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REVIEW ARTICLE

GENODERMATOSIS: A BRIEF REVIEW OF THIS GREY AREA IN DENTISTRY

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ABSTRACT

The past two decades have seen significant and unprecedented progress in human genetics owing to the advent of novel molecular biological technologies and major developments in computational methods. The field of genetics in dermatology has progressed at an astonishing rate. Most of the known single gene disorders have at least been mapped to a particular chromosomal region and the causative genes have been identified and studied in many of them. The genodermatoses are a large group of inherited single-gene disorders with skin manifestations. Many of these disorders are rare however, the recognition of their skin findings is important not only for the initiation of appropriate dermatologic therapy, but also for the detection of other associated abnormalities in these frequently multisystem disorders, including malignancy. However, most research work in genetics relating to genodermatoses has been confined to the western population. Very few reports have been published from Indian studies.

This review discusses common genodermatosis disorders associated with their oral manifestations.

INTRODUCTION

Dermatology, the specialized study of skin diseases, has become an important subdivision of the practice of medicine not only because of the many primary diseases that affect the skin, but also because of the common cutaneous manifestations of deeper visceral or systemic diseases. There is no universally accepted classification of these dermatological diseases. One large group of specific lesions which has been recognized in recent years is that known as the genodermatosis. (1) Genodermatosis are inherited skin disorders associated with structure and function. Most of these disorders are associated with the systemic conditions leading to morbidity and mortality. Genodermatosis are inherited genetic skin conditions often grouped into three categories: chromosomal, single gene, and polygenetic. "Genodermatosis" usually refers to diseases caused by monogenic abnormality. It has been clarified that the human genome consists of 22,000 genes, which produce about 100,000 proteins. Accordingly, almost all of the genes and proteins that are responsible for monogenic diseases including Genodermatosis are being clarified.

This review discusses common Genodermatosis disorders associated with their oral manifestations.

Ectodermal dysplasia

Ectodermal dysplasia (ED) is the group of inherited disorders involving skin, hair, nails and teeth. There are two main forms of ED. (2)

1. Hypohidrotic form/Christ-Seimens-Tourian Syndrome: X-linked - mapped in the proximal area of the long arm of band Xq-12-q13.1. Clinically the patients show frontal bossing, sunken cheeks, saddle nose, thick everted lips, wrinkled hyper pigmented periorbital skin and large low set ears also, fine, lusterless, sparse hair over scalp is seen in most patients. Dental manifestations include conical or pegged teeth, hypodontia or complete anodontia and delayed eruption of permanent teeth. (3) Regarding management, little can be offered, except advice concerning restriction of physical exertion, choice of suitable occupation, avoidance, if practicable of warm climates
2. Hidrotic form/Clouston's Syndrome: This is characterized by reduction in number of, sweat gland, sebaceous glands and hair follicles. Salivary glands may show ectasia of ducts and inflammatory changes. This is because of mutation in GJB6 gene which encodes for connexin 30.No treatment has been documented yet.

Xeroderma pignmentosa (XP)

The defect underlying the clinical manifestations is a nucleotide excision repair (NER) defect which leads to a defective repair of DNA damaged by ultra violet (UV) radiation associated with the consanguinity of parents of the patients. XP is characterized by clinical and cellular hypersensitivity to UV radiation manifesting as intolerance of skin and eyes to light. Leukoplakia, erythroplakia and squamous cell carcinoma (SCC) of the tip of the tongue, actinic cheilitis and SCC of the lips are associated with XP. [4] Chronic desquamative gingivitis was first described by Tomes and Tomes [5]

There is no cure for XP. The DNA damage is cumulative and irreversible. Persons with XP must avoid exposure to any sources of UV light including sunlight, fluorescent, halogen and mercury vapour lights. Genetic counseling implicating the effect of consanguineous marriages should be emphasized. [6]

Psoriasis

Psoriasis is a common and chronic inflammatory disease, which can affect the skin, nails and joints. It is characterized by immune-mediated epidermal hyper proliferation. [7, 8] The reports described a number of oral locations, such as lips, buccal mucosa, gingiva, palate, tongue and floor of the mouth. Clinically of the cases reviewed by Younai and Phelan [9] 44% of patients presented with white, 24% with erythematous, and 13% with mixed red and white intraoral lesions. The remaining lesions appeared ulcerative, vesicular, pustular, or indurated. [10]

Non steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and synthetic DMARDs; the available evidence suggests an acceptable efficacy and safety profile of both NSAIDs and synthetic DMARDs (methotrexate, cyclosporine A, sulfasalazine and leflunomide). More evidence is available (level 1B) supporting the efficacy of anti-tumour necrosis factor (anti-TNF) agents (adalimumab, etanercept, golimumab and infliximab) in treating the signs and symptoms of psoriasis. [11]

