NARRATIVE REVIEW

Oral manifestation of genodermatoses

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Abstract

Genodermatoses are inherited dermatological disorders associated with the structure and functions of skin and its appendages. Several genodermatoses presenting with multisystem involvement lead to increased morbidity and mortality. Dermatological diseases, besides including the skin and its supplements may also involve the oral cavity, which deserves special attention considering that they may be the only presenting sign of these disorders. The important aspect to be noted about these disorders is the rarity of the conditions and lack of awareness among the population which are the major drawbacks in the early diagnosis and prompt management of these diseases. This review intends to outline various genodermatoses with their characteristic oral manifestations.

Introduction

Genodermatoses or genetic diseases are a group of inherited skin disorders with a collection of cutaneous and systemic signs and symptoms. In the oral cavity, a wide spectrum of diseases occurs due to genetic modifications ranging from developmental disturbances of hard and soft tissues to precancerous and cancerous lesions. Dermatological diseases, besides including the skin and its supplements may also involve the oral cavity, which deserves special attention considering that they may be the early presenting clinical feature or the only sign of these disorders. The oral mucosal lesions in dermatological disorder can be life-threatening and also affect the quality of life in terms of pain, discomfort, social, and functional limitations.[1]

The rarity of the conditions and lack of awareness are the major complications in the management of these diseases. Several genodermatoses presenting with multisystem involvement may lead to increased morbidity and mortality.[2]

Classification

Genodermatoses are a vast group of disorders including common, uncommon, and very rare diseases. Categorizing these diseases into different groups are arduous because of the overlapping clinical features of many conditions. It is difficult to comprise all genodermatoses under one broad classification; hence, it is simplified under three classifications based on its distinct features.

According to William et al. 2005:[3]
1. Chromosomal
2. Single gene
3. Polygenetic.

According to Irvine and Mellerio in 2010:[4]
1. Inherited immunobullous disorders
   • Epidermolysis bullosa (EB) of different groups.
2. Disorders of keratinization
   • Ichthyosis
   • Palmoplantar keratoderma
   • Erythrokeratoderma
   • Follicular keratosis.
3. Hereditary disorders of pigmentation
   • Carney complex
   • Chediak-Higashi syndrome (CHS)
   • Griscelli syndrome.
4. Familial multiple tumor syndrome
   • Neurofibromatosis Type 1 and 2
   • Tuberous sclerosis complex (TSC)
   • Gardner syndrome
   • Cowden syndrome
   • Peutz-Jeghers syndrome.
5. Ectodermal dysplasias (EDAs) and disorders of ectodermal appendages
6. Disorders with defects in DNA repair and chromosomal instability
   • Bloom syndrome
   • Xerodermapigmentosum
   • Cockayne syndrome.
7. Poikilodermatous disorders
   • Rothmund-Thomson syndrome
   • Dyskeratosis congenital (DKC)
   • Acrokeratotic poikiloderma of Weary
   • Kindler syndrome.
8. Connective tissue disorders
   • Ehlers-Danlos syndrome (EDS)
   • Pseudoxanthoma elasticum
   • Marfan syndrome
   • Cutis laxa
   • Fabry disease
   • Williams syndrome
   • Menkes kinky hair syndrome.
9. Vascular and lymphatic disorders
   • Osler-Rendu-Weber syndrome Type 1 and 2
   • Lymphedema distichiasis syndrome.
10. Porphyrias
11. Disorders associated with immunodeficiency
   • Wiskott-Aldrich syndrome
   • Omenn syndrome.
12. Miscellaneous disorder
   • Bazex syndrome
   • Goltz syndrome
   • Pachydermoperiostosis
   • Nail-patella syndrome
   • Apert syndrome.

