia), the chin and lower jaw appear abnormally tiny (micrognathia). Obstructive sleep apnoea, which is characterised by frequent, brief pauses in breathing and air movement while sleeping, can affect children. Additionally, dental anomalies such as undeveloped (hypoplastic) or misplaced teeth may result from mouth and jaw deformities (malocclusion). There have also been reports of other dental anomalies, such as tooth agenesis (the absence of teeth), enamel opacity (the clouding or darkening of teeth's enamel) and inappropriate (ectopic) eruption of some upper teeth (maxillary molars) (**Figure 17**) [32, 33].

6. Conclusion

Anomalies of head and neck may arise sporadically or with a strong hereditary predilection. Isolated single anomalies may at times go undiagnosed unless they cause considerable aesthetic and functional concerns. Syndromes usually present more pronounced anomalies; however, treatment to such conditions remain questionable. Systemic involvement may further complicate the management in such cases.

Anomalies that affect dento-facial region are numerous. A thorough knowledge of these anomalies is of great importance to a clinician. Also, a vast amount of cultural, social and personal beliefs regarding the aetiology of such facial deformities and the affected person poses great challenge in providing treatment to such cases.

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References

[1] Mohan RP, Verma S, Singh U, Agarwal N. Gemination. BMJ Case Reports. 2013;**2013**:bcr2013010277. DOI: 10.1136/bcr-2013-010277

[2] Chetty M, Beshtawi K, Roomaney I, Kabbashi S. MACRODONTIA: A brief overview and a case report of KBG syndrome. Radiology Case Reports. 2021;**16**(6):1305-1310. DOI: 10.1016/j.radcr.2021.02.068

[3] Nunes E, de Moraes IG, de Novaes PMO, et al. Bilateral fusion of mandibular second molars with supernumerary teeth: Case report. Brazilian Dental Journal. 2002;**13**(2):137-141

[4] Guttal KS, Naikmasur VG, Bhargava P, et al. Frequency of developmental dental anomalies in the Indian population. European Journal of Dentistry. 2010;**4**(3):263-269

[5] Alani A, Bishop K, Dens invaginatus. Part 1: Classification, prevalence and aetiology. International Endodontic Journal. 2008;**41**(12):1123-1136. DOI: 10.1111/j.1365-2591.2008.01468.x

[6] Schulze CH. Anomalien und Missbildungen der menschlichen Zähne. Berlin: Quintessenz Verlags GmbH;1987. pp. 94-101

[7] Mohan RP, Verma S, Agarwal N, Singh U. Taurodontism. BMJ Case Reports. 2013;**2013**:bcr2012008490. DOI: 10.1136/bcr-2012-008490

[8] Chetty M, Roomaney IA, Beighton P. Taurodontism in dental genetics. BDJ Open. 2021;7(1):25. DOI: 10.1038/s41405-021-00081-6

[9] Smith CEL, Poulter JA, Antanaviciute A, Kirkham J, Brookes SJ, Inglehearn CF, et al. Amelogenesis imperfecta; genes, proteins, and pathways. Frontiers in Physiology. 2017;**8**:435. DOI: 10.3389/fphys.2017.00435

[10] Crawford PJ, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. Orphanet Journal of Rare Diseases. 2007;(2):17. DOI: 10.1186/1750-1172-2-17

[11] Barron MJ, McDonnell ST, Mackie I, Dixon MJ. Hereditary dentine disorders: Dentinogenesis imperfecta and dentine dysplasia. Orphanet Journal of Rare Diseases. 2008;**20**(3):31. DOI: 10.1186/1750-1172-3-31

[12] Lewis DM. Dentinogenesis imperfecta. J Okla Dent Assoc. 2007;**98**(8):24-27

[13] Nijakowski K, Woś P, Surdacka A. Regional odontodysplasia: A systematic review of case reports. International Journal of Environmental Research and Public Health. 2022;**19**(3):1683. DOI: 10.3390/ijerph19031683

[14] Alotaibi O, Alotaibi G, Alfawaz N. Regional odontodysplasia: An analysis of 161 cases from 1953 to 2017. The Saudi Dental Journal. 2019;**31**(3):306-310. DOI: 10.1016/j.sdentj.2019.04.012

[15] Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, et al. National population-based estimates for major birth defects, 2010-2014. Birth Defects Research. 2019;**111**(18):1420-1435

[16] Smarius B, Loozen C, Manten W, Bekker M, Pistorius L, Breugem C. Accurate diagnosis of prenatal cleft lip/palate by understanding the embryology. World Journal of Methodology. 2017;7(3):93-100

[17] Akhtar F, Syed Rizwan A. Bokhari-Down Syndrome. Treasure Island (FL): StatPearls Publishing; 2022

[18] Asim A, Kumar A, Muthuswamy S, Jain S, Agarwal S. Down syndrome: An insight of the disease. Journal of Biomedical Science. 2015;**22**:41

[19] Karmiloff-Smith A, Al-Janabi T, D'Souza H, et al. The importance of understanding individual differences in Down syndrome. F1000Res. 2016. DOI: 10.12688/f1000research.7506.1

[20] Carinci F, Pezzetti F, Locci P, Becchetti E, Carls F, Avantaggiato A, et al. Apert and Crouzon syndromes: Clinical findings, genes and extracellular matrix. The Journal of Craniofacial Surgery. 2005;**16**(3):361-368

[21] Conrady CD, Patel BC. Crouzon Syndrome. Treasure Island (FL): StatPearls Publishing; 2021

[22] Vorgias D, Bernstein B. Fetal Alcohol Syndrome. Treasure Island (FL): StatPearls Publishing; 2022

[23] Kaminen-Ahola N. Fetal alcohol spectrum disorders: Genetic andepigenetic mechanisms. Prenatal Diagnosis;**40**:1185-1192. DOI: 10.1002/pd.5731

[24] MARTELLI-JÚNIOR H, MIRANDA RT d, FERNANDES CM, BONAN PRF, PARANAÍBA LMR, et al. Goldenhar syndrome: Clinical features with orofacial emphasis. Journal of Applied Oral Science. 2010;**18**(6):646-649

[25] Anderson PJ, David DJ. Spinal anomalies in Goldenhar Syndrome. The Cleft Palate-Craniofacial Journal. 2005;**42**:477-480

[26] Taksande AM, Panwar AS, Saqqaf SA, Meshram R, Lohakare A. A typical presentation of Goldenhar syndrome in a child: A case report with review case report. Annals of Vascular Medicine & Research. 2020;**3**:1013

[27] Rizos M, Spyropoulos MN. Van der Woude syndrome: A review. Cardinal signs, epidemiology, associated features, differential diagnosis, expressivity, genetic counselling and treatment. European Journal of Orthodontics. 2004;**26**(1):17-24

[28] Nopoulos P, Richman L, Andreasen NC, Murray JC, Schutte B. Abnormal brainstructure in adults with Van der Woude syndrome. Clinical Genetics. 2007;**71**(6):511-517

[29] Surman TL, Logan RM, Townsend GC, Anderson PJ. Oral features in Apert syndrome: A histological investigation. Orthodontics & Craniofacial Research. 2010;**13**(1):61-67. DOI: 10.1111/j.1601-6343.2009.01478

[30] Ferrante MI, Giorgio G, Feather SA, Bulfone A, Wright V, Ghiani M, et al. Identification of the gene for oral-facial-digital type I syndrome. American Journal of Human Genetics. 2001;**68**(3):569-576

[31] Siebert JR. The oral-facial-digital syndromes. Handbook of Clinical Neurology. 2008;**87**:341-351. DOI: 10.1016/S0072-9752(07)87018-7

[32] Marszałek B, Wójcicki P, Kobus K, Trzeciak WH. Clinical features, treatment and genetic background of Treacher Collins syndrome. Journal of Applied Genetics. 2002;**43**(2):223-233

[33] Trainor PA, Dixon J, Dixon MJ. Treacher Collins syndrome: Etiology, pathogenesis and prevention. European Journal of Human Genetics. 2009;**17**(3):275-283. DOI: 10.1038/ejhg.2008.221

Chapter 7

Neuropathic Pruritus: An Underrecognized and Often Misdiagnosed and Difficult to Treat Medical Condition

Sevgi Akarsu

Abstract

It is estimated that approximately 8% of chronic pruritic cases are of neuropathic origin. Common neuropathic pruritic syndromes include different clinical presentations such as postherpetic pruritus, trigeminal trophic syndrome, anogenital pruritus, scalp dysesthesia, nerve compression syndromes (e.g., notalgia paresthetica, brachioradial pruritus), small-fiber neuropathy (secondary to various metabolic, infectious, autoimmune, and genetic diseases), and disorders affecting the central nervous system (occupying lesions, iatrogenic, infectious, neurodegenerative, or demyelinating diseases). Although general practitioners are most likely to see the itchy cases first and consider referring them to further medical advice, it would be a better approach for the physicians to cooperate with dermatologists and neurologists and physiotherapists in particular especially in chronic persistent itchy conditions. Neuropathic pruritus must first be differentiated from other possible etiologies of pruritus by medical history and physical examination, laboratory tests, skin biopsy, and radiological and functional evaluations. It often does not respond to classical antipruritic treatments and different treatment options such as neuroleptics, topical capsaicin, epidural steroid injections, botulinum injections, nerve blocks, and neurostimulation techniques have been tried with variable success responses. This chapter provides a comprehensive overview of the characteristics and clinical presentations of neuropathic pruritus and the diagnostic and therapeutic management used in such patients.

Keywords: pruritus, itching, dysesthesia, neuropathic, neural damage

1. Introduction

Itching (also called "pruritus" as a medical term) is defined as an unwanted sensation that occurs in the skin and mucous membranes (especially in the conjunctiva), stimulating the scratching reflex or desire. The multifactorial and complex pathogenesis of pruritus, which is a common and distressing symptom arising from various skin disorders and systemic diseases, makes it difficult to determine the underlying etiology [1–3]. Each patient should be evaluated and treated individually, as it may

be a manifestation of diseases of different etiologies and prognoses [1]. A complete medical history, clinical examination, and laboratory and radiological evaluation are important in the management of pruritus [2].

While the cause of acute pruritus can be understood more clearly, it is often more difficult to find the etiological factor in chronic pruritus. There is no single and definite classification in the categorization of itching [1]. There are two different classifications in the literature for this purpose [3, 4]. Twycross et al. grouped pruritic disorders into four categories based on their neuropsychological origin: (a) cutaneous origin: pruritoceptive, (b) neuronal origin: neuropathic, (c) originating from central mediators without neural damage: neurogenic, and (d) somatoform: psychogenic [3]. In the International Forum for the Study of Itch, it has been gathered under three main headings: itching on the skin with primary inflammation, itching on the normal skin, and itching on the skin with secondary scratching lesions of unknown origin. These three main groups are divided into six subgroups under the headings of dermatological, systemic, neurological, psychogenic, mixed, and others by clinical and laboratory evaluation [4]. Pruritus with an unknown origin or no dermatological/systemic cause, without skin damage or with only secondary scratching lesions, is defined as "idiopathic" pruritus. The fact that there are many diseases that need to be eliminated when evaluating a patient with idiopathic pruritus is challenging for both the patient and the physician. Therefore, the patient should be informed in detail about this long process [5, 6].

In every patient with pruritus, comorbidities, drug use or abuse, traveling, presence of itching in close family members, home and workplace conditions, presence of skin lesions, and contact with animals or other potential allergens should be questioned. The time of onset of symptoms (acute pruritus if less than six weeks, chronic pruritus if longer), localization of pruritus, whether it shows diurnal changes, and exacerbating causes should also be included in the medical history. The patient's own view of the etiology of pruritus should also be taken into account, as it may aid the diagnosis [1]. While the cause of acute pruritus can be easily determined by the history, the history alone is often not sufficient in chronic pruritus. Systemic diseases that may cause chronic pruritus include thyroid diseases, iron deficiency, kidney failure, cholestasis, hematological diseases (lymphomas, leukemia, multiple myeloma, paraproteinemia, polycythemia vera), malignancies, HIV and HCV infections, rheumatological diseases (Sjögren's syndrome, dermatomyositis), anorexia nervosa, and drug hypersensitivity [2]. While the cause can be found in 10–50% of patients with chronic pruritus, it cannot be found in 8–35% of them [2, 5]. Pruritus can also be of multifactorial origin (mixed), and this probability increases with age. Because of the subjective nature of itching, comprehensive evaluation is important. Although complex, successful treatment largely depends on identifying the cause of pruritus, so the etiology should be carefully investigated in each patient [1, 2, 5].

Pruritus, the mechanism of which is also quite complex, is increased or decreased by various mediators, receptors, and inhibitors at the levels of peripheral nerve endings, dorsal root ganglia, and central nervous system [1, 7–9]. Different activation mechanisms of different receptors and ion channels determine the subtype of itching sensation. The skin has a complex network of cells and mediators involved in the induction, perception, treatment, and control of pruritus. Histamine, neuropeptides, neurotrophins, amines, cytokines, proteases, and prostaglandins are only a small part of the factors that cause pruritus by activating specific receptors in certain anatomical parts [1]. Therefore, factors that collectively participate in different mediator and receptor compositions play a role in pruritus that occurs in various diseases [1, 2].

As a neuroimmunoendocrine organ, the skin is closely related to the peripheral sensory nervous system, the autonomic nervous system, and the central nervous system [7]. The sensation of itching is conveyed by primary afferent sensory neurons located in the dermis and epidermis and associated with various skin cells. The cell bodies of these neurons are localized in the cranial and dorsal root ganglia. After activation, itching begins as information is transmitted to the itch center *via* the spinal cord and the contralateral spinothalamic tract. The primary neurons pass through the ipsilateral dorsal spinal root ganglion, synapse with the secondary neuron in the substantia gelatinosa, and reach the thalamus by entering the contralateral anterolateral spinothalamic tract. Microneurographic studies have also shown the lamina 1 spinothalamic sub-neuron class specific for pruritus in neurons that were previously thought to perform only contralateral conduction. Here, tertiary neurons originating from the posterolateral thalamic nucleus cross the internal capsule and terminate in the sensory cortex in the postcentral gyrus. The sense of itching also stimulates the motor cortex to initiate scratching. Studies with the positron emission technique have shown that the central center of pruritus is the left primary sensory cortex. In the brain, factors possibly affecting the anterior cingulate cortex provide a reduction and modulation of itching sensation [8–10]. Although hundreds of itch-related mediators and receptors have been identified today, there are undoubtedly some waiting to be discovered. As our knowledge about cutaneous neuroimmunoendocrinology increases, including itch mediators and neuronal pathways involved in itch transmission, new strategies may be developed in the diagnosis and treatment of various pruritic diseases [7, 11].

Unlike neurogenic pruritus, in which the neural structure is considered normal but abnormally stimulated, neuropathic pruritus (NP) is related to a pathology located at any point in the afferent pathway of the nervous system [11–14]. Pruritus due to these neurological disorders may precede diagnosis and may be transient, persistent, or paroxysmal. Typically, various paresthetic sensations such as pain, tingling, burning, and numbness accompany the pruritus [11, 12]. Damage to any part of the peripheral (nerve fibers, nerve plexuses, and ganglia) and central (spinal cord, brainstem, thalamus, or cortex) somatosensory system can lead to NP [13, 14]. In this context, NP may occur in many metabolic, infectious, autoimmune, neurodegenerative, orthopedic, malignant, and iatrogenic entities [15]. Although it is estimated that approximately 8% of chronic pruritic cases are of neuropathic origin, epidemiological studies investigating the prevalence and incidence of NP are insufficient in the literature [16].

In this chapter, case reports, clinical trials, cohort studies, systematic reviews, and meta-analyses associated with NP published up until now have been evaluated. The Medline literature database was searched through PubMed using the keywords, individually and in combination: "pruritus," "itching,", "dysesthesia," "neuropathic," and "neural damage." Only articles available in original or translated English were reviewed. This article is intended to provide a comprehensive overview of the characteristics and clinical presentations of NP, and the diagnostic and therapeutic management used in such patients.

2. Clinical disorders causing neuropathic pruritus

2.1 Postherpetic neuralgia/pruritus

It is the most common complication of herpes zoster and is associated with persistent and resistant neuropathies. It is estimated that up to 30% of people with

postherpetic neuralgia have pruritus [17, 18]. Postherpetic pruritus is also a common cause of NP in the dermatomal area affected by the peripheral nerve region damaged by the varicella zoster virus [19–21].

2.2 Trigeminal trophic syndrome (TTS)

A rare complication of trigeminal nerve injury and a rare cause of NP, it is characterized by facial ulceration, anesthesia, and paresthesia in the same trigeminal dermatome. While it most commonly appears as unilateral ulceration of the nasal area, it can also be found on the scalp in the frontoparietal and auriculotemporal region, when nerve damage occurs in the V1 and V3 distribution, respectively. Trigeminal nerve damage can be caused by various causes such as iatrogenic causes, herpes zoster, brain infarction, trauma, malignancy, multiple sclerosis, and infectious diseases. Although the exact cause is unknown, it is predominantly seen in women [13, 14]. Because pruritus associated with TTS is often described as crawling and tickling, some patients are misdiagnosed as delusional about parasitic infestation. The intensive, persistent, and subconscious desire to scratch, which usually occurs during sleep, causes chronic and deep excoriations on the scalp. The resulting wounds can sometimes even reach the bones [20–22]. These patients often refer to dermatologists, but neurologists should be consulted to identify and treat the underlying cause [14, 16].

In the literature review by Sawada et al., the mean age of patients with TTS was found to be 53.3 ± 19.7 years (range, 6–91). It was seen more frequently on the right side of the face (57%); the most common area was the nasi (79%), followed by the cheek (28%). The importance of ophthalmology consultations was emphasized because of the detection of corneal lesions in 18% of the cases. Major etiological factors were determined as trigeminal nerve ablation (30%) and cerebrovascular accidents (30%), and the latent period was observed to range from days to 30 years [23].

2.3 Entrapment syndromes of specific peripheral nerves

Nerve compression syndromes such as notalgia paresthetica, brachioradial pruritus, cheiralgia paresthetica (radial nerve), meralgia paresthetica (lateral femoral cutaneous nerve), and gonalgia paresthetica (infrapatellar branch of the saphenous nerve) present with pruritus localized to a specific anatomical area along the corresponding dermatome [15, 16]. Two typical syndromes caused by spinal nerve-root injury (radiculopathy) are notalgia paresthetica (dorsal branches of T2-T6 spinal nerves) and brachioradial pruritus (radiculopathy in C3-C8) [13].

2.3.1 Notalgia paresthetica

Pruritus that occurs classically on the midscapular line in the T2-T6 dermatomal area may also be accompanied by sensory changes such as pain, paresthesia, numbness, and stinging. It is usually unilateral. The skin initially appears normal, but in chronic cases, pruritus may be accompanied by secondary skin changes, a hyperpigmented patch, or signs of macular amyloidosis. It occurs more frequently in women and in late adulthood [15, 24]. Although the pathophysiology is unclear, the mechanism is thought to be a sensorineural neuropathy. It is widely believed that it is caused by the damage of the cutaneous branches of the posterior parts of the spinal nerves as a result of compression due to degenerative diseases of the spine or spasm of the paraspinal muscles [14]. In some individuals, conditions such as intervertebral

disc herniation and degenerative disc diseases that may cause compression on nerves in the spine have been described. The localization of pruritus is often correlated with radiological findings of the vertebrae and decreased intraepidermal nerve fiber density (IENFD) in the skin. Movements that compress the nerve may also precipitate notalgia paresthetica [24, 25].