White sponge nevus

White sponge nevus (WSN) is a rare autosomal dominant disorder that predominantly affects nonkeratinizing stratified epithelia such as the oral mucosa. Mutations in cytokeratins (CK4 and CK13) genes have been identified. WSN is characterized by soft, white, and spongy plaques in the oral mucosa. The surface of the plaque is thick, folded, and may peel away from the underlying tissue. The clinical expression of WSN is variable regarding the size of the plaques, the affected areas, and its distribution, which can change with the time. [12]

Hereditary benign intraepithelial-dyskeratosis

Hereditary benign intraepithelial dyskeratosis is a rare autosomal dominant hereditary Genodermatosis. A segment of DNA localized at 4q35 is duplicated resulting in triple alleles for 2 linked markers suggesting that gene duplication is responsible for the disorder develop during childhood. It affects oral and ocular mucosa with onset usually at birth or early childhood. Oral lesions are usually asymptomatic and may vary in extent. Most oral lesions go unrecognized until examined. [13] It may appear as white, spongy, macerated lesions with or without fold. [14] Histopathological changes of the oral mucosa include increased epithelial thickness and numerous dyskeratotic cells and are very similar to the ocular changes. Dyskeratosis may be prominent in the superficial layers. Cells appearing to be engulfed by normal cells, the so called 'cell-within-cell' pattern can be seen. [15]

Pachyonychia congenital

Pachyonychia congenita (PC) describes a group of rare autosomal dominant skin disorders characterized predominantly by dystrophic, thickened nails, and painful and highly debilitating palmoplantar hyperkeratosis.[16,17,18,] PC was historically classified into at least two subtypes according to the clinical features: PC type 1 (MIM #167200, PC-1, or Jadassohn-Lewandowsky syndrome), the more common variant, is characterized mainly by nail changes, palmoplantar keratoderma (PPK), follicular keratosis and oral leukokeratosis, while PC type 2 (MIM #167210, PC-2, or Jackson Lawler syndrome) includes the features of PC-1 plus natal teeth, epidermal inclusion cysts, pilo sebaceous cysts such as steatocystomas and vellus hair cysts, and hair abnormalities, including alopecia, pili torti (twisted hair) and unruly hair. Oral findings show oral leukokeratosis, natal and neonatal teeth.

Like most Genodermatosis, no specific treatment or cure is known for PC-2. Therapy is generally directed towards symptomatic improvement. Mechanical thinning of thick nails and calluses with a variety of hand tools such as pumice stones, emery boards, paring knives, razor blades, may be helpful. Some patients use electrical tools, such as grinders, polishers, and sanders, to reduce thickened nails. Softening of the nails and calluses can also be achieved with overnight application of topical keratolytics under occlusion, such as pastes of 20%-40% urea or 15%-20% salicylic acid. Systemic retinoids make the keratin more flexible and less pronounced without complete clearing.

Dyskeratosis congenital

Dyskeratosis congenita is also known as Zinsser–Engman–Cole syndrome. Mutations in the DKC1 gene. The mutated gene appears to disrupt the normal maintenance of telomerase. Dysplastic changes of the nails intraorally, the tongue and buccal mucosa develop bullae; these are followed by erosions and eventually leukoplakia lesions. The leukoplakia lesions are considered to be premalignant. Thrombocytopenia is usually the first hematologic problem that develops followed by anemia.

Incontinentia pigmenti

It is inherited as an X-linked dominant trait. Single unpaired gene on the X-chromosome being lethal for most males. Lethal in the majority of affected males in utero and variably expressed in females. Cutaneous manifestations are classically subdivided into 4 stages: vesicular, verrucous, hyperpigmented, and atrophic. [19] Central nervous system abnormalities mental retardation, seizure disorders, motor difficulties, strabismus, cataracts, retinal vascular abnormalities, optic nerve atrophy oligodontia (hypodontia), delayed eruption, hypoplasia of the teeth. The teeth are small and cone-shaped; both the primary and permanent dentitions are affected. Histopathology; vesicular stage - intraepithelial clefts filled with eosinophils are observed. Verrucous stage - hyperkeratosis, acanthosis, and papillomatosis are noted. Hyperpigmentation stage - shows numerous melanin-

containing macrophages (melanin incontinence) in the sub epithelial connective tissue.

Warty dyskeratoma

Graham and Helwig [20, 21] first described warty dyskeratoma (WD) as isolated Darier's disease in 1954 and this malady was more properly called warty dyskeratoma by Szymanski in 1957. The etiology of WD is unclear, but a viral infection, smoking, autoimmunity, and ultraviolet light have been postulated to play a role.[22] The intraoral warty dyskeratoma appears as a pink or white, umbilicated papule located on the keratinized mucosa, especially the hard palate, and the alveolar ridge. Many authors have suggested a follicular origin for WD, but mucosal lesions that lack follicle could not be explained by their proposal. For this reason, some authors have insisted that oral WD may represent another entity rather than true WD. The treatment of choice of WD is surgical excision. Treatment with electro-desiccation and irradiation with X-ray had been tried, but these were followed by recurrence [3]. A case of successful treatment with tazarotenic acid gel has also been reported. [22]