Arora and Mane proposed a classification in 2016:

1. Genodermatoses affecting teeth and dentition
   • Ichthyosis
   • Sjogren-Larsson syndrome
   • Incontinentia pigment
   • EDS
   • Focal dermal hypoplasia syndrome
   • Gardner syndrome
   • EDA
   • Hyperimmunoglobulin E syndrome (Job syndrome).
2. Genodermatoses affecting periodontium and gingiva
   • Ichthyosis
   • Sjogren-Larsson syndrome
   • Papillon Lefèvre syndrome
   • Tuberous sclerosis
   • CHS
   • EDS
   • Focal dermal hypoplasia syndrome.
3. Genodermatoses affecting oral mucosa
   • Darier’s disease
   • Neurofibromatosis Type 1 and 2
   • CHS
   • EDS
   • Lipoid proteinosis
   • Focal dermal hypoplasia syndrome
   • Multiple hamartoma syndrome (Cowden syndrome)
   • Pachyonychia congenita
   • EB
   • Multiple endocrine neoplasia syndrome
   • White sponge nevus.
4. Genodermatoses affecting jaw bones and facies
   • Mccune-Albright syndrome
   • EDS
   • Marfan syndrome
   • Focal dermal hypoplasia syndrome
   • Gardner syndrome
   • Basal cell nevus syndrome
   • Orofacial digital syndrome Type 1.
5. Genodermatoses causing pigmentation of oral mucosa
   • Carney complex
   • Neurofibromatosis Type 1 and 2
   • Mccune-Albright syndrome
   • Lipoid proteinosis
   • Pseudoxanthoma elasticum
   • Peutz-Jeghers syndrome
   • Congenital erythropoietic porphyria
   • Hypomelanosis of ito
   • Sturge-Weber syndrome
   • Hereditary hemorrhagic telangiectasia syndrome.
6. Genodermatoses with malignant potential
   • Xeroderma pigmentosum (XP)
   • DKC.

In this review, the various genodermatoses along with their oral manifestations are discussed. [Table 1] shows Oral genodermatoses with their corresponding mutated genes.

EB
EB is a chronic blistering disease of the skin and mucosa. The three major types of EB are EB simplex, junctional EB, and dystrophic EB. Oral involvement has been reported in the junctional and dystrophic forms of the disease, which is characterized by bulla and vesicle formation following mild physical trauma. Oral manifestations include blistering and ulceration of the oral mucosa, abnormal tooth eruption, depapillation of tongue, ankyloglossia, ablated palatal rugae, and microstomia.

Ichthyoses
Ichthyoses form a large, clinically and etiologically heterogeneous group of cornification disorders that typically affect all or most of the skin surface. It is caused by abnormality in keratinization and exfoliation of the horny cell layer. Oral and dental findings reported in ichthyosis include gingivitis, periodontitis, enamel hypoplasia, high caries incidence, delayed primary and permanent teeth eruption, bruxism, bicuspid teeth, irregular morphology of teeth, and hyperkeratotic plaques on the tongue. Angular cheilitis and facial dermatitis may occur as side effects of oral retinoid therapy.
Palmoplantar keratoderma (PPK)

PPK is a common hereditary cutaneous disorder characterized by marked hyperkeratosis on the surface of palms and soles.\(^8\) Periodontitis can affect both the deciduous and permanent teeth. Initially, there tends to be gingival inflammation, which can be followed by destruction of periodontium leads to premature loss of primary teeth.

CHS

CHS is an autosomal recessive disease that affects the production of organelles in many cells including melanocytes, platelets, and leukocytes. Neutrophils are characterized by abnormal giant lysosomes containing enzymes and with impaired ability to release them.\(^9\) It is associated with severe gingivitis, periodontal disease and premature loss of dentition.

Neurofibromatosis

Neurofibromatosis comprises several distinct genetic disorders that lead to the formation of tumors surrounding nerves and many other pathological features. Oral lesions are present in 5-10% of cases, as papillomatous tumors of palate, buccal mucosa, tongue and lips, or as macroglossia, which is usually asymmetrical.\(^10\) Common sites of the oral solitary neurofibromas include tongue, buccal mucosa, alveolar ridge, labial mucosa, palate, gingiva, nasopharynx, paranasal sinuses, larynx, floor of the mouth, and salivary gland. Tumors may also arise within the bone.