2.3.2 Brachioradial pruritus

It is a pruritic condition described in the sun-exposed parts of the upper arm, wrist, and forearm in middle-aged and fair-skinned people. It is mainly localized neuropathic dysesthesia of the dorsolateral upper extremity, although occasionally the shoulders, back, anterior chest, and neck may also be involved [13]. It is bilateral at a rate of 75% and may become more generalized over time. The skin may develop excoriations, prurigo papules, mild atrophy, and signs of sun damage in the later stages. It is reported more frequently in women and people who engage in activities such as golf and tennis in sunny weather. This disorder occurs in people with fair skin, and the age range is quite wide. Typically, there is no itching on non-sun exposed areas of the arm. It regresses in the winter [14, 26]. Although the etiology is unknown, it is thought that cervical spine diseases that cause compression on the cervical nerves predispose to brachioradial pruritus, and the sun plays a triggering role [26, 27].

Cervical neuropathies and especially C3-C8 spinal nerve injuries have been demonstrated in most patients with brachioradial pruritus [27, 28]. In these people, a decrease in epidermal and dermal nerve fibers has been detected, and the nerves return to their normal state in symptom-free periods. Most of the patients stated that their complaints increased with sun exposure. Relief of pruritus with ice cube/cold application is diagnostic [29]. Although cervical spine pathologies (especially degenerative joint disease) are detected in the majority of patients with brachioradial pruritus, pruritus is not usually associated with neuropathy in these patients. Therefore, if cervical spine disease is strongly suspected or in patients whose symptoms worsen despite treatment, it is recommended to perform examinations such as MRI and to consult a neurologist in patients with accompanying neurological symptoms [27–29]. However, it should be kept in mind that brachioradial pruritus may occur due to compression of spinal tumors, especially in elderly individuals [30].

2.4 Small-fiber neuropathy (SFN)

In SFN arising from damaged small, unmyelinated C-, and thin-myelinated A-delta fibers, pruritus and pain may be localized (mostly in the distal extremities) or generalized [13]. It may occur secondary to various metabolic, infectious, autoimmune, and genetic diseases, mainly diabetes mellitus, sarcoidosis, amyloidosis, vitamin B12 deficiency, and viral infections. In addition, drugs (e.g., chemotherapy) and alcohol use can also induce SFN [31]. Chronic pruritus ($\geq$6 weeks), normal-appearing skin, and the presence of reduced IENFD were reported as obligatory criteria for SFN-related chronic generalized itching by Pereira et al. [32].

2.5 Post-burn or post-surgery scars and keloids

These scar tissues are usually associated with pruritus, possibly due to damage to the cutaneous nerves. Neurophysiological studies have revealed functional abnormalities in small nerve fibers. Scar tissue is prone to prolonged itching and

is often characterized by a burning and piercing sensation [33–35]. In one study, it was observed that approximately two-thirds of patients discharged from burn units complained of pruritus. Responses to sensory stimulation on burn-skin grafts were reduced or absent in the vast majority of patients [34]. The majority of patients with keloids also complained of pruritus, especially around the keloid margins [35].

2.6 Anogenital pruritus

It is defined as localized itching of the anus and perianal and/or genital skin. It is usually a symptom of underlying skin/mucosa disorder or anorectal pathology. Most patients are associated with an inflammatory dermatosis (e.g., contact dermatitis, psoriasis, lichen planus), infectious disease (e.g., fungal infection), or anorectal disease (e.g., perianal fissure). When no demonstrable cause is found, it is usually defined as idiopathic (primary) anogenital pruritus. In a significant proportion of idiopathic cases, degenerative changes (sclerosis, anterior and posterior osteophytes, narrowing of the intervertebral space) in the lower spine and sacrum radiographs and lumbosacral radiculopathy leading to nerve or nerve-root compression at the level of the L4-S2 vertebrae have been detected in nerve conduction studies [36]. Since Koh et al. reported a case of ipsilateral neuropathic scrotal pruritus secondary to direct nerve compression by an inguinal hernia, it may be recommended to perform investigations for inguinal hernia in the presence of anogenital pruritus [37]. Vulvar pruritus constitutes 66% of cases that apply to gynecologists due to vulvar problems and 73% of cases that apply to dermatologists. It can occur at any age. There is growing evidence to suggest that neurogenic factors may contribute to vulvar pruritus [38]. Several studies have shown increased expression of the transient receptor potential vanilloid 1 ion channel, which is well known for its role in modulating pain and itching signals in the vulvovaginal epithelium in patients with vulvodynia [39]. Although vulvodynia is classically considered a form of neuropathic pain, it may be accompanied by itching and burning in 20 and 70% of cases, respectively [40]. Vulvar pruritus can also be caused by nerve or nerve-root compression at the L4 to S2 vertebral levels due to spinal injuries or lumbosacral arthritis. In addition, 8.4% of herpes zoster cases affect the dermatomes that innervate the vulva, and long-term damage to the affected nerves can cause persistent pain and/or itching of the vulvar skin [41].

2.7 Scalp dysesthesia

It is a neuropathic phenomenon where itching is usually accompanied by paresthesia, hyperesthesia, and hypoesthesia. Neuropathic etiologies of scalp pruritus are often associated with cervical spine degenerative disc disease, TSS, and postherpetic neuralgia. In addition, it may be associated with brain malignancy (such as brainstem tumors, tumors infiltrating the trigeminal ganglion, cervical intramedullary glioma), multiple sclerosis, and stroke. Diabetic and geriatric patients have also been found to have higher rates of scalp pruritus [21, 42]. Cosmetic procedures such as face and brow lift can also cause NP when they cause local nerve damage. Paresthesia and dysesthesia are the most common complications in open and endoscopic brow lift procedures, with rates up to 5.4 and 6.2%, respectively. It was observed that the scalp dysesthesia, which appeared 1–2 weeks after the procedure, regressed after an average of 3 months. The occurrence of pruritus and paresthesia is relatively common but usually minimal, and patients report that dysesthesia is not significant

enough to prevent them from undergoing reoperation [43, 44]. In addition, postinfectious trichodynia (58.4%), which is generally associated with telogen effluvium and defined as pain, pruritus, burning, and/or paresthesia on the scalp with light hair touching or brushing, has been reported after COVID-19 infection. Symptoms of trichodynia appeared an average of 1–2 weeks after the diagnosis of COVID-19, lasting 4–5 weeks, and regressed in 44% of patients. These patients reported relief of trichodynia with sleeping, cold water washing, application of superpotent topical steroids, combing, massage, and scratching [21, 45].

2.8 Elderly dysesthesia

The high prevalence of pruritus in the geriatric age group (between 7 and 45.9%) tends to increase with age. Geriatric patients are more likely to have diseases and conditions that predispose them to pruritus, such as shingles and postherpetic neuralgia, stroke, diabetes mellitus, and TTS. Age-related neuropathic changes and disruption of pruritus-inhibiting fibers, as well as the frequent occurrence of degenerative spine diseases in geriatric patients, make these individuals prone to neurogenic pruritus [46]. In these patients, besides the secondary lesions due to scratching, complaints such as burning, stinging, and numbness called dysesthesia may also be encountered [21, 46].

2.9 Disorders affecting the central nervous system

Central space-occupying lesions such as abscess, cysts, tumors, vascular malformations, or syringomyelia may cause neuropathic pruritus. Neural damage induced by trauma (accidents or iatrogenic) or infectious diseases (meningitis, encephalitis, prion disease) has also been associated with the occurrence of pruritus [16, 47–49]. It has also been reported that unilateral pruritus develops after ischemic/hemorrhagic stroke or hemicraniectomy (e.g., due to ruptured arteriovenous malformation) [50]. Posterior inferior cerebellar artery stroke, also known as Wallenburg syndrome, is often associated with neuropathic pain and pruritus in the ipsilateral trunk and extremities and the contralateral trigeminal region. Lateral medullary infarction usually causes 20% of TTS resulting from vertebrobasilar strokes and most commonly presents as NP with V2–V3 distribution [21].

Paroxysmal pruritus associated with neuroinflammatory conditions (demyelinating diseases) such as multiple sclerosis and neuromyelitis optica is clinically an acute onset and recalcitrant pruritus that is usually triggered by the onset of movement and has frequent attacks during the day. It has been theorized that transversely diffused ephatic activation of partially demyelinating pain-transmitting neurons causes paroxysmal pruritus [51–53]. In the study of Ingrasci et al., pruritus was reported in 35% of a total of 77 multiple sclerosis patients. It was frequently characterized as acute (74%), paroxysmal (59%), and tingling (55%). The most common triggering factor was temperature increase (52%), while cold temperatures had no effect. Multiple sclerosis patients with pruritus had significantly more fatigue, heat sensitivity, cognitive impairment, and signs of depression or anxiety, as well as more T2 hyperintensity in the posterior cervical cord and anterior pons/ventromedial medulla. Again, T2 hyperintensities in the anterior pons/ventromedial medulla were strongly associated with localized pruritus on the face or scalp. As a result, paroxysmal NP localized to the extremities, face or scalp, most frequently, is seen in multiple sclerosis patients. Patients with pruritus are more likely to have multiple sclerosis-related comorbidities and demyelinating lesions in the spinal cord or brainstem [51]. Muto et al. have

suggested that most of the opticospinal form of multiple sclerosis is neuromyelitis optica, and it was found that paroxysmal pruritus was more prominent in these cases [52].

3. Diagnosis of neuropathic pruritus

NP must first be differentiated from other possible underlying etiologies of pruritus. The diagnosis and management of NP are very difficult, especially due to its multidimensional nature in terms of its clinical presentation and possible underlying causes [11, 12, 15].

Laboratory tests and other further investigations recommended for pruritus due to systemic diseases are summarized in the European guideline. In this guideline, lumbar puncture and MRI in the case of suspected neurological disorder, cerebrospinal fluid analysis (oligoclonal bands) and brain MRI (CT) in multiple sclerosis, histopathology and cerebrospinal fluid analysis and brain MRI (CT) in brain tumors, thoracic spine MRI (CT) in notalgia paresthetica, and thoracic and cervical spine MRI for brachioradial pruritus have been recommended [2].

3.1 Medical history and physical examination

NP is difficult to diagnose and may be missed in routine history, examination, and tests. A detailed medical history is required to diagnose NP and exclude other possible etiologies that may cause chronic pruritus [14, 15]. The characteristics of the pruritus, its onset and possible associated events, and the appearance of the skin at the onset of symptoms should be questioned in detail [13]. NP should be suspected in patients with chronic pruritus that begins in normal-appearing skin without an associated systemic condition causing pruritus. Patients with NP are not expected to have a primary skin disease or lesion, but secondary excoriations or chronic scratch lesions (e.g., chronic nodular prurigo, lichenification) may develop due to the chronic itch-scratching cycle [14, 16]. In addition, the distribution pattern of pruritus at the onset and during the course of the disease (e.g., dermatomal in post-herpetic neuralgia or brachioradial pruritus, stocking, and glove distribution in SFN) may provide more clues for the diagnosis of NP and the localization of pathology within the somatosensory system [13, 15]. Although the affected area of the somatosensory system is crucial for pruritus localization, NP that is initially localized may become generalized later on [26, 54].

The severity of pruritus, accompanying sensory symptoms, fluctuation of pruritus during the day, and alleviating factors should be evaluated. Although clinical sensory symptoms such as the presence of additional dysesthesias including stinging and tingling, pruritus occurring with attacks rather than being continuous, and relief with cold packs or cold application have been suggested as diagnostic criteria for SFN-related pruritus, it may not completely exclude non-neuropathic pruritic conditions [31, 32]. For example, in atopic dermatitis, sensory symptoms such as crawling, tickling, and stinging may accompany itching [55]. In NP, there may be alloknesis (induction of itching after application of a non-itchy stimulus, e.g., a perception of intense itching after a light touch on the skin with cotton wool or a brush) and hyperknesis (exaggerated itching response to an itchy stimulus). These phenomena reflect neuronal sensitization processes that contribute to the chronicity of pruritus [56]. A general medical history of comorbidities and concomitant medications can also help inform patients about the ultimate limitations of therapeutic options [1, 14].

Although standardized questionnaires have been successfully developed to screen for neuropathic pain, questionnaires used for NP are very limited. A Neuropathic Pruritus 5 (NP5) score was proposed by Huguen et al. to differentiate NP from non-NP based on patient-reported results. The presence of two of the five independent factors for NP (presence of sudden sharp localized pain, no burning, worsening of pruritus with activity, not worsening with stress, and relief of pruritus with cold weather) has been shown to provide 76% sensitivity and 77% specificity in distinguishing NP from non-NP [57]. Also, for small-fiber polyneuropathy, there is also a patient-centered questionnaire study with questions on itchy skin [58].

3.2 Laboratory tests, skin biopsy, and radiological and functional evaluations

Certain laboratory tests are necessary to exclude other conditions that cause chronic pruritus, such as renal insufficiency, cholestasis, and hematooncological diseases [1, 2]. In addition, disease-specific testing should be performed in selected patients with a suspected neurological condition (such as cerebrospinal fluid analysis for suspected brain tumor, oligoclonal bands for multiple sclerosis diagnosis) [15, 16]. In patients diagnosed with SFN, evaluation of glycosylated hemoglobin, vitamin B12 and folate serum levels, HIV and hepatitis B and C serology, TSH, and antinuclear antibodies is necessary to detect possible causes [31].

Skin biopsy may provide important clues for the determination of neurocutaneous morphological changes and examination of epidermal neural architecture in neuropathic pruritic conditions [13]. Decreased IENFD, which is the gold standard in the diagnosis of SFN, is also observed in neuropathic compression and radiculopathy syndromes such as brachioradial pruritus. Clinically, the magnitude of the reduction in IENFD seems to affect the perception of dysesthesia [29, 31]. To determine IENFD, after staining a skin sample from non-lesional itchy skin *via* punch biopsy with an axonal marker (e.g., protein gene product 9.5), nerve fibers crossing the basement membrane from the dermis to the epidermis are counted and divided by the length of the dermoepidermal junction. The lateral lower leg should be selected for biopsy, as reference values are currently only available for the innervation region of the sural nerve. If another body area is affected, a skin sample should be taken from an unaffected symmetrical area for comparison [59].

MRI and CT play an important role in detecting space-occupying lesions (such as tumors, abscesses, and vascular or inflammatory lesions) and their anatomical relationship with peripheral or central neural structures [30, 36, 60], as well as in the diagnosis of neurological conditions such as stroke, meningitis, or degenerative neuroinflammatory diseases that can cause NP [49–53]. In the diagnostic study of itchy neuropathic compression syndromes, MRI, CT, high-resolution sonography, or MR neurography are also used to identify underlying pathologies such as compression of the nerve roots or spinal cord, disc prolapse or herniation, degenerative vertebral changes, osteophytes, or neuroforaminal stenosis [25, 27]. While there is a correlation between MRI findings and localization of dysesthesias in brachioradial pruritus, such a relationship is not clear for notalgia paresthetica [29].

Morphological examinations of neuroanatomical changes associated with small unmyelinated C fibers and thin myelinated A-delta fibers transmitting itching can be performed with functional assessments. In quantitative sensory testing, a validated test battery using thermal and mechanical standardized stimuli can determine perception and pain thresholds and a possible gain or loss of function of different nerve fibers by measuring the response to suprathreshold stimuli. Although this non-invasive method provides a comprehensive neurophysiological profile of sensory

neuropathies, it is time consuming and requires expert staff and patient collaboration [61]. Although large myelinated sensory fibers are not involved in itch transmission, SFN may occur as part of a polyneuropathy with the involvement of large fibers. Therefore, patients with SFN-related NP should seek the opinion of a neurologist for nerve conduction studies or electromyography [31, 32]. Pathological nerve conduction studies can also be demonstrated in patients with pruritic compression diseases (as reported in brachioradial pruritus and anogenital neuropathic pruritus) [29, 36]. Evaluation of evoked potentials and microneurography are methods of investigating selective nerve fiber dysfunction and are mostly performed in research studies but may only be considered in selected clinical cases [62, 63].

4. Treatment and management of neuropathic pruritus

NP may become more difficult to manage by negatively affecting the patient's quality of life, especially in chronic conditions that were misdiagnosed and could not be diagnosed despite multiple tests. While it is ideal to target the cause of pruritus, such as decompression of the spine or resection of the tumor, these interventions are often incurable and rarely practical. Therefore, treatment is usually directed toward symptomatic therapy to improve quality of life [14, 16, 20].

More rapid therapeutic relief can be achieved with local anesthetics and antipruritics, especially in patients with localized mild acute pruritus. A topical 5–10% ketamine, 5% amitriptyline, and 5% lidocaine combination, topical ketamine combined with amitriptyline, and 8% topical capsaicin patches have been shown to be effective at varying rates against NP [64–67]. Other topical treatments that can relieve mild pruritus include topical menthol, pramoxine, and lidocaine [14, 16]. The local combination of the calcineurin inhibitor tacrolimus and gabapentin has been shown to be effective against TTS and not associated with systemic effects [68].

High doses of anticonvulsant drugs such as gabapentin, pregabalin, phenytoin, and carbamazepine and low doses of antidepressants such as tricyclic antidepressant amitriptyline are frequently used in moderately severe NP. The combination of selective serotonin and norepinephrine inhibitor mirtazapine and gabapentin used to treat neuropathic pain may also be beneficial for NP. Kappa opioids, which are particularly beneficial for chronic resistant pruritus, may be effective against NP [11, 16, 34]. In particular, fMRI studies of butorphanol have been shown to reduce activity in areas of the brain associated with itching activity, such as the claustrum, insula, and putamen [69].

Those with severe NP may benefit from more invasive treatments such as botulinum toxin A injections, nerve blocks, transcutaneous electrical nerve stimulation, IV ketamine, and IV phenytoin [70–74]. Botulinum toxin A, which is used to prevent cholinergic transmission and reduce substance P along the itch pathways, is injected into several points at 1–2 cm intervals along the affected area. Although outcomes are variable, it has been shown to improve NP in persistent postherpetic pruritus, brachioradial pruritus, notalgia paresthetica, and keloids [70, 71]. IV phenytoin provides rapid relief of neuropathic dysesthesias and is an acute rescue therapy for trigeminal neuralgias [73]. Recently, Morin et al. reported three cases of severe localized NP refractory to treatment that was successfully and rapidly treated with dronabinol, an oral synthetic formulation of delta-9-tetrahydrocannabinol [74].

As in TTS, patient education and counseling are necessary to prevent and reverse repetitive manipulation of self-induced ulcerations at the itch site. Cognitive behavioral therapy, such as habit reversal and relaxation training, can be used to control

the itch-scratch cycle and improve quality of life [20, 23]. Again, an exercise regimen consisting of physical rehabilitation and spinal range of motion exercises, mild mobilization, and muscle stretching has been found to be beneficial in patients with scalp dysesthesia [21].