Keratosis follicularis

Darier disease, also known as keratosis follicularis or dyskeratosis follicularis, is a rare autosomal dominant Genodermatosis. It is clinically manifested by hyperkeratotic papules primarily affecting seborrheic areas on the head, neck and thorax, with less frequent involvement of the oral mucosa. When oral manifestations are present, they primarily affect the palatal and alveolar mucosa, are usually asymptomatic, and are discovered in routine dental examination. More recently, it has been related to mutations in the gene encoding the sarco/endoplasmic reticulum Ca2+ ATPase pump (SERCA2), resulting in abnormal organization or maturation of complexes responsible for cell adhesion, thus leading to the disturbance.[23,24] The systemic treatment of the Darier disease is symptomatic. Several treatments have been presented in the literature, such as utilization of topical retinoids, systemic steroids and antibiotics; however, they provide limited benefits.[7] More radical treatments have been reported, including surgical excision, abrasion, application of carbon dioxide and laser Photodynamic therapy has been also considered; however, it should not replace systemic retinoids in patients requiring systemic treatment. Regardless of the clinical severity and treatment option, the patient should receive genetic counseling with information on the inherited condition and risk of transmission to the offspring. [25]

Peutz–Jeghers syndrome (PJS)

PSJ is inherited as an autosomal dominant trait. 35% of cases represent new mutations. Mutation of a gene known as LKB1/STK11, which encodes for a serine/heroine kinase has Characterized by freckle like lesions of the hands, perioral skin, and oral mucosa in conjunction with intestinal polyposis. Chemopreventive strategies for familial adenomatous polyposis syndrome management have led to investigation into cyclooxygenase (COX) inhibitors for Peutz-Jeghers syndrome (PJS). Few authors have demonstrated that COX-2 was highly up-regulated in a murine model of Peutz-Jeghers syndrome LKB1 mutant mice. Rapamycin has been shown to be effective. [26]

Ehlers–Danlos syndrome

A group of inherited connective tissue disorders Ehlers-Danlos syndrome (EDS), classic type is a connective tissue disorder characterized by skin hyper extensibility, abnormal wound healing, and joint hyper mobility. It includes two previously designated subtypes (EDS type I and EDS type II) that are now recognized to form a continuum of clinical findings. At least 50% of individuals with classic EDS have an identifiable pathogenic variant in *COL5A1* or *COL5A2*, the genes encoding type V collagen; however, this number may be an underestimate, since no prospective molecular studies of*COL5A1* and *COL5A2* have been performed in a clinically well-defined group.

Epidermolysis bullosa

Epidermolysis bullosa (EB) represents a spectrum of conditions that are characterized by blistering and mechanical fragility of the skin. The four major EB groups include intraepidermal EB (Simplex), junctional EB, dermolytic EB (Dystrophic), and mixed EB (Kindler syndrome. [27] Dystrophic type - The initial lesions are vesicles or bullae. The bullae rupture, resulting in erosions or ulcerations that ultimately heal with scarring. Appendages such as finger nails may be lost. The oral manifestations are typically mild, with some gingival erythema and tenderness. (Table 1)[27]

Table1 Different types of EB

Type	Inheritance	Clinical features	Differential diagnosis
EB simplex	Autosomal dominant, rarely recessive	Localized blisters or grouped vesicles, limited mucosal involvement, palmoplantar hyperkeratosis, nail dystrophy +, normal teeth and hair	Pompholyx, bullous impetigo, friction blisters, thermal burns
Junctional EB	Autosomal recessive	Widespread blistering, scarring, significant granulation tissue, severe mucosal involvement, dental pitting, alopecia, nail dystrophy	Chronic bullous dermatosis of childhood, bullous ichthyosiform erythroderma, toxic epidermal necrolysis, dystrophic EB
Dystrophic EB	Both autosomal dominant and recessive	Hemorrhagic blisters, scarring, milia, pseudosyndactyly, severe mucosal involvement, physical and sexual retardation, significant morbidity and mortality	Toxic epidermal necrolyses, junctional EB

Tuberous sclerosis complex (TSC) (Epiloia, Bovrne Ville's Disease)

TSC is a name referred to the condition previously known as Tuberous sclerosis, which represents a genetic disorder of hamartoma formation in many organs, particularly the skin, brain, eye, kidney and the heart. The characteristic skin lesions are angiofibromas, shagreen patch, periangual fibromas and ash-leaf white macules, classically, although not invariably seen in association with epilepsy and mental retardation. The term complex emphasizes the multisystem involvement. Onset before the age of 5years with cutaneous changes or with epilepsy is usual, although the disease may remain latent until adolescence or adult life, A definitive diagnosis of TSC requires two major features, and brain MRI, CT, renal US or echo may be necessary.

CONCLUSION

Genodermatosis are conglomeration of cutaneous and systemic signs and symptoms Skin disorders are potentially important to dentists in diverse ways. The skin disease itself might have oral manifestations, and drugs used to treat skin disorders may impact on dental management. It is an area where close co-operation between different professionals is beneficial.

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