TSC

TSC is an autosomal dominant, systemic disorder characterized by the formation of hamartomas in multiple organ systems, most commonly the brain, skin, kidney, and eye. Oral lesions have been reported in about 11% of patients. These lesions mainly consist of fibrous growths affecting the oral mucosa of the anterior gingiva, lips, tongue, and palate. Pitted enamel hypoplasia is another characteristic oral manifestation of the disease found in 58% of patients.\(^11\)

Gardner syndrome

Gardner syndrome is characterized by multiple epidermoid cysts, premalignant intestinal polyps, osteomas and fibrous tumors of skin and other organs. Oral manifestations are large osteomas of the mandibular ramus region or condyle limiting the mandibular opening, increased prevalence of odontomas, supernumerary teeth, and impacted teeth.\(^12\)

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is a rare disorder characterized by intestinal polyposis and the pigment of the skin and mucous membrane.\(^13\) The significant oral changes are perioral and/or oral pigmentation, which develops in childhood. Non sun-dependent freckling of the skin around the lips and the vermilion zone of the lips is a common feature. Intraorally, the

Table 1: Oral genodermatoses with their corresponding mutated genes

<table>
<thead>
<tr>
<th>Oral genodermatoses</th>
<th>Mutated gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB</td>
<td>KRT5/KRT14/COL7A1</td>
</tr>
<tr>
<td>Ichthyoses</td>
<td>ABCA12/FLJ39501/FLG/STS</td>
</tr>
<tr>
<td>PPK</td>
<td>KRT1/KRT16/TRPV3</td>
</tr>
<tr>
<td>CHS</td>
<td>CHS1 gene in 1q42-43 band</td>
</tr>
<tr>
<td>NF</td>
<td>NFI and NF2</td>
</tr>
<tr>
<td>TSC</td>
<td>TSC1 (9q34), TSC2 (16p13.3)</td>
</tr>
<tr>
<td>Gardner syndrome</td>
<td>APC (5q21q22)</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
</tr>
<tr>
<td>DKC</td>
<td>NOP10/NHP2</td>
</tr>
<tr>
<td>EDS</td>
<td>COL5A1</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>FBN1</td>
</tr>
<tr>
<td>Cowden’s syndrome</td>
<td>PTEN (10q22-23)</td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>C934G/C937G</td>
</tr>
</tbody>
</table>

lesions are usually flat, painless, brown pigmented patches of the buccal mucosa, tongue or labial mucosa. Microscopically, these lesions show mild acanthosis with elongation of rete pegs and increased production of melanin pigment in the basal layer without increase in the melanocyte number.\(^14\)

EDA

EDA is the term used to describe a group of rare, inherited disorders characterized by dysplasia of tissues of ectodermal origin which primarily involves nails, teeth, skin, and occasionally dysplasia of mesodermally derived tissues.\(^15\) Craniofacial structures affected in this disease are depressed and hypoplastic midface region, high and broad cheek bone. The chin may be pointed and the lips are everted and protuberant. In nontreated patients, craniofacial deviations increase with advancing age with a tendency toward a Class III pattern with anterior growth rotation. The other characteristic facial features are frontal bossing, depressed nasal bridge, prominent supra orbital ridges, prominent and obliquely set ears and the lower third of the face appears small due to lack of alveolar bone development. In the oral cavity, the most striking feature is oligodontia.\(^16\) Teeth in the anterior region of maxilla and mandible are conical in shape. There is a wide midline diastema and hypoplastic labial frenum. Consistent variations in the number and morphology of teeth occurs which appear to be a characteristic dental phenotype for EDAs with different modes of inheritance. Taurodontism, if present is frequently seen on the second deciduous molars. A few patients have congenital anodontia. There are generally more teeth in the maxilla than in the mandible, sometimes complete edentulous arches may be
seen. Most often the lower incisors and premolars are missing, followed by the upper premolars and incisors. The edentulous EDA patients do not have any alveolar processes either. In those patients with some natural teeth, there is a striking difference in the intraoral height and breadth of the bone. In areas where no teeth have developed, the alveolar bone is missing and the bone ridge is very thin in contrast to the normal alveolus surrounding an occasional tooth. Many patients complain of dryness of oral mucosa due to reduced salivary secretion. Analysis of the saliva has revealed a reduced buffer capacity and an increased number of bacterial cultures. Most affected EDA patients are susceptible to dental caries.