5. Conclusion

The diagnosis of NP is difficult due to its different clinical presentations and complex etiological factors. In addition to a thorough medical history and physical examination, some laboratory tests, skin biopsy, and radiological examinations are necessary to detect typical signs and symptoms and rule out other possible causes for chronic pruritus. In special cases, neurology expert opinion may be considered for functional evaluations such as quantitative sensory tests and nerve conduction studies. In general, the treatment of NP is difficult, and there is often no response to classical antipruritic treatments such as antihistamines and corticosteroids. Instead, local or systemic treatments suppressing neuronal stimulation and agents repairing the skin barrier are given. Although there are no controlled studies on the treatment of NP, anticonvulsants such as carbamazepine and phenytoin; neuroleptics such as gabapentin and pregabalin; low-dose antidepressants; regional, intrathecal, or paravertebral nerve blocks; cervical epidural steroid injections; intravenous anesthetics; botulinum injections; topical capsaicin; topical anesthetics; topical amitriptyline/ketamine mixture; and topical menthol and neurostimulation techniques are applied with variable success responses depending on the underlying cause of neuropathy.

In conclusion, despite the different options available for diagnosis and treatment, neuropathic pruritic syndromes still remain a clinical challenge in routine clinical practice. Although itchy cases usually refer to dermatologists, it would be a better approach for dermatologists to cooperate with neurology and physical therapy departments in terms of the possibility of neuropathic origin, especially in chronic, persistent itchy conditions that are resistant to treatment.

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References

[1] Roh YS, Choi J, Sutaria N, Kwatra SG. Itch: Epidemiology, clinical presentation, and diagnostic workup. Journal of the American Academy of Dermatology. 2022;**86**:1-14. DOI: 10.1016/j.jaad.2021.07.076

[2] Weisshaar E, Szepietowski JC, Dalgard FJ, Garcovich S, Gieler U, Giménez-Arnau AM, et al. European S2k guideline on chronic pruritus. Acta Dermato-Venereologica. 2019;**99**:469-506. DOI: 10.2340/00015555-3164

[3] Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, et al. Itch: Scratching more than the surface. QJM. 2003;**96**:7-26. DOI: 10.1093/qjmed/hcg002

[4] Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: A position paper of the international forum for the study of itch. Acta Dermato-Venereologica. 2007;**87**:291-294. DOI: 10.2340/00015555-0305

[5] Pereira MP, Kremer AE, Mettang T, Ständer S. Chronic pruritus in the absence of skin disease: Pathophysiology, diagnosis and treatment. American Journal of Clinical Dermatology. 2016;**17**:337-348. DOI: 10.1007/s40257-016-0198-0

[6] Robert M, Misery L, Brenaut E. Chronic pruritus in the absence of skin disease: A retrospective study of 197 French inpatients. Acta Dermato-Venereologica. 2020;**100**(16):adv00274, 10.2340/00015555-3630

[7] Shumway NK, Cole E, Fernandez KH. Neurocutaneous disease: Neurocutaneous dysesthesias. Journal of the American Academy of Dermatology. 2016;**74**:215, quiz 229-228, quiz 230. DOI: 10.1016/j.jaad.2015.04.059

[8] Azimi E, Xia J, Lerner EA. Peripheral mechanisms of itch. Current Problems in Dermatology. 2016;**50**:18-23. DOI: 10.1159/000446012

[9] Carstens E, Akiyama T. Central mechanisms of itch. Current Problems in Dermatology. 2016;**50**:11-17. DOI: 10.1159/000446011

[10] Pogatzki-Zahn EM, Pereira MP, Cremer A, Zeidler C, Dreyer T, Riepe C, et al. Peripheral sensitization and loss of descending inhibition is a hallmark of chronic pruritus. Journal of Investigative Dermatology. 2020;**140**:203-211.e4. DOI: 10.1016/j.jid.2019.05.029

[11] Meixiong J, Dong X, Weng HJ. Neuropathic itch. Cell. 2020;**9**:2263. DOI: 10.3390/cells9102263

[12] Steinhoff M, Oaklander AL, Szabó IL, Ständer S, Schmelz M. Neuropathic itch. Pain. 2019;**160**(Suppl. 1):S11-S16. DOI: 10.1097/j.pain.0000000000001551

[13] Oaklander AL. Common neuropathic itch syndromes. Acta Dermato-Venereologica. 2012;**92**:118-125. DOI: 10.2340/00015555-1318

[14] Steinhoff M, Schmelz M, Szabó IL, Oaklander AL. Clinical presentation, management, and pathophysiology of neuropathic itch. The Lancet. Neurology. 2018;**17**:709-720. DOI: 10.1016/S1474-4422(18)30217-5

[15] Pereira MP, Wiegmann H, Agelopoulos K, Ständer S. Neuropathic itch: Routes to clinical diagnosis. Frontiers in Medicine (Lausanne). 2021;**8**:641746. DOI: 10.3389/fmed.2021.641746

[16] Stumpf A, Ständer S. Neuropathic itch: Diagnosis and management. Dermatologic Therapy. 2013;**26**:104-109. DOI: 10.1111/dth.12028

[17] van Wijck AJM, Aerssens YR. Pain, itch, quality of life, and costs after herpes zoster. Pain Practice. 2017;**17**:738-746. DOI: 10.1111/papr.12518

[18] Oaklander AL. Mechanisms of pain and itch caused by herpes zoster (shingles). The Journal of Pain. 2008;**9** (1 Suppl. 1):S10-S18. DOI: 10.1016/j.jpain.2007.10.003

[19] Lee HJ, Kim GW, Kim WJ, Mun JH, Song M, Kim HS, et al. Clinical characteristics of postherpetic pruritus: Assessment using a questionnaire, von Frey filaments and Neurometer. The British Journal of Dermatology. 2015;**172**:1672-1673. DOI: 10.1111/bjd.13569

[20] Patnaik S, Imms JB, Varadi G. The neuropathic itch: Don't scratch your head too hard! Clinical Case Reports. 2020;**9**:914-916. DOI: 10.1002/ccr3.3688

[21] Ju T, Vander Does A, Yosipovitch G. Scalp dysesthesia: A neuropathic phenomenon. Journal of the European Academy of Dermatology and Venereology. 2022;**36**:790-796. DOI: 10.1111/jdv.17985

[22] Kautz O, Bruckner-Tuderman L, Müller ML, Schempp CM. Trigeminal trophic syndrome with extensive ulceration following herpes zoster. European Journal of Dermatology. 2009;**19**:61-63. DOI: 10.1684/ejd.2008.0564

[23] Sawada T, Asai J, Nomiyama T, Masuda K, Takenaka H, Katoh N. Trigeminal trophic syndrome: Report of a case and review of the published work. The Journal of Dermatology. 2014;**41**:525-528. DOI: 10.1111/1346-8138.12490

[24] Akram A. Notalgia paresthetica: Cervical spine disease and neuropathic pruritus. Cureus. 2021;**13**:e12975. DOI: 10.7759/cureus.12975

[25] Huesmann T, Cunha PR, Osada N, Huesmann M, Zanelato TP, Phan NQ, et al. Notalgia paraesthetica: A descriptive two-cohort study of 65 patients from Brazil and Germany. Acta Dermato-Venereologica. 2012;**92**:535-540. DOI: 10.2340/00015555-1344

[26] Kwatra SG, Stander S, Bernhard JD, Weisshaar E, Yosipovitch G. Brachioradial pruritus: A trigger for generalization of itch. Journal of the American Academy of Dermatology. 2013;**68**:870-873. DOI: 10.1016/j.jaad.2012.11.026

[27] Marziniak M, Phan NQ, Raap U, Siepmann D, Schürmeyer-Horst F, Pogatzki-Zahn E, et al. Brachioradial pruritus as a result of cervical spine pathology: The results of a magnetic resonance tomography study. Journal of the American Academy of Dermatology. 2011;**65**:756-762. DOI: 10.1016/j.jaad.2010.07.036

[28] Shields LB, Iyer VG, Zhang YP, Shields CB. Brachioradial pruritus: Clinical, electromyographic, and cervical MRI features in nine patients. Cureus. 2022;**14**:e21811. DOI: 10.7759/cureus.21811

[29] Pereira MP, Lüling H, Dieckhöfer A, Steinke S, Zeidler C, Ständer S. Brachioradial pruritus and notalgia paraesthetica: A comparative observational study of clinical presentation and morphological pathologies. Acta Dermato-Venereologica. 2018;**98**:82-88. DOI: 10.2340/00015555-2789

[30] Pham C, Cox S, Smith J. Brachioradial pruritus in a patient with metastatic breast cancer to her cervical spine. JAAD Case Reports. 2020;**6**:619-621. DOI: 10.1016/j.jdcr.2020.04.034

[31] Misery L, Bodere C, Genestet S, Zagnoli F, Marcorelles P. Small-fibre neuropathies and skin: News and perspectives for dermatologists. European Journal of Dermatology. 2014;**24**:147-153. DOI: 10.1684/ejd.2013.2189

[32] Pereira MP, Derichs L, Hörste GMZ, Agelopoulos K, Ständer S. Generalized chronic itch induced by small-fibre neuropathy: Clinical profile and proposed diagnostic criteria. Journal of the European Academy of Dermatology and Venereology. 2020;**34**:1795-1802. DOI: 10.1111/jdv.16151

[33] Chung BY, Kim HB, Jung MJ, Kang SY, Kwak IS, Park CW, et al. Post-burn pruritus. International Journal of Molecular Sciences. 2020;**21**:3880. DOI: 10.3390/ijms21113880

[34] McGovern C, Quasim T, Puxty K, Shaw M, Ng W, Gilhooly C, et al. Neuropathic agents in the management of pruritus in burn injuries: A systematic review and meta-analysis. Trauma Surgery & Acute Care Open. 2021;**6**:e000810. DOI: 10.1136/tsaco-2021-000810

[35] Lee SS, Yosipovitch G, Chan YH, Goh CL. Pruritus, pain, and small nerve fiber function in keloids: A controlled study. Journal of the American Academy of Dermatology. 2004;**51**:1002-1006. DOI: 10.1016/j.jaad.2004.07.054

[36] Cohen AD, Vander T, Medvendovsky E, Biton A, Naimer S, Shalev R, et al. Neuropathic scrotal pruritus: Anogenital pruritus is a symptom of lumbosacral radiculopathy. Journal of the American Academy of Dermatology. 2005;**52**:61-66. DOI: 10.1016/j.jaad.2004.04.039

[37] Koh WL, Liu TT. A cured patient who came back for consultation: Neuropathic scrotal pruritus relieved after ipsilateral inguinal hernia repair. International Journal of STD & AIDS. 2010;**21**:658-659. DOI: 10.1258/ijsa.2010.010185

[38] Raef HS, Elmariah SB. Vulvar pruritus: A review of clinical associations, pathophysiology and therapeutic management. Frontiers in Medicine (Lausanne). 2021;**8**:649402. DOI: 10.3389/fmed.2021.649402

[39] Tympanidis P, Casula MA, Yiangou Y, Terenghi G, Dowd P, Anand P. Increased vanilloid receptor VR1 innervation in vulvodynia. European Journal of Pain (London, England). 2004;**8**:129-133. DOI: 10.1016/S1090-3801(03)00085-5

[40] Phillips NA, Brown C, Foster D, Bachour C, Rawlinson L, Wan J, et al. Presenting symptoms among premenopausal and postmenopausal women with vulvodynia: A case series. Menopause. 2015;**22**:1296-1300. DOI: 10.1097/GME.0000000000000526

[41] Oaklander AL, Rissmiller JG. Postherpetic neuralgia after shingles: An under-recognized cause of chronic vulvar pain. Obstetrics and Gynecology. 2002;**99**:625-628. DOI: 10.1016/s0029-7844(01)01663-5.s

[42] Rattanakaemakorn P, Suchonwanit P. Scalp pruritus: Review of the pathogenesis, diagnosis, and management. BioMed Research International. 2019;**2019**:1268430. DOI: 10.1155/2019/1268430

[43] Byun S, Mukovozov I, Farrokhyar F, Thoma A. Complications of browlift techniques: A systematic review.

Aesthetic Surgery Journal. 2013;**33**:189-200. DOI: 10.1177/1090820X12471829

[44] Guillot JM, Rousso DE, Replogle W. Forehead and scalp sensation after brow-lift: A comparison between open and endoscopic techniques. Archives of Facial Plastic Surgery. 2011;**13**:109-116. DOI: 10.1001/archfacial.2010.97

[45] Starace M, Iorizzo M, Sechi A, Alessandrini AM, Carpanese M, Bruni F, et al. Trichodynia and telogen effluvium in COVID-19 patients: Results of an international expert opinion survey on diagnosis and management. JAAD International. 2021;**5**:11-18. DOI: 10.1016/j.jdin.2021.07.006

[46] Shevchenko A, Valdes-Rodriguez R, Yosipovitch G. Causes, pathophysiology, and treatment of pruritus in the mature patient. Clinics in Dermatology. 2018;**36**:140-151. DOI: 10.1016/j.clindermatol.2017.10.005

[47] Pereira MP, Görg M, Zeidler C, Ständer S. Periumbilical neuropathic pruritus in an infant: Presentation of a spinal intramedullary neoplasm. Journal of the European Academy of Dermatology and Venereology. 2022;**36**:e132-e133. DOI: 10.1111/jdv.17696

[48] Crane DA, Jaffee KM, Kundu A. Intractable pruritus after traumatic spinal cord injury. The Journal of Spinal Cord Medicine. 2009;**32**:436-439. DOI: 10.1080/10790268.2009.11753261

[49] Ganguly S, Krishna CV, Parmar NV, Kuruvila S, Phansalkar DS. Unilateral pruritus following stroke. Indian Journal of Dermatology, Venereology, and Leprology. 2015;**81**:186-188. DOI: 10.4103/0378-6323.152294

[50] Agarwal A, Fernandez BA. Unilateral neurogenic pruritus following intracranial surgery. Cureus. 2020;**12**:e8661. DOI: 10.7759/cureus.8661

[51] Ingrasci G, Tornes L, Brown A, Delgado S, Hernandez J, Yap QV, et al. Chronic pruritus in multiple sclerosis and clinical correlates. Journal of the European Academy of Dermatology and Venereology. 2023;**37**:154-159. DOI: 10.1111/jdv.18561

[52] Muto M, Mori M, Sato Y, Uzawa A, Masuda S, Uchida T, et al. Current symptomatology in multiple sclerosis and neuromyelitis optica. European Journal of Neurology. 2015;**22**:299-304. DOI: 10.1111/ene.12566

[53] Xiao L, Qiu W, Lu Z, Li R, Hu X. Intractable pruritus in neuromyelitis optica. Neurological Sciences. 2016;**37**:949-954. DOI: 10.1007/s10072-016-2523-z

[54] Ward RE, Veerula VL, Ezra N, Travers JB, Mousdicas N. Multilevel symmetric neuropathic pruritus (MSNP) presenting as recalcitrant "generalized" pruritus. Journal of the American Academy of Dermatology. 2016;**75**:774-781. DOI: 10.1016/j.jaad.2016.05.027

[55] Rosen JD, Fostini AC, Chan YH, Nattkemper LA, Yosipovitch G. Cross-sectional study of clinical distinctions between neuropathic and inflammatory pruritus. Journal of the American Academy of Dermatology. 2018;**79**:1143-1144. DOI: 10.1016/j.jaad.2018.05.1236

[56] Andersen HH, Akiyama T, Nattkemper LA, van Laarhoven A, Elberling J, Yosipovitch G, et al. Alloknesis and hyperknesis-mechanisms, assessment methodology, and clinical implications of itch sensitization. Pain. 2018;**159**:1185-1197. DOI: 10.1097/j.pain.0000000000001220

[57] Huguen J, Brenaut E, Clerc CJ, Poizeau F, Marcorelles P, Quereux G,

et al. Comparison of characteristics of neuropathic and non-neuropathic pruritus to develop a tool for the diagnosis of neuropathic pruritus: The NP5. Frontiers in Medicine (Lausanne). 2019;**6**:79. DOI: 10.3389/fmed.2019.00079

[58] Treister R, Lodahl M, Lang M, Tworoger SS, Sawilowsky S, Oaklander AL. Initial development and validation of a patient-reported symptom survey for small-fiber polyneuropathy. The Journal of Pain. 2017;**18**(5):556-563. DOI: 10.1016/j.jpain.2016.12.014

[59] Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, et al. European Federation of Neurological Societies; peripheral nerve society. European Federation of Neurological Societies/peripheral nerve society guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the peripheral nerve society. European Journal of Neurology. 2010;**17**(903-12):e44-e49. DOI: 10.1111/j.1468-1331.2010.03023.x

[60] Pham M, Bäumer T, Bendszus M. Peripheral nerves and plexus: Imaging by MR-neurography and high-resolution ultrasound. Current Opinion in Neurology. 2014;**27**(4):370-379. DOI: 10.1097/WCO.0000000000000111

[61] Maier C, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, et al. Quantitative sensory testing in the German research network on neuropathic pain (dfns): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain. 2010;**150**:439-450. DOI: 10.1016/j.pain.2010.05.002

[62] Donadio V, Liguori R. Microneurographic recording from unmyelinated nerve fibers in neurological disorders: An update. Clinical Neurophysiology. 2015;**126**:437-445. DOI: 10.1016/j.clinph.2014.10.009

[63] Merkies IS, Faber CG, Lauria G. Advances in diagnostics and outcome measures in peripheral neuropathies. Neuroscience Letters. 2015;**596**:3-13. DOI: 10.1016/j.neulet.2015.02.038

[64] Poterucha TJ, Murphy SL, Sandroni P, Rho RH, Warndahl RA, Weiss WT, et al. Topical amitriptyline combined with topical ketamine for the management of recalcitrant localized pruritus: A retrospective pilot study. Journal of the American Academy of Dermatology. 2013;**69**:320-321. DOI: 10.1016/j.jaad.2013.03.013

[65] Lee HG, Grossman SK, Valdes-Rodriguez R, Berenato F, Korbutov J, Chan YH, et al. Topical ketamine-amitriptyline-lidocaine for chronic pruritus: A retrospective study assessing efficacy and tolerability. Journal of the American Academy of Dermatology. 2017;**76**:760-761. DOI: 10.1016/j.jaad.2016.10.030

[66] Misery L, Erfan N, Castela E, Brenaut E, Lantéri-Minet M, Lacour JP, et al. Successful treatment of refractory neuropathic pruritus with capsaicin 8% patch: A bicentric retrospective study with long-term follow-up. Acta Dermato-Venereologica. 2015;**95**:864-865. DOI: 10.2340/00015555-2085

[67] Yosipovitch G. The 8% capsaicin - a hot medicine for neuropathic itch. Journal of the European Academy of Dermatology and Venereology. 2018;**32**:1403. DOI: 10.1111/jdv.15187

[68] Nakamizo S, Miyachi Y, Kabashima K. Treatment of neuropathic itch possibly due to trigeminal trophic syndrome with 0.1% topical tacrolimus

and gabapentin. Acta Dermato-Venereologica. 2010;**90**:654-655. DOI: 10.2340/00015555-0953

[69] Papoiu ADP, Kraft RA, Coghill RC, Yosipovitch G. Butorphanol suppression of histamine itch is mediated by nucleus accumbens and septal nuclei: A pharmacological fMRI study. Journal of Investigative Dermatology. 2015;**135**:560-568. DOI: 10.1038/jid.2014.398

[70] Wallengren J, Bartosik J. Botulinum toxin type A for neuropathic itch. The British Journal of Dermatology. 2010;**163**:424-426. DOI: 10.1111/j.1365-2133.2010.09783.x

[71] Portugal DM, Ferreira EF, Camões-Barbosa A. Botulinum toxin type A therapy for bilateral focal neuropathic pruritus in multiple sclerosis: A case report. International Journal of Rehabilitation Research. 2021;**44**:382-383. DOI: 10.1097/MRR.0000000000000495

[72] Yamanaka D, Kawano T, Shigematsu-Locatelli M, Nishigaki A, Kitamura S, Aoyama B, et al. Peripheral nerve block with a high concentration of tetracaine dissolved in bupivacaine for intractable post-herpetic itch: A case report. JA Clinical Reports. 2016;**2**:43. DOI: 10.1186/s40981-016-0069-y

[73] Schnell S, Marrodan M, Acosta JN, Bonamico L, Goicochea MT. Trigeminal neuralgia crisis - intravenous phenytoin as acute rescue treatment. Headache. 2020;**60**:2247-2253. DOI: 10.1111/head.13963

[74] Morin CB, Raef HS, Elmariah SB. Neuropathic itch treated with oral cannabinoids: A case series. JAAD Case Reports. 2021;**17**:38-42. DOI: 10.1016/j.jdcr.2021.09.006

Chapter 8

Lipoatrophia Semicircularis

Francisco Urbina and María Isabel Herane

Abstract

Lipoatrophia semicircularis was first described in 1974. It is a rare, but benign and reversible subcutaneous tissue atrophy that mainly affects women. It consists of unilateral or bilateral transverse, semicircular, and depressed bands that appear on the anterior and lateral region of the thighs, with an approximate height of 72 cm from the ground. Its origin has not been clearly established, and several hypotheses have been raised, including circulatory abnormalities, microtraumas, wearing of tight trousers, electromagnetic fields generated in the work environment, or electrostatic charges generated from computers or printers at office works; this "electric factor" would provoque bioelectric changes in the skin, causing direct damage to adipocytes through activated macrophages that release cytokines, including tumor necrosis factor alpha (TNF-α). Isolated cases could be reasonably attributed to the wearing of constricting jeans (in fashion) or microtraumas produced by repetitive leaning against sharp desk furniture, among others. However, the description of multiple cases in the same company or office, a fact reported in several countries, points to an environmental origin. It has also been proposed a multifactorial origin, in which repeated trauma, environmental conditions, and individual electrosensitivity may contribute to the origin of the process.

Keywords: lipoatrophia semicircularis, semicircular lipoatrophia, semicircular lipoatrophy, lipoatrophia, lipoatrophy, fat tissue, adipose tissue, adipocytes, electromagnetic fields, electrostatic charges

1. Introduction

The first three cases of lipoatrophia semicircularis (LS) were described in 1974 [1], with further 19 cases in the following years, also in the German literature [2, 3]. The majority of them were female, with band-like depressions symmetrically affecting the anterolateral aspect of the thighs. The lesions were asymptomatic, with normal overlying skin. Histopathological studies—when done—essentially showed destruction of the fat cells, with atrophy of the fatty tissue. No obvious etiology was demonstrated, but an impaired circulation abnormality of the lateral circumflex artery and repeated local trauma were initially speculated [3].

Since then, another report appeared in the English medical literature in 1981 [4], with another three cases, and subsequently worldwide, including Belgium, France, Italy, Japan, Netherlands, Spain, and the U.S.A., thus being considered an emerging pathology.

Its prevalence ranges from 25 to 37% of office workers, affecting preferably women in their third or fourth decades of life, with women to men rate of about 6/1 [5]. In other series of 74 cases, the prevalence was 16.48%, with an age average of 49.18% [6]. In only one reference a different rate was collected: 55 cases of LS were detected among over 3000 employees in five buildings of a bank in Madrid (Spain); the prevalence was 1.8% and the female/male ratio was 2.3/1 [7].

2. Etiopathogenesis

Some initial isolated reports were reasonably attributed to local trauma, such as the place of support on a thigh of a bucket for collecting vegetables [8], leaning against desks [9, 10], ironing boards, bath's border for washing [11], dresser with mirror [12] or wash bowl while applying make-up [13–15], knocking against the edge of the laundry [16], resting against the counter [17], crossing legs beneath the office desk [18], wearing tight jeans, trousers (**Figures 1** and **2**) or girdle [11, 19–22], or hold-up stockings [23], frequent use of sports tights [24], elastic bands [25] or hosiery with an elastic component [18], or appearance of lesions some weeks after the introduction of a new chair at office work [26]. Interestingly, in the case described after wearing tight jeans [19], the same authors described identical lesions a year after in a sister of their initial patient, who developed them after wearing the discarded jeans [27]. Also illustrative of the action of a mechanical pressure was the fact that the lesions spontaneously disappeared during summer and reappeared at the same place during winter, months in which the affected female patient wore hosiery with an elastic component [18]. However, there are also some reports in which no trauma was identified [4, 28, 29], even with spontaneous resolution of lesions [30].

The lesions affecting forearms have been attributed to tight sleeves of underwear [31] or tucking up skirts and leaning over tables, or hard surfaces [32]. A single case of multilocular and rapidly progressing lesions affecting the trunk and limbs was reported in a 51-year-old adipose patient [33].

There are few descriptions of LS in infancy [34–36], with the exception of a supposed outbreak of cases of LS in a public school in Barcelona, which caused great alarm, but that finally proved to be an epidemic somatoform disorder [37]. In isolated reports, diverse and probably fortuitous cases of LS have been described in association with systemic lupus erythematosus and methotrexate injections [38], after intragluteal injection of benzathine penicillin [39], Behçet disease [40], Sjögren syndrome [41], incomplete CREST syndrome [42], multiple sclerosis [43], segmental dysfunction of the third ipsilateral lumbar root [44] and in relation with a homolateral tibial cyst [45].

The first description of a series of patients working at the same place was done in the Netherlands, after sending letters to 100 employees of the firm in which the initial case was observed [26]. Ten cases were detected, all of them were female, with lesions of LS in their thighs, mostly bilateral. The lesions had appeared several weeks after the chair of their working office was replaced for another with a slightly elevated front edge, which exactly corresponded to the localization of lipoatrophy (higher in short women as they sat further forward on the chair). In all but one patient, the lesions resolved after the chair was changed again. It was also stated that the manufacturer of that chair had received complaints from other companies where the same chair was used.

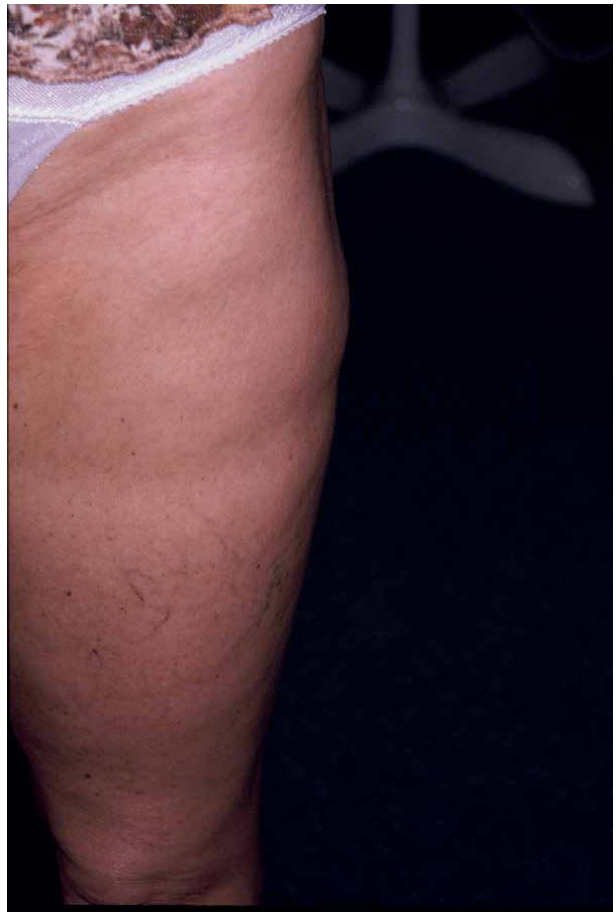

Figure 1.
Typical distribution of LS with two parallel semicircular and depressed bands on the thigh (with permission of John Wiley & Sons Copyright Clearance Center, License No. 5282800364186, April 5, 2022).

Figure 2.
The depressions perfectly match with prominent folds formed by trousers while sitting (with permission of John Wiley & Sons Copyright Clearance Center, License No. 5282800364186, April 5, 2022).

A few years after, a sitting posture or pressure of the seat surface of chairs study was done in office workers, including electromyographic and pressure measurements, and video analysis [46]. Considerable postural differences were detected in the LS group of employees (21 subjects, 3 male and 18 female, 11 of them diagnosed as having LS), including less use of the lumbar support of the chair, static postures while sitting and too high sitting surface of the chair.

Other report of collective cases was done in France in the year 2000, with four index cases affecting young women, most of them working at desks in the same company. The company, a telecommunication enterprise, had recently moved to a new office with salient-edged furniture, all desks measuring 70 cm high and 1 cm thick. The active and dynamic young staff often stand up leaning on their desks to exchange files with colleagues sitting in front. Having this data, 58 out of 65 employees were examined: a total of 18 cases of LS were detected, 15 cases with bilateral depressions of their thighs, affecting 12 women and 6 men; the height of the lesions was constant and it was the same as the height of the desk, 70 cm [47]. Similarly, a year before, seven cases were reported from London (one man and six women working at the same office) in which the most logical explanation for the origin of lesions was repetitive trauma on their highs produced by the sharp edge of the desks [48]. Other 55 cases of LS were detected in a Spanish company from a total cohort of 3055 employees [49]. A case–control study was done, including 39 females and 16 males; all lesions were located on the thighs. Only female sex and leaning the thighs over the edge of a table were the two variables that showed a statistically significant relation with LS after logistic regression with x^2 adjusted for age and sex. No statistically significant relationship was found with weight, height, body mass index, wearing jeans, clothing fibers, or autoimmune diseases.

The outbreak of cases, first in a Belgian bank insurer [50], and later in Barcelona (Spain) [51] added enough reasons for considering an environmental origin. Belgium cases presented after bank employees moved to a new building equipped with new furniture and data cable but kept most computer equipment; 6 months later 135 individuals had developed LS, reaching 900 cases in a period of about 8 years. Brussels cases finally involved 1300 office workers in a bank over a 12-year period, and the cases from Barcelona reached 1137 subjects from February 2007 to October 2008 [51]. Concomitant series of patients began to appear, adding new information to the process. In that sense, seven cases of LS (six women and one man from a total of 16 workers equally distributed by sex) were reported after an enterprise made a building reform [52]. The cases of LS appeared between 6 and 8 months after using the new installations. The median age was 39 years, and the lesions were bilateral in three cases and unilateral in four. The lesions were located on their thighs, between 72 and 74 cm up from the floor. Environmental working conditions were analyzed. Relative humidity varied from 32 to 45%; magnetic and electrical field measures were not optimum. As corrective measures, the humidity was raised to 55%, chairs were changed to optimal ergonometric features, electrical resistance, and ground-mass electrical discharge from metallic structures were improved. After 12 months, clinical and echographic evaluations were performed: four patients had completely improved and three had recovered between 40 and 70% of the adipose lost.

Small series of cases have been reported intermittently, describing female office employees [53], sometimes working at "intelligent buildings" or over metallic desks equipped with computers [54], or affecting males sharing the same working desk [55].

With hundreds of affected patients, it became obvious that LS was office-job related, occurring preferably in female administrative employees, about 6 weeks or more after moving to a new "intelligent" or renovated building; these were equipped with modern-design furniture (chairs and desks), where personnel worked in proximity with numerous electric devices equipped with new data cables, such as computers, printers, and telephones among other. Thus, an electromagnetic theory was outlined, but without discarding that mechanical pressure may act as a facilitating factor [56]. It was detected that electric fields beneath the desks were higher than the normal background; also, a higher superficial electric resistance on working tables and desktop devices was noticed, resulting in an electrostatically charged desk. Consecutively, after coupling with a conductor (employee thighs, 72 cm up from the floor) a discharge was produced on that zone. A dry atmosphere from air conditioning and a low environmental humidity add favorable factors for electrostatic discharges. Therefore, LS may be produced by activated macrophages through electrical stimulation. Macrophages release cytokines, including tumor necrosis factor alpha (TNF-α), provoking direct damage of adipocytes. New chairs may be a contributing factor, acting by compression pressures and push-up forces on the posterior zones of the thighs, thus inducing a reduction of anterior blood flow which could make fatty tissue more vulnerable [56]. In further publications, the same authors in a step-by-step analysis of all presumed causes of LS, conclude as a hypothesis that it originates from a high electric field between the desk and the legs of the individual and that electrostatic discharges are not necessarily involved [57]. They also point out that some people may be more sensitive than others, employing the term "electro-hypersensitivity." In another *in vitro* study, they used the alkaline comet assay to investigate DNA damage in different cells exposed to strong electric currents. They found that adipocytes were more vulnerable, presenting more DNA damage than other cells, including macrophages and white blood cells. In a second experiment, it was found that the blood of LS patients showed statistically significant DNA damage in white cells after electrostimulation, in contrast with controls without LS [58].

All the electric parameters of the skin (potential energy, impedance, electric energy conservation, and resistance) are susceptible to be influenced by electric fields, with biological repercussions [59]. Electroactivation of macrophages has been reported *in vitro* through several frequencies of electromagnetic fields [60]. It has also been demonstrated that exposure to weak power-frequency, magnetic fields can adversely affect the lipogenic process; by means of an intermittent exposure to a 50 Hz magnetic field of 100 μT for 42 hours, it was observed a significant reduced cytoplasmatic lipid content of human adipose tissue stem cells [61]. In a preliminary experimental study *in vitro*, the same investigators reported the potential action of weak magnetic fields on adipocyte differentiation, with a significative descent of fatty acid synthesis and inhibition of mechanisms involved in adipocyte differentiation; magnetic field exposition induces changes at intracellular signaling pathways through blocking of p-ERK1/2 (extracellular signal-regulated kinase 1 and 2), inhibiting the expression of the differentiating factor PPARγ (peroxisome proliferator activator receptor-gamma) necessary for the progression of adipocyte differentiation [62]. All these findings support the hypothesis that magnetic fields may be involved in the origin of LS.

On the other hand, other authors have concluded that electrostatic charges, but not electromagnetic ones are mainly involved in LS [63]. In a company of 390 workers, 42 women had lesions of LS, mostly located on the anterior thighs. A technical study of the building was performed, where no abnormal electromagnetic

measurements were found. On the contrary, electrostatic findings and occupational behaviors were found to be relevant. Fifteen patients suffered discharges after touching objects, 14 wore pants and 12 synthetic fibers among other clothing types. All furniture was appropriately grounded and showed no electrostatic charges, while chairs did. No electrostatic accumulation was found in screens and carpeted floors, but certain footrests, the output of printers, and printed sheets from laser printing and copiers were electrostatically charged. Environmental relative humidity was closer to 45%. The sum of all these factors, favored by the common use of footwear containing rubber or synthetic soles, clothing with silk, rayon, wool, or synthetic fibers, facilitate static charge accumulation; this usually discharges to the ground in those areas with higher contact pressure, especially through contact with the desk, a phenomenon that occurs several times during office work. This area is the anterior part of the highs, especially in women wearing pants that are more adjusted at this zone, and also acting on a fatty tissue different from males. A quite interesting observation was the fact that two cases presented with lesions about 10 cm above the knees, in contrast with the more common location on the thighs, 72 cm up from the floor; they were the only two employees who regularly wore skirts, in which their end parts coincided with the location of lesions of LS. They also concluded that people at risk were mainly women wearing synthetic clothes, in special short-sleeved shirts, pants, and footwear with rubber soles. Men infrequently wear adjusted clothes and preferably wear long-sleeved shirts, which facilitates dispelling the electrostatic charges through the desk, bypassing their bodies [63].

A recent study was done between 2018 and 2021 comprising 449 office workers from the same public institution at different buildings in Barcelona (Spain) [6]. The prevalence was 16.48%, with 74 cases detected (71 women and 3 men). Most of them were between their 40s and 50s, with the majority of lesions located on the thighs. With 80% of employees working from home ("teleworking") during the peak of Covid19 pandemic between 2020 and 2021, only 23% showed the disappearance of LS lesions, which was not statistically significant. No clear reason was found, but it was suggested that perhaps the same working conditions were present at home. Body mass index was also not relevant in the disappearance of lesions.

3. Clinical findings

LS is characterized by depressed areas on the skin surface, with distribution in long, horizontal, and generally symmetric bands located on the anterolateral aspects of both thighs in 89.5% of cases, and usually located at 72 cm from the floor, representing the usual height of office desks. Interestingly, in the case of a very tall worker (1.95 m height) who elevated 20 cm on the table of his desk for recurrent lumbalgia, the depressed band appeared at 92 cm from the floor [64]. Similarly, in a series of 10 cases, shorter women had higher lesions up the thighs [26].

The lesions are flesh-colored, barely visible in incident light, and usually asymptomatic (85.5%) [65]. Depressions are semicircular, transverse, often as bilateral and symmetrical bands, 5–20 cm long, 2 cm in width, 1–5 mm in depth [66], and no pigmentation is present. When more than one is present, they appear in a parallel arrangement. The overlying skin is normal and there is no history of preceding inflammation.

Lesions are usually, but not always asymptomatic. When present, local symptoms are mainly described as pruritus (sometimes a week before lesions appear) [66], tired

and heavy legs, paresthesia, cramps or pain (mainly overnight) spontaneous and/or after exercising. In a minimal percentage of cases, general symptoms have been reported, including asthenia, myalgia, and headache. However, in a case series from Barcelona, 26 patients from a total of 34 (76.4%) presented accompanying symptoms: the most frequent sensation of cramps when in contact with metallic objects in the office (like door handles), and heavy legs [67].

No associated features are seen, and distal edema has not been described.

It mainly affects women in their 20s or 30s [22]. The differences observed in the female-to-male ratio (6/1) may be due to a greater proportion of subcutaneous fat in females, predisposing to this condition. Physical constitution and hormonal changes during pregnancy may contribute to the development of LS. Women as well are more likely to present to a medical practitioner with this condition because of cosmetic concerns [22].

The median time for the development of the lesions is 2.5 months. Lesions disappeared spontaneously over a ranging period of time from 9 months to 4 years after some cause is identified and remedial action is taken [22]. Location of lesions has been also described in other areas, such as posterior and inside thighs, trunk, or upper limbs [65].

3.1 Classification based on diagnostic criteria

Recently, Bru-Gorraiz et al. [65] have proposed a classification of LS based on clinical features:

Type I. Typical LS: Bilateral and symmetrical lesions involving the anterior or anterolateral surface of the thighs. Horizontal bands with length at least three times the width.
Type $I_{u.}$ Unilateral LS: Similar to type I, but unilateral.
Type II. LS in bands on the lower limbs. Length of lesions is at least three times the width.
- II a. Atypical location of LS like inside thighs, posterior surface of thighs, and other locations.
- II b. Atypical distribution of bands (vertical and oblique).

Type III. Nonspecific lipoatrophy.
- III a. Other locations (hips, face, upper limbs, and abdomen).
- III b. Other morphology (round and oval). Length is two times the width.

Clinical outcomes are more favorable in the first two groups where 76% of patients showed total or partial improvement of the lesions, *versus* 25.8% of the last two groups [65].

4. Diagnosis

The diagnosis is essentially clinical, considering the presence of bands related to the height of furniture or related to repeated micro traumas. These bands can be visible or palpable.

Laboratory exams or complementary investigations are not necessary for this diagnosis, except to establish differential diagnosis in patients with suspected connective tissue disorders. Antinuclear antibodies, anti-DNA, anti-SCl-70, C3 and C4

complement fractions, rheumatoid factor, and other routine blood, and biochemistry analysis have always been normal when done.

However, in 2013 a case–control study was done in 21 cases of LS from Madrid [68], in which serum adipokines (leptin, chemerin, and vaspin) and high sensibility C-reactive protein (hs-CRP) were analyzed. Statistically significative differences were found in LS cases, with raised levels of hs-CRP and leptin, and low chemerin. The authors conclude that there is an underlying inflammatory process in LS, affecting adipocyte differentiation. Leptin is the main adipokine; its functions include energy homeostasis and also stimulation of lipolysis; chemerin participates in producing mature adipocytes. No further publications have been done in this respect.

5. Histopathological findings

Regarding histopathology in cases of the so-called idiopathic localized lipoatrophy [69], two patterns have been described, involutional and inflammatory. The most common is the involutional type, in which adipose tissue is present but abnormal. Lobules of fat are well-defined, various sized, varying from small to medium-sized lipocytes on a background of hyaline material. Lipocytes are in general smaller than normal, have a more prominent nuclei and often appear with a rounder shape. The lipocytes appear embedded in hyaline material varying, from sparse to abundant. Capillaries are numerous. In some cases, the involutional changes are more evident at the periphery of the lobule and look normal toward the center. Individual mononuclear inflammatory cells are occasionally seen. Different staining show scattered, fine, curled elastic fibers within the lobules in the hyaline zone. Focal mucin-positive cells can be seen in the perivascular location in some cases. On the other hand, the inflammatory pattern shows normal appearing lipocytes, a normal vasculature, and scattered aggregates of lymphocytes, histiocytes, and plasma cells on a background of hyaline degeneration in broad areas of the fat, similar to lupus panniculitis or traumatic panniculitis [69].

In LS most patients have refused biopsies. When done, these have essentially shown a partial loss of fat, sometimes replaced by new collagen [30], and absence of panniculitis signs. In one case a nearly complete loss of adipose lobules was reported, without signs of inflammation or fibrosis [70]; other cases have shown loosely dispersed fat lobules with medium-sized adipocytes [14], decreased size of adipocytes with intermingled eosinophilic and hyaline material and some histiocyte and lymphocyte infiltration [20, 40], mild accentuation of interlobular septa with atrophy and centrilobular fibrosis of some adipocytes without inflammation [23], hemorrhage in the fat tissue compatible with panniculitis [16], complete loss of adipose tissue [34] and involutional adipocytes, numerous capillaries, and a sparse lymphohistiocytic infiltrate with calcification [36].

The immunohistochemical study has been done only in one case, showing adipocyte positivity for vimentin and S-100 protein, with few positive histiocytes for CD68 [20].

It has been questioned if three histopathological patterns exist (involutional, inflammatory, and "normal") or if they represent different stages of localized lipoatrophy depending on the time in which biopsies are taken [14].

Histopathological features in some cases have shown normal findings [41, 71].

5.1 Ultrastructural features

In a report of two cases, adipocytes abnormalities, fibrillogenesis, and sclerosis were noticed in one case, while the other with persistent lipoatrophia showed rarefaction of collagen fibers [11]. An electron microscope study was also done on one patient with LS and Behçet disease [40]. The images showed fat-laden macrophages with lysosomes, numerous fat droplets, and electron-dense granules in the cytoplasm. Lymphocytes were found in the detachment produced between the fat and basal lamina. A complete loss of the basal lamina beneath the adipose layer was described. The cytoplasm of the fat cells was vacuolated.

6. Other studies

Ultrasound of the affected zone is not always conclusive, sometimes with negative findings, although visible and palpable lesions exist [41, 66]. On other occasions, it has shown an important subcutaneous loss [72]. Ultrasound imaging of the semicircular depression has revealed a preserved epidermis and dermis, with a focal decreased thickness of the subcutaneous tissue [71, 73], or slight compression of the adipose tissues [14] in the same axis of the visible site of atrophy. An increased echogenicity of the subcutaneous tissue can be present [74]. Illustrative findings of a case are shown in **Figure 3**.

High-frequency longitudinal sonography shows similar findings, with a reduced thickness of subcutaneous tissue and a slightly fibrotic component [25].

Magnetic Resonance Imaging (MRI) has shown a loss of the superficial subcutaneous adipose tissues in four cases. No alteration in the thickness of subcutaneous septa was found and fat lobules were normal in size and shape [31, 53, 75, 76]. No alterations were found in subjacent muscles in another report, and the focal atrophy of subcutaneous fatty tissue was not replaced by fibrous or other types of tissue [72]. In other cases, the subcutaneous tissues of the thighs were normal, but the muscles under the affected area were slightly indented [22]. Sometimes the subcutaneous tissue and muscles have shown normal findings [15].

Electromyography has been normal when done in a few cases [31, 32, 47, 76]. Nevertheless, surface electromyography measurements of the quadriceps in six subjects with LS and five without, showed a more constant static pattern in muscle activity in LS individuals, contrasting with a more dynamic pattern in those without LS, thus confirming that LS people adopt more static postures at office work [46].

Ultrasound and MRI are useful to differentiate lipoatrophy from other alterations of fat tissues. Panniculitis shows thickening of interlobular septa with smaller fat lobules. In lipoatrophy interlobular septa and fat lobules are normal and a loss of superficial fat tissue is present [20].

7. Differential diagnosis

Cellulitis is perhaps the most common finding in women that can provoke some difficulties in the clinical diagnosis of LS. To differentiate them clinically, it is helpful to stretch the skin with the fingers, and try to detect depression, which is not a feature of cellulitis [6]. Another probably common form of localized lipoatrophia is

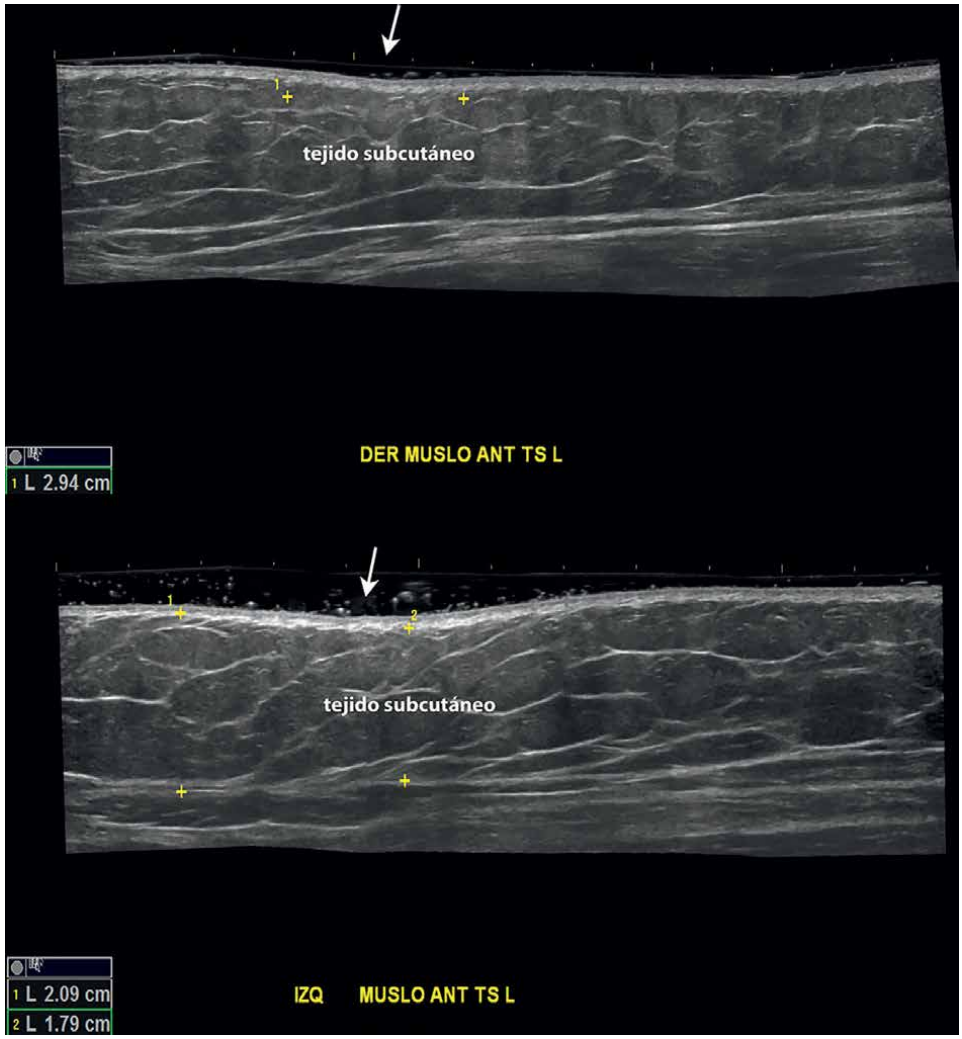

Figure 3.
Ultrasound of semicircular lipodystrophy in both thighs. Slight atrophy and heterogeneous echostructure of the subcutaneous cellular tissue in both thighs. The subcutaneous echostructure alteration predominates in the superficial segment (top image; right side). The image at the bottom shows the measurement of the subcutaneous thickness of the affected area (2.09 cm) compared to the adjacent segment that is toward the head (1.79 cm). The arrows point out the segments of subcutaneous atrophy (Image courtesy of Dr. Ximena Wortsman).

the so-called "leg crossers' dimple," which affects patients with a long history of leg crossing. The lesion consists of an indentation on the leg, which correlates with the site where the patella rests over the other knee. It is more common in females and it is probably caused by repeated local pressure that may destroy adipocytes. Some cases may present with lichenification of the zone, perhaps related with recurrent rubbing in patients that frequently jitter while crossing legs ("agitated leg crossers") [77].

In infancy, there are several acquired conditions that clinically may present with linear circumferential or partially circumferential lesions associated with trauma, or because of wearing elastic bands of socks or pantlegs [78]. They produce inflammation in the fat and dermis and hyperpigmentation, plus raised or atrophic bands. At this age, other infantile curvilinear lesions should be considered, such as child abuse,

amniotic band syndrome, linear and whorled hyperpigmentation, and incontinentia pigmenti. All these clinical pictures differ from LS in clinical history, histopathological findings, and presence of hyperpigmentation.

Partially localized lipoatrophy has been described in connection with subcutaneous, intramuscular, or intra-articular injections. Treatment with methotrexate [38], corticosteroids, insulin (prior to the development of purified insulin in the 1970's) [79], and benzathine penicillin [39, 80] have been associated with lipoatrophy. Its appearance is common in children, and varies from simple pitting areas of the skin to large and disfiguring athrophies. The trauma of injection rather than the medication injected is mainly the cause of the panniculitis. The lesions appear only on injection sites, which rarely adopt a band distribution, and a loss of subcutaneous fat is present. Depressed cutaneous lesions resulting from insulin injection spontaneously disappear within 1–3 years. Other agents implicated in localized lipoatrophy are vasopressin, human growth hormone, iron dextran, and diphtheria–pertussis–tetanus (DPT) vaccine.

In patients with autoimmune disorders, localized subcutaneous atrophy of the extremities can be seen. Connective tissue diseases represent a predisposing factor for the development of bands or rounded atrophic lesions. LS should be differentiated from other atrophies in patients with lupus erythematosus, morphea, panniculitis, and lupus panniculitis, which may affect children and adults. In morphea the plaques are pearly and whitish, the skin is indurated and sometimes an erythematous halo is visible [81]; this is never found in LS. Some cases adopt a linear distribution, characterized by single and unilateral streaks of cutaneous induration that may involve deeper structures like dermis, subcutaneous tissue, and occasionally muscle and underlying bone. Lupus lesions tend to be localized in arms, face, and buttocks, mainly as deep nodules of a long evolution, covered with normal skin or lesions that evolve to atrophic scars during regression [31]. Lupus panniculitis lesions are usually located in the upper body and present with a scarring appearance [67]. Factitious panniculitis is clinically visible as recurrent episodes of nodules mainly located in the extremities, associated with other factitious lesions; histopathological findings show granulomatous panniculitis.

Underlying autoimmune diseases -if present- are responsible for a protracted course. Localized lipoatrophy associated with recessive dystrophic epidermolysis bullosa has also been reported [82].

Other causes of localized lipoatrophy include treatment with oral retroviral drugs in HIV/AIDS patients and association with lyme disease (*Borrelia burgdorferi* infection).

Two other clinical pictures of localized band lipoatrophy that may resemble LS have been described: annular lipoatrophy and annular lipoatrophy of the ankles.

The first entity was described by Ferreira–Marques in 1953 [83], affecting the forearm of a woman, with further two other cases reported by Bruinsma in 1967 [84]. In annular lipoatrophy, a circular and depressed pseudosclerodermic band of 1 cm wide and 0.5–2 cm deep around the arm is described. It appears mainly between 40 and 70 years old, it is monolateral, with a maximum width of 1 cm, and might be associated with pigmentation. The band is preceded by swelling and tenderness of the entire limb and fever in the original case. Distal swelling of the arm plus neuralgia and arthralgia pain associated with muscle weakness are additional features. Bruinsma's first case was also associated with myopathy. The band was persistent for more than 20 years. Histopathological studies showed loss of the subcutaneous fat replaced by strands of connective tissues and polyarthritis with venous thrombi.

Annular atrophy of the ankles was reported initially in 1970 and later in 1975 [85, 86]. The lesions appear in the ankles but can also affect feet and legs; most cases have been reported between 6 and 35 years old, with bilateral distribution and wider than LS and lipoatrophia annularis, ranging from 9 to 11 cm. The skin appears normal, although edema before atrophy was described in one case. No changes in color or consistency occur and local symptoms or muscle involvement are absent. Histopathological study shows an early inflammatory stage, with mononuclear infiltration in the subcutis, neoformation of blood vessels, and replacement of adipose lobules with connective tissue.

8. Treatment

There is no specific medical treatment for LS. It must be kept in mind that preadipocytes remain present at lipoatrophic lesions and new adipocytes make recovery always possible [56]. Most cases regress with time in variable periods, ranging from weeks to months, (sometimes spontaneously [30]) or even years. Some authors reported regression lapses between 9 months to 4 years [17], while others described 93% of clinical regression after 6 months (complete 62% and partial 32%) [87]; in other reports of 30 cases, 75% showed a favorable evolution after 3 months, with total regression of lesions in 43.4%, partial in 30.4%, and without changes in 26.2% [88]. If a predisponent factor is detected and avoided, impairment will be faster [12, 13, 15, 16, 26]. In a series of seven cases, the time taken for lesion improvement varied between 2 weeks and 4 months after stopping leaning against the desks or after smooth barriers were fitted along the edges of the tables [48]. However, lesions may also disappear without following any specific indication [30], or without being discovered the origin of the mechanical trauma [17]. Spontaneous remissions have been observed in 24 workers after holidays away from their workplace [63], or after stopping working due to pregnancy leave, absence from work for long periods, or on retirement [50].

8.1 Preventive measures and corrective actions

Preventive measures and corrective actions [7, 51, 57, 65, 66, 87, 89] are crucial for the treatment of this condition, and can be divided into distinct areas:

8.1.1 Environmental

- Maintain an adequate environmental humidity between 50 and 55% at the office and throughout the building.
- Install electrical ground connection for desks in order to remove electrostatic charges.
- The edges of the desk must be made of isolating material.
- Avoid electric cables beneath desks, laying them on the floor at the back of the desks.

- Biweekly application of anti-electrostatic carpet finish.
- Placement of electrostatic discharge mats in common passageways.
- Apply anti-electrostatic products (spray or varnish) on surfaces prone to retaining electrostatic charges.
- Apply anti-electrostatic products daily when cleaning the floor.
- Avoid metallic furniture and metallic chest of drawers.
- Avoid trays for the computer keyboard, which should be located on top of the desk.
- Remove the computer from the main desk and place it on a side table.
- Avoid material and devices that may accumulate static electricity.
- Installation of ionisators to freshen air and clean dust may be helpful.
- If possible, replacement of entire cabling with ferrite cables, which reduce electromagnetic fields.

8.1.2 Staff

- Avoid wearing tight clothes when sitting for long periods of time.
- Avoid wearing synthetic clothes.
- In the case of upper limbs avoid compressive underwear or tucking up skirts.
- Avoid wearing rubber soles on shoes and avoid shuffling.

8.1.3 Ergonomic

- Use suitable chairs and adjust their height to avoid contact of the thighs with the desk.
- Work on desks with rounded and wide edges.
- Avoid micro traumatisms on the thighs (not leaning against desks, sitting at borders of the tables, or others).
- Adopt correct sitting postures and do not rest feet on the legs of the chair, supporting the back as much as possible on the back of the chair.
- Get up during work and walk a few steps at least every hour.
- Avoid repeated rubbing on the chair.

8.2 Laboral protocols

Finally, if many cases are detected at the same office building, LS should be considered as an environmental laboral factor or office staff risk that must be evaluated by a multi-disciplinary team (medical staff, Departments of occupational health, occupational risk prevention, morphological sciences, ergonomics, and biomechanics, etc.), following some of the diverse protocols established in many cities, such as Barcelona [90], Madrid [91] Basque country [92] and other. Their main purpose is the recognition of the problem, giving behavior guidelines to technical personnel and companies, and preventing the appearance of new cases. They mainly include two sections: a medical action protocol and a technical one, which evaluates job conditions. Medical protocols should include diagnosis, clinical data and clinical examination, case follow-up, and active search for other possible causes. The technical part includes taking measurements at work offices, including electrical installations, furniture (design, materials and height, geometry of edges and collection of cables on desks, materials of chairs, and footrests), installations of all types of equipment (computers, printers, scanners, photocopiers, and telephones), type of floor (material and use of carpets), ventilation system, air conditioning and humidification, personal posture, and clothing habits. Electrical measurements must include electric and magnetic fields, electrostatic charges (in different conditions of relative humidity), as well as diverse electrical parameters (current-voltage, frequency, and resistance of grounding). Both protocols must be coordinated with the company, and once the cases have been established, all information obtained on the process and causes must be offered to the staff, establishing the necessary prevention and treatment measures indicated above.

9. Conclusions

The origin of LS is probably multifactorial, in which a synergy occurs between mechanical and electrical environmental factors, common in modern buildings. Currently, there are two main hypotheses (perhaps also acting together): electromagnetic (produced by computer equipment, electrical appliances, and wiring) and electrostatic (produced by continuous friction between chairs and synthetic clothing, leading to the accumulation of electrostatic charges which are subsequently released through contact of the thighs with grounded furniture, such as the desk). However, in many single reported cases or in small series of patients there was no office exposure, and the lesions could be reasonably attributed to other diverse traumatic factors, which at least are thought to be contributors. Besides, an individual electrosensitivity, in which many other environmental factors participate (humidity, desk materials, sitting posture, and synthetic clothing, among others) may play a determinant role in the development of LS.

Conflict of interest

The authors declare no conflicts of interest.

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References

[1] Gschwandtner WR, Münzberger H. Lipoatrophia Semicircularis. Linear and circular atrophy of the subcutaneous fat in the extremities. Der Hautarzt. 1974;**25**(5):222-227

[2] Gschwandtner WR, Münzberger H. Lipoatrophia semicircularis. Wiener Klinische Wochenschrift. 1975;**87**(5):164-168

[3] Bloch PH, Runne U. Lipoatrophia semicircularis in the male. Coincidence of arterial variations and micro-traumas as a possible disease cause. Der Hautarzt. 1978;**29**:270-272

[4] Karkavitsas C, Miller JA, Kirby JD. Semicircular lipoatrophy. The British Journal of Dermatology. 1981;**105**:591-593. DOI: 10.1111/j.1365-2133.1981.tb00805.x

[5] Díaz Sarmiento R, Peña Rodríguez R, Asúnsolo del Barco A. Lipoatrofia semicircular: Una revisión sistemática de la literatura. Med Segur Trab (Internet). 2011;**57**(222):77-94

[6] Borin-Bertuzzi M, Alonso-Iglesias O, Borin-Arámbulo MA. Lipoatrofia semicircular en trabajadores de oficinas públicas. Medicina y Seguridad del Trabajo. 2021;**67**(263):88-98. DOI: 10.4321/s0465-546x2021000200002

[7] Reinoso Barbero L, González Gómez MF, Díaz Garrido R, Piñaga SM. Lipoatrofia semicircular: ¿otras medidas eficaces? Gaceta Sanitaria. 2012;**26**(4):387. DOI: 10.1016/j.gaceta.2012.02.006

[8] Bordel-Gómez MT. Lipoatrofia semicircular unilateral. Piel. 2006;**21**(8):414-415

[9] de Rie MA. Impressions in the thighs; semicircular lipoatrophy. Nederlands Tijdschrift voor Geneeskunde. 1998;**142**(14):796-797

[10] Presta F, Del Giglio M, Girolomoni G. Lipoatrophia semicircularis: A case report and review of the literature. Giornale Italiano di Dermatologia e Venereologia. 2016;**151**(4):441-444

[11] Schnitzler L, Verret JL, Titon JP. Lipoatrophia semi-circularis of the thigh. Annales de Dermatologie et de Vénéréologie. 1980;**107**(5):421-426

[12] Chaabouni R, Bahloul E, Sellami K, Turki H. Un creux sur les cuisses. La Revue de Médecine Interne. 2021;**42**(7):515-516. DOI: 10.1016/j.revmed.2020.12.006

[13] Hodak E, David M, Sandbank M. Semicircular lipoatrophy-A pressure induced atrophy? Clinical and Experimental Dermatology. 1990;**13**:464-465. DOI: 10.1111/j.1365-2230.1990.tb02147.x

[14] Sigl J, Lázar M, Tittes J, Wendt J, Kancz S, Kiefer FW, et al. Lipoathrophia semicircularis-A distinct entity? International Journal of Dermatology. 2020;**59**(11):e385-e387. DOI: 10.1111/ijd.15138

[15] Anderson BE, DeCapite T. What is your diagnosis? Semicircular lipoatrophy. Cutis. 2007;**80**(464):477-488

[16] Nagore E, Sánchez-Motilla JM, Rodríguez-Serna M, Vilata JJ, Aliaga A. Lipoatrophia semicircularis-A traumatic panniculitis. Report of seven cases and review of the literature. Journal of the American Academy of Dermatology. 1998;**39**(5pt2):879-881. DOI: 10.1016/s0190-9622(98)70371-8

[17] Gómez Espejo C, Pérez-Bernal A, Camacho-Martínez F. A new case of semicircular lipoatrophy associated with repeated external microtraumas and review of the literature. Journal of the European Academy of Dermatology and Venereology. 2005;**19**:459-461. DOI: 10.1111/j.1468-3083.2005.01092.x

[18] Arunachalam M, Betti S, Galeona MI, Grandi V, Difonzo E. Is lipoatrophia semicircularis a rare disease? Report of three cases. Australasian Journal of Dermatology. 2014;**55**:212-213. DOI: 10.1111/ajd.12049

[19] Mascaró JM, Ferrando J. Lipoatrophia semicircularis: The perils of wearing jeans? International Journal of Dermatology. 1982;**21**(3):138-139. DOI: 10.1111/j.1365-4362.1982.tb02058.x

[20] Zafra-Cobo MI, Yuste-Chaves M, Garabito-Solovera E, Santos-Briz A, Morán-Estefanía M, Unamuno-Pérez P. Lipoatrofia semicircular inducida por presión. Actas Dermo-Sifiliográficas. 2008;**99**:396-398. DOI: 10.1016/S0001-7310(08)74699-4

[21] Herane MI, Urbina F, Sudy E. Lipoatrophia semicircularis: A compressive lipoatrophy consecutive to persistent mechanical pressure. The Journal of Dermatology. 2007;**34**:390-393. DOI: 10.1111/j.1346-8138.2007.00295.x

[22] Hinogami H, Sakai H, Shirabe H. Case of semicircular lipoatrophy: Relation between its characteristic distribution and anatomical muscle structure. The Journal of Dermatology. 2014;**41**:749-751. DOI: 10.1111/1346-8138.12568

[23] Bertolani M, Mele S, Manuguerra R, Dominici MM, Lotti T, Feliciani C, et al. Comment on "Lipoatrophia Semicircularis-A distinct entity?". International Journal of Dermatology. 2021;**60**(10):e421-e422. DOI: 10.1111/ijd.15600

[24] Rex J, Ribera M, Bielsa I, Ferrándiz C. Lipoatrofia semicircular de los muslos. Actas Dermo-Sifiliográficas. 2000;**91**(6):285-287

[25] Isoletta E, Vassallo C, Messina M, Solbiati LA, Brazzelli V. An old diagnosis resurfacing in times of lockdowns: A case of lipoatrophia semicircularis induced by elastic band use. International Journal of Women's Dermatology. 2021;**7**:828-829. DOI: 10.1016/ijwd.2021.03.011

[26] De Groot AC. Is lipoatrophia semicircularis induced by pressure? The British Journal of Dermatology. 1994;**131**(6):887-890. DOI: 10.1111/j.1365-2133.1994.tb08595.x

[27] Mascaró JM, Ferrando J. The perils of wearing jeans: Lipoatrophia semicircularis. International Journal of Dermatology. 1983;**22**:333. DOI: 10.1111/j.1365-4362.1983.tb02153.x

[28] Bachmeyer C, Haddad A. Lipoatrophie semi-circulaire des cuisses. Presse Médicale. 2011;**40**:980-981. DOI: 10.1016/j.lpm.2011.02.020

[29] Mallett RB, Champion RH. Lipoatrophia semicircularis. The British Journal of Dermatology. 1989;**121**:94-95. DOI: 10.1111/j.1365-2133.1989.tb06003.x

[30] Betti R, Urbani CE, Inselvini E, Crosti C. Semicircular lipoatrophy. Clinical and Experimental Dermatology. 1992;**17**:382-383. DOI: 10.1111/j.1365-2230.1992.tb00241.x

[31] López-Villaescusa MT, Rodríguez-Vázquez M, Vera-Barón R, Pardal-Fernández JM, Martínez-Martínez ML, Faura-Berruga C. Lipoatrofia semicircular de brazos.

Piel (Barc). 2013;**28**(9):514-516. DOI: 10.1016/j.piel.2013.03.021

[32] Pardal-Fernández JM, López-Villaesclusa M,Rodríguez-Vázquez M. Falsa amiotrofia de los antebrazos por lipoatrofia semicircular. Revista de Neurologia. 2013;**56**(8):443-444. DOI: 10.33588.rn.5608.2013035

[33] Thiele B, Ippen H. Multilocular progressive lipoatrophia semicircularis. Der Hautarzt. 1983;**34**(6):292

[34] Ayala F, Lembo G, Ruggiero F, Balato N. Lipoatrophia semicircularis. Report of a case. Dermatologica. 1985;**170**(2):101-103

[35] Franzese A, Di Maio S, Di Martino L, Mantovani MP, Maglione F, Balato N. Primo caso di lipoatrophia semicircolare in etá pediatrica. Minerva Pediatrica. 1987;**39**(23-4):1177-1180

[36] Spencer DM, Parks AJ, Sydor LC, Pellegrini AE. Yellow nodule within an atrophic thigh patch. Localized lipoatrophy, semicircular type. Archives of Dermatology. 1994;**130**(8):1056-1057. DOI: 10.1001/archderm.130.8.1056

[37] Rius C, Baselga E, Tizón J, Fuentes P, Muñoz-Garza FZ, Roigé G, et al. Investigation of a suspected oubreak of lipoatrophia semicircularis in children. Medicina Clínica (Barcelona). 2017;**149**(3):101-106. DOI: 10.1016/j.medcli.2017.01.032

[38] Haas N, Henz BM, Bunikowski R, Keitzer R. Semicircular lipoathrophy in a child with systemic lupus erythematosus after subcutaneous injection with methotrexate. Pediatric Dermatology. 2002;**19**(5):432-435. DOI: 10.1046/j.1525-1470.2002.00201.x

[39] Kayikcioglu A, Akyürek M, Erk Y. Semicircular lipoathrophy after intragluteal injection of benzathine penicillin. The Journal of Pediatrics. 1996;**129**(1):166-167. DOI: 10.1016/s0022-3476(96)70208-1

[40] Cho SB, Bae BG, Kwon JE, Park JM, Bang D. Ultraestructural features of lipoatrophia semicircularis in Behcet's disease. Clinical and Experimental Rheumatology. 2010;**28**(4 Suppl 60): S97-S98

[41] Batalla A, Flórez A, Villamil E, De la Torre C. Lipoatrofia semicircular: Enfermedad relacionada con el edificio o asociación con enfermedad autoinmunitaria? Piel (Barc). 2012;**27**(1):8-10. DOI: 10.1016/j.piel.2011.07.007

[42] Asherson RA, Shoenfeld Y. Annular, semicircular lipoatrophy of the thighs associated with incomplete CREST syndrome: Raynaud's, telangiectasias and esophageal dysmotility. Journal of Clinical Rheumatology. 2003;**9**:129-133. DOI: 10.1097/01.RHU.0000062516.05411.72

[43] Inglés Azorín B, Calonge García ME, Goicoechea García M, Parra Almoguera JA, Fernández A, Vallmitjane Fernández V, et al. Lipoatrofia semicircular: Patología dermatológica poco frecuente en atención primaria. SEMERGEN. 2016;**42**(Espec Congr15):14

[44] Crossman J, Wagner UA, Schmitt O. Lipoatrophia semicircularis – An orthopaedic diagnosis? Zeitschrift für Orthopädie. 1998;**136**(3):278-280. DOI: 10.1055/s2008-1054236

[45] Leonforte JF. Lipoatrophia semicircularis associated with an osteous cyst. Cutis. 1983;**31**(4):428-435

[46] Hermans V, Hautekiet M, Haex B, Spaepen AJ, Van der Perre G. Lipoatrophia semicircularis and the relation with office work. Applied

Ergonomics. 1999;**30**:319-324. DOI: 10.1016/s0003-6870(98)00037-4

[47] Senecal S, Victor V, Choudat D, Hornez-Davin S, Confo F. Semicircular lipoatrophy: 18 cases in the same company. Contact Dermatitis. 2000;**42**:101-102. DOI: 10.1034/j.1600-0536.2000.042002101.x

[48] Gruber PC, Fuller LC. Lipoatrophy semicircularis induced by trauma. Clinical and Experimental Dermatology. 2001;**26**(3):269-271. DOI: 10.1046/j.1365-2230.2001.00812.x

[49] Reinoso-Barbero L, González-Gómez MF, Bélanger-Quintana D, Piñaga-Solé M, Fernández-Fernández M, Garrido-Astray MC, et al. Case-control study of semicircular lipoatrophy, a new occupational disease in office workers. Journal of Occupational Health. 2013;**55**(3):149-157. DOI: 10.1539/joh.12-0269-oa

[50] Curvers B, Maes A. Lipoatrophia semicircularis: A new office disease? 900 cases reported in Belgium. Available from: http://www.sfowler.com/esdjournal/lipoatrophia.htm. [Accessed: May 14, 2022]

[51] Pérez A, Nebot M, Maciá M, Panadés R. An outbreak of 400 cases of lipoatrophia semicircularis in Barcelona: Effectiveness of control measures. Journal of Occupational and Environmental Medicine. 2010;**52**(7):751-757. DOI: 10.1097/JOM.ObO13e3181e80747

[52] Sanz P, Nogué S, Farrús X, Molina JM. Lipoatrofia semicircular en oficinistas. Medicina Clínica (Barcelona). 2010;**134**(3):135-136. DOI: 10.1016/j.medcli.2009.02.030

[53] Caram ME, Bollea Garlatti LA, Torre AC, Bibiloni N, Alcalá Cepeda GM, Galimberti RL. Lipoatrofia semicircular, una patología emergente. Dermatología Cosmética, Médica y Quirúrgica. 2015;**13**(2):113-115

[54] Ángel-Ortega AO, Sierra-Santos L. Lipoatrofia semicircular: 3 casos clínicos. SEMERGEN. 2016;**43**(2):154-155. DOI: 10.1016/j.semerg.2016.05.011

[55] Ribeiro E, Saint-Lezer A, Julliot-Rolland L, Mercié P, Longy-Boursier M. La lipoatrophie semi-circulaire des cuisses: a propos d'un cas. La Revue de Médecine Interne. 2012;**33**:e41-e43. DOI: 10.1016/j.revmed.2011.05.007

[56] Maes A, Curvers B, Verschaeve L. Lipoatrophia semicircularis: An electromagnetic hypothesis. Electromagnetic Biology and Medicine. 2003;**22**:183-193. DOI: 10.1081/JBC-120024627

[57] Verschaeve L, Maes A. Support for the hypothesis that electro-stimulation is responsible for lipoatrophia semicircularis. Medical Hypothesis. 2009;**73**:802-806. DOI: 10.1016/j.mehy.2009.01.058

[58] Verschaeve L, Maes A. In vitro investigations related to the hypothesis that lipoatrophia semicircularis finds its origin in electro-stimulation. Journal of Applied Toxicology. 2009;**29**:478-482. DOI: 10.1002/jat.1430

[59] Flagothier C, Quatresooz P, Pierard G-E. Lipolyse électromagnétique et lipoatrophie semi-circulaire des cuisses. Annales de Dermatologie et de Vénéréologie. 2006;**133**:577-580. DOI: 10.1016/s0151-9638(06)70967-x

[60] Pessina GP, Aldinucci C. Pulsed electromagnetic fields enhance the induction of cytoquines by peripheral blood mononuclear cells challenged with phytohemagglutinin. Bioelectromagnetics. 1998;**19**(8):445-451

[61] Martínez MA, Trillo MA, Cid MA, Paino CL, Úbeda A. Power-frequency magnetic fields inhibits adipogenic differentiation in human ADSC. Cellular Physiology and Biochemistry. 2015;**37**:2297-1310. DOI: 10.1159/000438585

[62] Úbeda Maeso A, Martínez Pascual MA, Cid Torres MA, Trillo Ruíz MA, Paíno Belarrinaga CL. Campos ambientales débiles y lipoatrofia semicircular. Seguridad y Medioambiente. 2011;**123**(31):10-19

[63] Linares-García Valdecasas R, Cuerda-Galindo E, Ramiro Bargueño J, Naranjo García P, Vogelfrang-Gancarz D, Palomar Gallego MA. Semicircular lipoatrophy: An electrostatic hypothesis. Dermatology. 2015;**230**:222-227. DOI: 10.1159/000370045

[64] Reinoso-Barbero L, Díaz R, Piñaga M, Bravo MF. Lipoatrofia semicircular: A propósito de un paciente muy alto. Anales del Sistema Sanitario de Navarra. 2012;**35**(2):313-315. DOI: 10.4321/s1137-66272012000200013

[65] Bru-Gorraiz FJ, Comunión-Artieda A, Bordel-Nieto I, Martin-Gorgojo A. Lipoatrofia semicircular: Estudio y seguimiento clínico de 76 casos en Madrid. España. Propuesta de clasificación. Actas Dermosifiliograf. 2022;**113**:15-21. DOI: 10.1016/j.ad.2021.05.013

[66] Hauva Gröne JJ. Lipoatrofia semicircular, una visión general a una patología laboral emergente en Chile. Cienc Trab. 2013;**15**(47):81-85

[67] Hernández-Ruiz ME, Gelabert ML, Bennássar A, Ferrando J. Lipoatrofia Semicircular. Descripción de una serie de casos. Piel (Barc). 2015;**30**:4-10. DOI: 10.1016/jpiel2014.06.015

[68] Reinoso-Barbero L, Díaz-Garrido R, González-Gómez MF, Olarrea J, Gómez-Gallego F, Bandrés F. Occupational semicircular lipoatrophy associated with serum adipokine abnormalities. Medicina Clínica (Barcelona). 2015;**145**(8):338-340. DOI: 10.1016/j.medcli.2014.12.024

[69] Peters MS, Winkelmann RK. The histopathology of localized lipoatrophy. The British Journal of Dermatology. 1986;**114**(1):27-36. DOI: 10.1111/j.1365-2133.1986.tb02776.x

[70] Rongioletti F, Rebora A. Annular and semicircular lipoathrophies. Report of three cases and review of the literature. Journal of the American Academy of Dermatology. 1989;**20**(3):433-436. DOI: 10.1016/s0190-9622(89)70053-0

[71] Boleira M. Lipoatrophia semicircularis. Journal of the American Academy of Dermatology. 2011;**64**:AB41

[72] Nogué S, Sanz P, Tomás X, Farrús X. Imagen de la semana. Medicina Clínica (Barcelona). 2008;**130**(9):360. DOI: 10.1157/13117362

[73] Wortsman X, Ferreira-Wortsman C. Ultrasound in sports and occupational dermatology. Journal of Ultrasound in Medicine. 2021;**40**(8):1675-1692. DOI: 10.1002/jum.15550

[74] Taleb E, Goldberg I, Sprecher E, Geller S. Semi-circular depression on the leg diagnosed by high-frequency ultrasound. Acta Dermato-Venereologica. 2021;**101**:adv00524. DOI: 10.2340/00015555-3889

[75] Ogino J, Saga K, Tamagawa M, Akutsu Y. Magnetic resonance imaging of semicircular lipoathropy. Dermatology. 2004;**209**:340-341. DOI: 10.1159/000080861

[76] Eker A, Yigitoglu PH, Kaptanoglu AF. The value of magnetic resonances

imaging in localized lipoatrophy. Bezmialem Science. 2019;**7**(3):245-246. DOI: 10.14235/bas.galenos.2018.1903

[77] Kalouche H, Whitfeld MJ. Legs crossers' dimple: A form of localized lipoatrophia. The Australasian Journal of Dermatology. 2006;**47**:253-257. DOI: 10.1111/j.1440-0960.2006.00291.x

[78] Berk DR, Bayliss SJ. Sock-line bands in infancy. The British Journal of Dermatology. 2007;**157**(5):1063-1064. DOI: 10.1111/j.1365-2133.2007.08175.x

[79] Herold DA, Albrecht G. Local lipohypertrophy in insulin treatment. Der Hautarzt. 1993;**44**(1):40-42

[80] Kuperman-Beade M, Laude TA. Partial lipoatrophy in a child. Pediatric Dermatology. 2000;**17**(4):302-303. DOI: 10.1046/j.1525-1470.2000.01759.x

[81] Krafchik BR. Localized morphea in children. Advances in Experimental Medicine and Biology. 1999;**455**:49-54. DOI: 10.1007/978-1-4615-4857-7_7

[82] Nohara T, Fujita Y, Takashima S, Natsuga K, Shimizu H. Image gallery: Multiple localized lipoatrophia in reccesive dystrophic epidermolysis bullosa. The British Journal of Dermatology. 2019;**180**(3):e64. DOI: 10.111/bjd.17356

[83] Ferreira-Marques J. Lipoatrophia annularis; case of a so far not reported disease of panniculus adiposus. Arch Dermatol Syph (Berlin). 1953;**195**:479-491

[84] Bruinsma W. Lipoatrophia annularis, an abnormal vulnerability of the fat ty tissue. Dermatologica. 1967;**134**:107-112

[85] Shelley WB, Izumi AK. Annular atrophy of the ankles. Archives of Dermatology. 1970;**102**(3):326-329

[86] Jablonska S, Szczepanski A, Gorkiewicz A. Lipo-atrophy of the ankles and its relation to other lipo-atrophies. Acta Derm Venereol (Stockh). 1975;**55**(2):135-140

[87] Ortega Díaz de Ceballos A, Cuevas Moreno F, Aguado PE. Lipoatrofia semicircular. Nuestra experiencia dos años después (2007-2009). Med Segur Trab (Internet). 2009;**55**(217):33-40

[88] Cuevas Moreno F, Ortega Díaz de Ceballos A, Aguado PE. Estudio clínico-evolutivo de 30 nuevos casos de lipoatrofia semicircular. La Mutua (Madrid). 2008;**19**:79-83

[89] Mayor Cruells JM. La lipoatrofia semicircular, ¿una nueva enfermedad profesional emergente? DYNA. 2007;**82**(8):450-454

[90] Generalitat de Catalunya (Departament de Treball, Departament de Salut) and Consorci Sanitari de Barcelona. Lipoatrofia semicircular: Protocolo de Actuación 2009. Available from: http://www.trebal.gencat>web>. content>publicacions>imatges>protocol. [Accessed: May 14, 2022]

[91] Biblioteca Virtual. Protocolo de Actuación del IRSST sobre la Lipoatrofia Semicircular. Available from: http://www.madrid.org/ publicamadridculpubli@madrid.org. [Accessed: May 14, 2022]

[92] Osalan (Instituto Vasco de Seguridad y Salud Laborales) y Gobierno Vasco. Guía para la actuación de los servicios de prevención ante casos de lipoatrofia semicircular. Available from: http:// www.osalan.euskadi.eus. [Accessed: May 14, 2022]

Chapter 9

Short QT Syndrome: Update on Genetic Basis

Estefanía Martínez-Barrios, José Cruzalegui, Sergi Cesar, Fredy Chipa, Elena Arbelo, Victoria Fiol, Josep Brugada, Georgia Sarquella-Brugada and Oscar Campuzano

Abstract

Short QT syndrome (SQTS) is an extremely rare inherited arrhythmogenic entity. Nowadays, less than 200 families affected worldwide have been reported. This syndrome is characterized by the presence of a short QT interval leading to malignant ventricular tachyarrhythmias, syncope and sudden cardiac death. It is one of the most lethal heart diseases in children and young adults. Both incomplete penetrance and variable expressivity are hallmarks of this entity, making it difficult to diagnose and manage. Currently, rare variants in nine genes have been associated with SQTS (*CACNA1C*, *CACNA2D1*, *CACNB2*, *KCNH2*, *KCNJ2, KCNQ1*, *SLC22A5*, *SLC4A3* and *SCN5A*). However, only pathogenic variants in four genes (*KCNH2*, *KCNQ1*, *KCNJ2* and *SLC4A3*) have been found to definitively cause SQTS. The remaining genes lack a clear association with the disease, making clinical interpretation of the variants challenging. The diagnostic yield of genetic tests is currently less than 30%, leaving most families clinically diagnosed with SQTS without a conclusive genetic diagnosis. We reviewed and updated the main genetic features of SQTS, as well as recent evidence on increasingly targeted treatment.

Keywords: sudden cardiac death, arrhythmias, short QT syndrome, genetics, QT interval variability

1. Introduction

Short QT syndrome is a rare inherited cardiac channelopathy characterized by the presence of short QT intervals and a high risk of malignant arrhythmias in the context of a structurally normal heart. Described more than 20 years ago by Gussak et al. [1], it was not until 2004 when the first genetic variants associated with the disease were published in *KCNH2* [2] *KCNQ1* [3] and *KCNJ2* [4], named SQT1, SQT2 and SQT3, respectively. Since then, pathogenic variants have been described in six other genes associated with the disease, however, due to the low number of cases and the lack of a correct genotype-phenotype correlation, it is difficult to confirm the definitive pathogenic role of these genes as cause of SQTS. We aim to update current advances in SQTS, especially focused on genetics.

2. Prevalence

Today, it is difficult to establish the real prevalence of SQTS in the population, mainly due to the rarity of the disease and its possible underdiagnosis. The estimated prevalence is less than 1/10.000 in adults and about 1/2.000 in children and adolescents [5–8]. SQTS is potentially lethal for children in the first year of life, leading to a cardiac arrest rate close to 4%, making it one of the causes of sudden infant death syndrome (SIDS) [9].

3. Diagnosis

SQTS is diagnosed by the presence of a QTc ≤ 340 ms, or a QTc ≤ 360 ms when one of the following clinical criteria is met: detection of a clearly pathogenic genetic variant in one of the genes associated with the disease, family history of SQTS, family history of syncope or sudden cardiac death (SCD) before 40 years of age or survival of a ventricular tachycardia (VT) /ventricular fibrillation (VF) episode in the absence of heart disease [10]. However, its diagnosis can be challenging due to the large variability of the QT interval in healthy subjects.

Resting ECG should be performed at a normal heart rate when SQTS is suspected [11]. In addition, a stress test could be useful and a slope of the QT/HR ratio of less than −0.9 ms/beat/min could help distinguish affected subjects from healthy individuals [12]. Some studies support that QTc values should be adjusted in each population according to factors such as sex and age, and assessed in conjunction with other ECG criteria [13, 14]. For instance, a recent study in children and young adults demonstrated that a QTcB <316 ms, J-Tpeak cB < 181 ms (corrected by using Bazett's formula) and the presence of early repolarization (ER) could be indicative of SQTS in patients younger than 20 years of age [15]. Tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) could be part of the clinical evaluation, as systolic function may also be impaired and patients may present a dispersion of contraction in myocardium [16]. In contrast, invasive electrophysiological study (EPS) with programmed ventricular pacing is not recommended for SCD risk stratification [10] .

4. Clinical findings

SQTS is characterized by a short QT interval in the ECG, with an asymmetric and sharp T wave, especially in precordial leads. Short or absent ST segments and paroxysmal episodes of atrial or ventricular fibrillation (**Figures 1** and **2**). The most common symptoms are palpitations (30%), syncope (25%) and cardiac arrest (40%) [17]. Ventricular and atrial fibrillation is present in most patients [18]. Cardiac events usually occur in adrenergic situations (noise or exercise), although occasionally it can also occur at rest [19]. Despite no studies focused on diet, any food modifying significantly the potassium levels may affect the QT interval. Symptoms occur in all age groups, with an increasing rate of SCD between 14 and 40 years of age. The probability of presenting with SCD as the first symptom increases with age, reaching 41% at 40 years of age [5]. A slightly male predominance was suggested, but recent analysis showed that although males present syncope more frequently than females, they show a lower risk of arrhythmic events and/or SCD [20]. In addition,

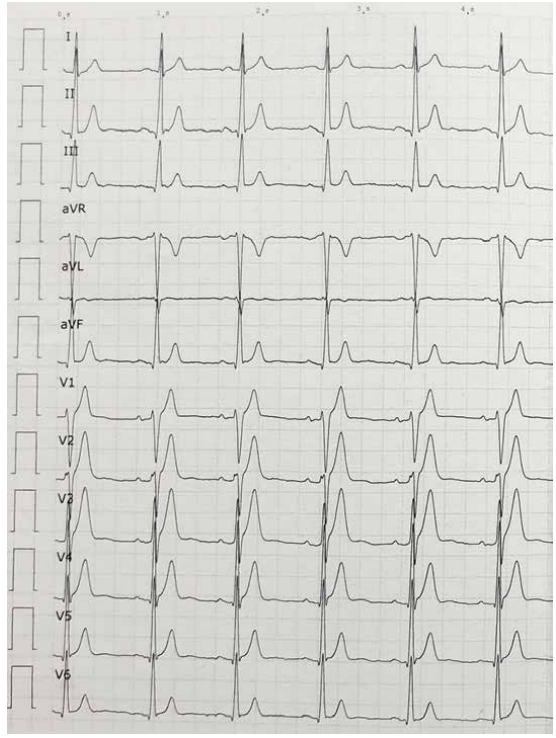

Figure 1.
ECG taken from a 39-year-old patient with SQTS; QT interval: 310 ms, QTc: 355 ms (corrected by using Bazett's formula).

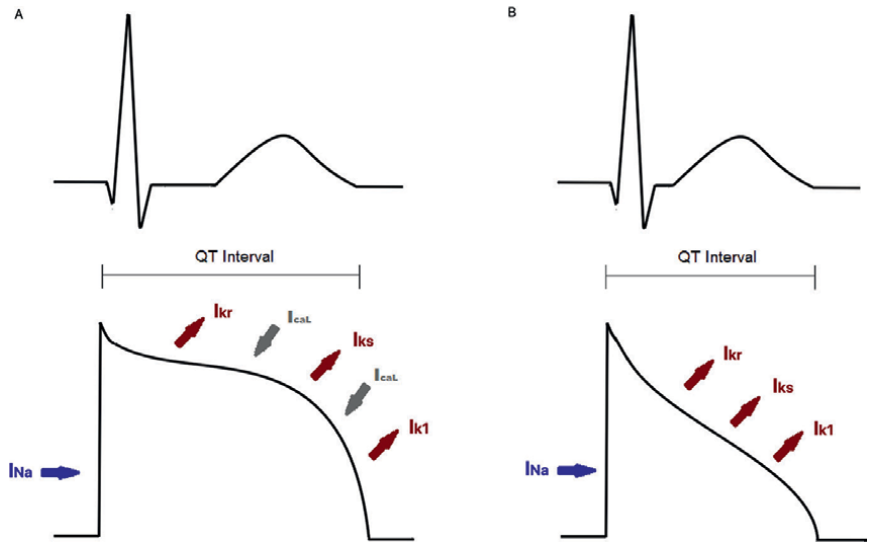

Figure 2.
ECG diagram and cellular ionic currents under normal conditions (A) and SQTS (B). Voltage-gated Na+ and K+ currents define the ventricular action potential and the QT interval of the ECG. The functional effect of IKs, IKr or IK1 gain-of-function or INa or CaL loss-of-function on the ventricular action potential results in the shortening of the action potential associated with SQTS.

some studies suggest that genes located on the X chromosome may be involved in the regulation of the QTc interval [21].

5. Genetic basis

Short QT syndrome occurs mainly in an autosomal dominant pattern of inheritance with high phenotypic and genetic heterogeneity. To date, potential deleterious rare variants located in nine genes (*CACNA1C*, *CACNA2D1*, *CACNB2*, *KCNH2*,

SQTS	Prevalence	Genes	Effect of variant	Current affected	Phenotypic overlap
SQT1	<15%	*KCNH2*	GOF	I_{Kr}	LQTS, BrS
SQT2	<5%	*KCNQ1*	GOF	I_{Ks}	LQTS
SQT3	<3%	*KCNJ2*	GOF	I_{K1}	LQTS, CPVT
SQT4	<1%	*CACNA1C*	LOF	I_{ca}	LQTS, BrS
SQT5	<1%	*CACNB2*	LOF	I_{ca}	LQTS, BrS
SQT6	<1%	*CACNA2D1*	LOF	I_{ca}	LQTS, BrS
SQT7	<1%	*SCN5A*	LOF	I_{Na}	LQTS, BrS
SQT8	<1%	*SLC4A3*	LOF	AE3	.
SQTS-mimic	<1%	*SLC22A5*	LOF	.	CDSP

AE3: Anion exchanger; BrS: Brugada syndrome; CDSP: Systemic primary carnitine deficiency; GOF: gain-of-function; ICa: Voltage-gated calcium currents; IKr: Rapidly activating potassium currents; IKs: Slowly activating potassium currents; IK1: Inward rectifier potassium currents; LOF: loss-of-function; LQTS: Long QT syndrome; SQTS: Short QT syndrome.

Table 1.
Genes associated with Short QT Syndrome or Shorter than normal QT interval and its phenotypic overlap with the main arrhythmogenic syndromes.

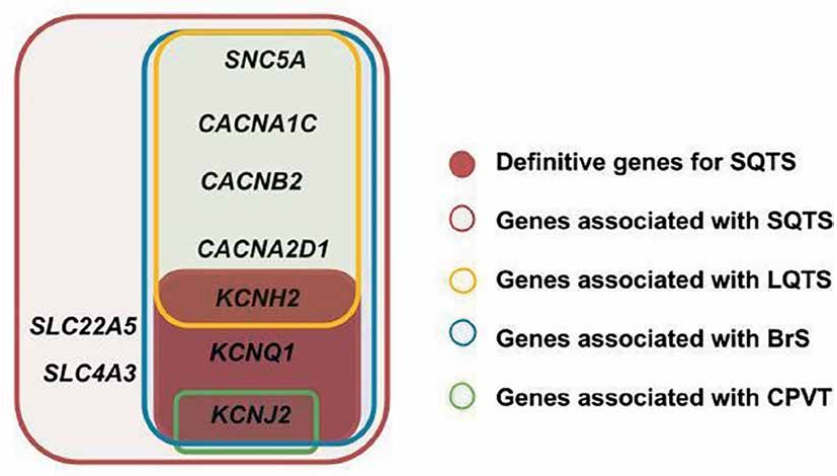

Figure 3.
Diagram of the overlap between the genes associated with the short QT syndrome (SQTS) and the main channelopathies: Brs: Brugada syndrome; LQTS: long QT syndrome and CPVT: catecholaminergic polymorphic ventricular tachycardia.

KCNJ2, *KCNQ1*, *SLC22A5*, *SLC4A3* and *SCN5A*) have been associated with SQTS (**Table 1**) [22]. However, only three genes (*KCNH2*, *KCNQ1* and *KCNJ2*) have been shown to cause SQTS definitively so far, and the *SLC4A3* gene presents moderate evidence [23]. The association of the other genes with SQTS remains controversial (**Figure 3**) [24].

6. Genes definitely associated with SQTS

Pathogenic variants in the *KCNH2*, *KCNQ1* and *KCNJ2* genes are responsible for SQTS type 1, 2 and 3 respectively. These variants are usually of the gain-of-function type and generate prolonged K^+ channel activation, accelerated cardiac repolarization with shorter refractory periods, resulting in the short QT phenotype [25].

The *KCNH2* gene (ID: 3757) encodes a voltage-activated potassium channel belonging to the eag family, subfamily H, member 2 (Kv 11.1 α/hERG subunit). It mediates the rapidly activating component of the delayed rectifying potassium current in the heart (I_{Kr}) [26–28]. Gain-of-function hERG variants lead to abbreviated ventricular repolarization and SQTS; in contrast, loss-of-function hERG variants are responsible for Long QT Syndrome (LQTS). The pathogenic variants p.Thr618Ile and p.Asn588Lys are the most frequently associated with SQTS [29]. Several functional studies have demonstrated the pathophysiological role of these variants, and their contribution to the SQTS phenotype seems clear [30]. Although other rare variants in the *KCHN2* gene associated with SQTS have been described, many of them require further functional or segregation studies to elucidate their definitive pathological role.

The *KCNQ1* gene (ID: 3784), encodes a voltage-activated potassium channel (Kv7.1 α-subunit) required for repolarization. This protein can form complexes associated with MinK (the *KCNE1* gene) and MiRP2 (the *KCNE3* gene) proteins, both potassium channel. When associated with *KCNE1*, it forms the I_{Ks} current, and induces rapid activation of the potassium-selective outward current. It can also associate with the MiRP2 protein and other associated proteins to form the potassium channel [3, 31]. Deleterious variants in this gene are associated with SQT2 and account for less than 5% of SQTS cases. In addition, some *de novo* variants in the *KCNQ1* gene have been associated with a particular phenotype *in utero* with clinical diagnosis of atrial fibrillation (AF), along with concomitant bradycardia and SQTS [32]. The rare variants p.Val141Met and p.Val307Leu have the clearest association with SQT2 to date [22], being potential targets for various therapeutic models. For example, functional and computational simulation studies identified channel-specific blockade of I_{K1} or I_{Ks} as a possible antiarrhythmic strategy in SQT2, depending on the identified deleterious variants (p.Val141Met and p.Val307Leu, respectively) [33, 34].

The *KCNJ2* gene (ID: 37591) encodes the integral membrane protein and an inward rectifier-type potassium channel, subfamily J, Member 2 (Kir2.1 α-subunit). Inward rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it (IK1 current) [4, 35]. Currently, pathogenic variants with the most evidence of causality for SQT3 are the variants p.Asp172Asn and p.Glu299Val [36, 37]. The *KCNJ2* gene has also been associated with other channelopathies, mainly catecholaminergic polymorphic ventricular tachycardia (CPVT) [38].

6.1 Gene moderately associated with SQTS

In 2017, the *SLC4A3* gene (Solute Carrier Family 4 Member 3, ID: 6508) was associated with SQTS, presenting an unusual mechanism for the development of malignant arrhythmia. *SLC4A3* encodes plasma membrane anion exchange protein 3 (AE3) and acts by mediating part of the Cl-/HCO3- exchange in cardiac myocytes. To date, only one rare variant in this gene has been identified in two families (p.Arg370His). This loss-of-function variant would cause an increase in pH_i and a decrease in $[Cl-]_i$, shortening the AP duration and reducing the QT interval [39]. This gene is associated with SQT type 8; however, further studies are needed to clarify the definitive role of this gene in SQTS.

6.2 Other genes associated with SQTS

Loss-of-function alterations in genes encoding different subunits of cardiac Ca^{2+} channels have been associated with SQTS syndrome with an autosomal dominant inheritance pattern, each accounting for less than 1% of all SQTS cases [40]. However, evidence-based review of this association (ClinGen) leaves the causation of SQTS by mutations in these genes currently in dispute [24].

The *CACNA1C* gene (ID: 775) encodes an alpha-1 subunit of a voltage-dependent calcium channel (calcium channel, voltage-dependent, L-type, alpha 1C subunit, Cav1.2 α subunit). Calcium channels mediate the influx of calcium ions into the cell upon membrane polarization. To date, all variants identified in *CACNA1C* decrease inward currents at early phases of cell repolarization (I_{CaL}) and induce transmural and epicardial dispersion of repolarization, leading to a combined phenotype of SBr and short QTc interval [41]. Currently, more than 10 rare variants in the *CACNA1C* gene have been potentially associated with SQTS, so-called SQT4. However, there is insufficient evidence to establish a definitive association and further studies are needed [22]. Gain-of-function variants in this gene have also been associated with LQTS.

The *CACNB2* gene (ID: 783) encodes a subunit of a voltage-dependent calcium channel protein, a member of the voltage-gated calcium channel superfamily (Cav1.2 β subunit). The beta subunit of voltage-dependent calcium channels contributes to the calcium channel function by increasing peak calcium current, shifting the voltage dependencies of activation and inactivation, modulating G protein inhibition and controlling the alpha-1 subunit membrane targeting. Only one rare variant in the *CACNB2* gene has been associated with SQTS (p.Ser481Leu) to date, known as SQT5. This variant is also found to be associated with BrS [40].

The *CACNA2D1* gene (ID: 781) encodes a member of the alpha-2/delta subunit family, a protein in the voltage-dependent calcium channel complex (Cav1.2 α2/δ1 subunit). The protein regulates calcium current density and activation/inactivation kinetics of the calcium channel (I_{CaL}) [40]. Only one variant has been identified in this gene (p.Ser755Thr), but its high frequency in the Ashkenazi population and conflicting evidence refutes its pathogenic role in SQTS [24]. It is associated with the so-called SQTS type 6. This gene has also been associated with other channelopathies, mainly LQTS.

The *SCN5*A gene (ID: 6331) encodes the alpha subunit of the type 5 sodium channel (Nav1.5) that mediates voltage-dependent sodium ion permeability in the cardiomyocyte. So far, only a rare variant in the *SCN5*A gene (p.R689H) has been described to be associated with SQTS (called SQT7). Carriers of this variant show a

characteristic BrS phenotype with concomitant shortened QT intervals, but without a conclusive clinical diagnosis of SQTS. Therefore, its association is in dispute.

6.3 Gene associated with a SQTS-mimic phenotype

The *SLC22A5* gene (ID: 6584) encodes a high-affinity sodium ion-dependent carnitine transporter protein (Solute Carrier Family 22 Member 5). So far, only the pathogenic variant p.Phe17Leu has been associated with SQTS, following an autosomal recessive inheritance pattern [42]. However, because the short QT phenotype is reversible with carnitine supplementation, the association of this gene with SQTS remains inconclusive [24].

7. Genetic counselling

Due to the low number of cases reported worldwide, the real penetrance and incidence of SQTS is difficult to estimate. Although some pathogenic variants exhibit 100% penetrance, approximately 40% of patients may remain asymptomatic [29]. Current guidelines recommend the analysis of four genes: *KCNH2*, *KCNQ1*, *KCNJ2* and *SLC4A3*, despite last gene need more conclusive data concerning definite role [23]. Despite controversial association data between calcium channel genes and SQTS, current guidelines recommend the analysis of *CACNA1C*, *CACNA2D1* and *CACNB2,* frequently associated with BrS. Genetic diagnosis of SQTS has a diagnostic yield of less than 30% [43] with the *KCNH2* gene as the most cost-effective option [10]. Familial genetic analysis is recommended, both to clarify the pathogenic role of newly identified variants and to identify family members at risk for SCD.

8. Risk stratification and management

Risk stratification is the main current challenge in the clinical setting, especially in asymptomatic patients carrying a pathogenic genetic alteration. In addition, patients with QTc intervals ≤340 ms should be considered at higher risk for SCD, despite the fact that no conclusive results have been published so far. ICD implantation is the treatment of choice for all patients with SQTS, especially for those who have survived aborted cardiac arrest or who have had spontaneous sustained VT [44]. However, there is also a significant risk of device-related complications, mainly due to inappropriate shocks from the over detection of T waves (high and narrow) seen in SQTS. Drugs that prolong the QT interval (quinidine and sotalol) should be considered for all patients at risk for SQTS in both asymptomatic and symptomatic patients who do not have an ICD, especially in young children [43]. Quinidine is currently the agent of choice, since in patients with SQT1, in addition to prolonging the QT interval and ventricular refractory period, it leads to the normalization of ST segments and T waves and the prevention of VF induction. However, the personalized use of drugs aimed at the treatment of patients carrying certain types of variants is becoming increasingly common. A study on human-induced, pluripotent stem cell-derived cardiomyocytes demonstrated that in addition to quinidine, ivabradine, ajmaline and mexiletine may be drug candidates for preventing tachyarrhythmias in patients carrying the p.Asn588Lys variant in the *KCNH2* gene [45]. In addition, modelling studies indicated that high-dose amiodarone may be a potential drug treatment for SQTS2,

especially those patients carrying the p.Val307Leu variant in the *KCNQ1* gene [46]. Recently, a study show that vernakalant (sodium and potassium channel blocker) can prolong action potential and reduce arrhythmias in human-induced pluripotent stem cell-derived cardiomyocytes from a patient diagnosed of SQTS type-1 due to p.Asn588Lys, suggesting an effective candidate drug for treating arrhythmias [47]. Although more studies are needed to confirm these findings, the development of personalized treatments for inherited arrhythmias is currently in expansion.

9. Conclusions

Currently, SQTS is still a relatively unknown disease. First described in 2000, the small number of families diagnosed with SQTS worldwide makes the establishment of a risk stratification scale difficult. Clarification of electrophysiological and clinical abnormalities associated with the disease and the genetic origin, has only been carried out in recent years. However, only four genes (*KCNH2*, *KCNQ1*, *KCNJ2, SLC4A3*) have been definitively associated with the disease and a comprehensive genetic analysis only identify the causative alteration in no more than 30% of diagnosed families. It is crucial to perform more genotype-phenotype analyses in diagnosed SQTS families as well as segregation studies and *in vitro/ion vivo* functional tests that will allow clarification of the pathophysiological mechanism involved this lethal arrhythmogenic syndrome. Survivors of SCD have a high recurrence rate of episodes, thus implantation of an ICD is recommended in this group of patients. The pharmacological approach may also be effective in some cases, especially in the pediatric population, and the use of personalized medicine is becoming increasingly feasible. Personalized clinical evaluation, genetic analysis and the adoption of effective therapeutic measures by specialists help to improve the evolution of diagnosed patients with an increasingly positive long-term outcome.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, et al. Idiopathic short QT interval: A new clinical syndrome? Cardiology. 2000;**94**:99-102. DOI: 10.1159/000047299

[2] Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004;**109**:30-35. DOI: 10.1161/01.CIR.0000109482.92774.3A

[3] Bellocq C, Van Ginneken ACG, Bezzina CR, Alders M, Escande D, Mannens MMAM, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation. 2004;**109**:2394-2397. DOI: 10.1161/01.CIR.0000130409.72142.FE

[4] Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circulation Research. 2005;**96**:800-807. DOI: 10.1161/01.RES.0000162101.76263.8C

[5] Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, Novelli V, et al. Novel insight into the natural history of short QT syndrome. Journal of the American College of Cardiology. 2014;**63**:1300-1308. DOI: 10.1016/J.JACC.2013.09.078

[6] Kobza R, Roos M, Niggli B, Abächerli R, Lupi GA, Frey F, et al. Prevalence of long and short QT in a young population of 41,767 predominantly male Swiss conscripts. Heart Rhythm. 2009;**6**:652-657. DOI: 10.1016/J.HRTHM.2009.01.009

[7] Funada A, Hayashi K, Ino H, Fujino N, Uchiyama K, Sakata K, et al. Assessment of QT intervals and prevalence of short QT syndrome in Japan. Clinical Cardiology. 2008;**31**:270-274. DOI: 10.1002/CLC.20208

[8] Anttonen O, Junttila MJ, Rissanen H, Reunanen A, Viitasalo M, Huikuri HV. Prevalence and prognostic significance of short QT interval in a middle-aged Finnish population. Circulation. 2007;**116**:714-720. DOI: 10.1161/CIRCULATIONAHA.106.676551

[9] Mazzanti A, Underwood K, Nevelev D, Kofman S, Priori SG. The new kids on the block of arrhythmogenic disorders: Short QT syndrome and early repolarization. Journal of Cardiovascular Electrophysiology. 2017;**28**:1226-1236. DOI: 10.1111/JCE.13265

[10] Priori SG, Blomström-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eurospace. 2015;**17**:1601-1687

[11] Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, et al. Short QT syndrome: Clinical findings and diagnostic-therapeutic implications. European Heart Journal. 2006;**27**:2440-2447. DOI: 10.1093/EURHEARTJ/EHL185

[12] Giustetto C, Scrocco C, Schimpf R, Maury P, Mazzanti A, Levetto M, et al.

Usefulness of exercise test in the diagnosis of short QT syndrome. Europace. 2015;**17**:628-634. DOI: 10.1093/EUROPACE/EUU351

[13] Providência R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal Ferreira MJ, Gonçalves L, et al. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. Heart. 2018;**104**:502-508. DOI: 10.1136/HEARTJNL-2017-311673

[14] Hazeki D, Ninomiya Y, Ueno K, Yoshinaga M. Tentative screening criteria for short QT interval in children and adolescents. Circulation Journal. 2018;**82**:2627-2633. DOI: 10.1253/CIRCJ.CJ-18-0213

[15] Suzuki H, Horie M, Ozawa J, Sumitomo N, Ohno S, Hoshino K, et al. Novel electrocardiographic criteria for short QT syndrome in children and adolescents. Europace. 2021;**23**:2029-2038. DOI: 10.1093/EUROPACE/EUAB097

[16] Frea S, Giustetto C, Capriolo M, Scrocco C, Fornengo C, Benedetto S, et al. New echocardiographic insights in short QT syndrome: More than a channelopathy? Heart Rhythm. 2015;**12**:2096-2105. DOI: 10.1016/J.HRTHM.2015.05.024

[17] Mazzanti A, O'Rourke S, Ng K, Miceli C, Borio G, Curcio A, et al. The usual suspects in sudden cardiac death of the young: A focus on inherited arrhythmogenic diseases. Expert Review of Cardiovascular Therapy. 2014;**12**:499-519. DOI: 10.1586/14779072.2014.894884

[18] Raschwitz LS, El-Battrawy I, Schlentrich K, Besler J, Veith M, Roterberg G, et al. Differences in Short QT Syndrome Subtypes: A systematic literature review and pooled analysis. Frontiers in Genetics. 2020 Jan 17;**10**:1312. DOI: 10.3389/fgene.2019.01312

[19] Viskin S, Zeltser D, Ish-Shalom M, Katz A, Glikson M, Justo D, et al. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. Heart Rhythm. 2004;**1**:587-591. DOI: 10.1016/J.HRTHM.2004.07.010

[20] El-Battrawy I, Schlentrich K, Besler J, Liebe V, Schimpf R, Lang S, et al. Sex-differences in short QT syndrome: A systematic literature review and pooled analysis. European Journal of Preventive Cardiology. 2020;**27**:1335-1338. DOI: 10.1177/2047487319850953

[21] El-Battrawy I, Besler J, Liebe V, Schimpf R, Tülümen E, Rudic B, et al. Long-term follow-up of patients with short QT syndrome: Clinical profile and outcome. Journal of the American Heart Association. 2018 Dec 4;**7**(23):e010073. DOI: 10.1161/JAHA.118.010073

[22] Campuzano O, Fernandez-Falgueras A, Lemus X, Sarquella-Brugada G, Cesar S, Coll M, et al. Short QT syndrome: A comprehensive genetic interpretation and clinical translation of rare variants. Journal of Clinical Medicine. 2019 Jul 16;**8**(7):1035. DOI: 10.3390/jcm8071035

[23] Wilde AAM, Semsarian C, Márquez MF, Sepehri Shamloo A, Ackerman MJ, Ashley EA, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. EP Europe. 2022;**2022**:1-61

[24] Walsh R, Adler A, Amin AS, Abiusi E, Care M, Bikker H, et al.

Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. European Heart Journal. 2022;**43**:1500-1510. DOI: 10.1093/EURHEARTJ/EHAB687

[25] Priya PK, Jayaraman S. Effect of Percentage Reduction in Action Potential Duration of M-cells on Re-entry in Short QT Syndrome. Annual International Conference on IEEE Engineering and Medical Science. 2020;**2020**:2585-2588. DOI: 10.1109/EMBC44109.2020.9175751

[26] Guasti L, Crociani O, Redaelli E, Pillozzi S, Polvani S, Masselli M, et al. Identification of a posttranslational mechanism for the regulation of hERG1 K+ channel expression and hERG1 current density in tumor cells. Molecular and Cellular Biology. 2008;**28**:5043-5060. DOI: 10.1128/MCB.00304-08

[27] Kang Y, Guo J, Yang T, Li W, Zhang S. Regulation of the human ether-a-go-go-related gene (hERG) potassium channel by Nedd4 family interacting proteins (Ndfips). The Biochemical Journal. 2015;**472**:71-82. DOI: 10.1042/BJ20141282

[28] Li K, Jiang Q, Bai X, Yang YF, Ruan MY, Cai SQ. Tetrameric assembly of K + channels requires ER-located chaperone proteins. Molecular Cell. 2017;**65**:52-65. DOI: 10.1016/J.MOLCEL.2016.10.027

[29] Hu D, Li Y, Zhang J, Pfeiffer R, Gollob MH, Healey J, et al. The phenotypic spectrum of a mutation hotspot responsible for the short QT syndrome. JACC Clinical Electrophysiology. 2017;**3**:727-743. DOI: 10.1016/J.JACEP.2016.11.013

[30] Du C, Zhang H, Harmer SC, Hancox JC. Identification through action potential clamp of proarrhythmic consequences of the short QT syndrome T618I hERG "hotspot" mutation. Biochemical and Biophysical Research Communications. 2022;**596**:49-55. DOI: 10.1016/J.BBRC.2022.01.057

[31] Oliveras A, Roura-Ferrer M, Solé L, De La Cruz A, Prieto A, Etxebarria A, et al. Functional assembly of Kv7.1/Kv7.5 channels with emerging properties on vascular muscle physiology. Arteriosclerosis, Thrombosis, and Vascular Biology. 2014;**34**:1522-1530. DOI: 10.1161/ATVBAHA.114.303801

[32] Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, Oliva A, Burashnikov E, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiovascular Research. 2005;**68**:433-440. DOI: 10.1016/J.CARDIORES.2005.06.023

[33] Lee HC, Rudy Y, Liang H, Chen CC, Luo CH, Sheu SH, et al. Pro-arrhythmogenic eof the V141M KCNQ1 mutation in short QT syndrome and its potential therapeutic targets: Insights from modeling. Journal of Medical and Biological Engineering. 2017;**37**:780-789. DOI: 10.1007/S40846-017-0257-X

[34] Adeniran I, Whittaker DG, El Harchi A, Hancox JC, Zhang H. In silico investigation of a KCNQ1 mutation associated with short QT syndrome. Scientific Reports. 2017 Aug 16;**7**(1):8469. DOI: 10.1038/s41598-017-08367-2

[35] D'Avanzo N, Cheng WWL, Doyle DA, Nichols CG. Direct and specific activation of human inward rectifier K+ channels by membrane phosphatidylinositol 4,5-bisphosphate. The Journal of Biological Chemistry. 2010;**285**:37129-37132. DOI: 10.1074/JBC.C110.186692

[36] Jeong DU, Lee J, Lim KM. Computational study to identify the

effects of the KCNJ2 E299V mutation in cardiac pumping capacity. Computational and Mathematical Methods in Medicine. 2020 Mar 31;**2020**: 7194275. DOI: 10.1155/2020/7194275

[37] Du C, Rasmusson RL, Bett GC, Franks B, Zhang H, Hancox JC. Investigation of the effects of the short QT syndrome D172N Kir2.1 mutation on ventricular action potential profile using dynamic clamp. Frontiers in Pharmacology. 2022 Jan 18;**12**:794620. DOI: 10.3389/fphar.2021.794620

[38] Martínez-Barrios E, Cesar S, Cruzalegui J, Hernandez C, Arbelo E, Fiol V, et al. Clinical genetics of inherited arrhythmogenic disease in the pediatric population. Biomedicines. 2022 Jan 5;**10**(1):106. DOI: 10.3390/biomedicines10010106

[39] Thorsen K, Dam VS, Kjaer-Sorensen K, Pedersen LN, Skeberdis VA, Jurevičius J, et al. Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3 causes short QT syndrome. Nature Communications. 2017 Nov 22;**8**(1):1696. DOI: 10.1038/s41467-017-01630-0

[40] Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007;**115**:442-449. DOI: 10.1161/CIRCULATIONAHA.106.668392

[41] Templin C, Ghadri JR, Rougier JS, Baumer A, Kaplan V, Albesa M, et al. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). European Heart Journal. 2011;**32**:1077-1088. DOI: 10.1093/EURHEARTJ/EHR076

[42] Gélinas R, Leach E, Horvath G, Laksman Z. Molecular autopsy implicates primary carnitine deficiency in sudden unexplained death and reversible short QT syndrome. Canadian Journal of Cardiology. 2019;**35**:1256

[43] Bjerregaard P. Diagnosis and management of short QT syndrome. Heart Rhythm. 2018;**15**:1261-1267. DOI: 10.1016/j.hrthm.2018.02.034

[44] Dewi IP, Dharmadjati BB. Short QT syndrome: The current evidences of diagnosis and management. Journal of Arrhythmia. 2020;**36**:962-966. DOI: 10.1002/JOA3.12439

[45] Zhao Z, Li X, El-Battrawy I, Lan H, Zhong R, Xu Q, et al. Drug testing in human-induced pluripotent stem cell-derived cardiomyocytes from a patient with short QT syndrome Type 1. Clinical Pharmacology and Therapeutics. 2019;**106**:642-651. DOI: 10.1002/CPT.1449

[46] Luo C, Wang K, Zhang H. Modeling the effects of amiodarone on short QT syndrome variant 2 in the human ventricles. Annual International Conference on IEEE Engineering and Medical Biological Society. 2017;**2017**:4273-4276. DOI: 10.1109/EMBC.2017.8037800

[47] Xu Q, Huang X, Meng Z, Li Y, Zhong R, Li X, et al. Antiarrhythmic effects of Vernakalant in human-induced pluripotent stem cell-derived cardiomyocytes from a patient with short QT syndrome Type 1. Journal of Cardiovascular Developmental Diseases. 2022;**9**:112. DOI: 10.3390/JCDD9040112

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Life expectancy is often associated with economic, educational, and public health development. These factors were previously thought to be the exclusive privilege of the developed countries of the world, but the outbreak of COVID-19 seemingly evened the global playing field. COVID-19, the Ebola virus, and HIV and AIDS were considered "rare diseases" at the time of their occurrence and their outbreaks led to new thinking about public health issues. Technological advancements in telecommunication, aviation, industrial processing, agriculture, military armaments, and more, along with their impacts on climate and environment, have led to increasing levels of contaminants, posing a major public health problem. Exposure to toxins and chemicals via processed foods, work/occupation, or the environment is increasingly causing rare diseases that are difficult to diagnose and treat, especially in undeveloped areas of the world with inadequate health facilities and diagnostic skills. This book examines some of these rare diseases. It includes nine chapters that discuss conditions such as Behcet's disease, malignant mesothelioma, dentofacial anomalies, neuropathic pruritus, lipoatrophia semicircularis, and short QT syndrome.

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