**XP**

XP is a rare recessive disease characterized by photosensitivity, pigmentation disorders, premature skin ageing, neoplasia, and abnormal DNA repair. Some patients with XP also have neurological complications. Oral findings are leukoplakia, erythroplakia, and squamous cell carcinoma (SCC) of the tip of the tongue, actinic cheilitis, and SCC of the lips. In the general population, SCC most frequently affects the posterolateral and ventral surfaces of the tongue and floor of the mouth of elderly users of tobacco and alcohol and runs an aggressive course. By contrast, XP associated SCC affects the tip of the tongue of persons younger than 20 years of age and runs a slowly progressive course. Actinic cheilitis is a potentially malignant lesion that affects the lower lip of white patients who were frequently exposed to sun. Pain is a consequence of fibrous area, resulting from successive labial surgery, that stretches when the patients opens the mouth for feeding, speaking, breathing, and for oral hygiene performance. Therefore, the patient has poor hygiene and consequently, a high rate of dental plaque, caries, and periodontal disease.

**DKC**

DKC is a group of rare inherited disorders characterized by pigmentation and atrophy of the skin, nail dystrophy, leukoplakia, bone marrow failure, and a predisposition to malignancy. As per Walne et al. in DC both the hard and the soft tissues in the oral cavity are affected. Oral mucosal changes manifest in the form of a white keratotic patch. Earlier cases reported of vesicles and ulcerations preceding the development of leukoplakia. Dental caries, periodontitis and oral ulcerations, bleeding and atrophic glossitis, lichenoid lesions, and pigmementsations are noted. Enamel ground section shows thin enamel, indistinct incremental lines of Retzius, scanty enamel spindles, short enamel tufts, absence of gnarled enamel, abundance of enamel lamellae and flat interface between enamel and dentine. Hypodontia, delayed eruption, and short blunted roots are observed clinically.

**Cowden’s syndrome**

Cowden’s syndrome multiple hamartomas of ectodermal, endodermal, and mesodermal origin are the characteristic feature of this rare syndrome. Oral findings are present in 80% of patients and may serve as an important clinical marker in early diagnosis. Oral hamartomas occur mainly on gingiva, buccal and palatal mucosa. The oropharynx, larynx, and nasal mucosa may also be involved. The typical appearance of multiple, coalescent, and flat topped mucosal papules has been described as cobblestone-like and is seen in 40% of patients.

**Apert syndrome**

Apert syndrome is a rare congenital Type I acrocephalosyndactyly syndrome, characterized by craniosynostosis (premature fusion of cranial sutures), severe syndactyly of the hands and feet, and dysmorphic facial features. Oral manifestations include impaction, severe crowding, delayed eruption of dentition, thick gingiva, supernumerary teeth or genetically missing teeth, Class III malocclusion, anterior open bite, bilateral posterior cross bite, or unilateral posterior cross bite. The configuration of the palatal arch is characterized by bilateral swellings of the palate processes, resulting in a pseudocleft in the midline. Other frequent oral findings include hypotonic lips, bifid uvula, delayed or ectopic eruption, and malocclusion.

**Marfan’s syndrome**

Marfan’s syndrome is a heritable genetic disorder of the connective tissue. People with Marfan’s syndrome tend to be unusually tall, thin built with long limbs and scoliosis. The most serious complications are defects of the heart valves and aorta which includes aortic aneurysms and mitral valve prolapse and left ventricular dysfunction. Syndrome also affects the lungs, eyes, dural sac surrounding the spinal cord, skeleton, and hard palate. Oral features are retrognathic maxilla and mandible, deep narrow palate leading to crowding of teeth, Angle’s Class II molar relationship, and lack of space which is caused by palatal position of upper laterals in relation to the centrals. Root deformity, abnormal pulp shape, and pulpal inclusions are a frequent finding in patients with Marfan’s syndrome. Early diagnoses of both craniofacial and dental defects aid in satisfactory prognosis.

**EDS**

EDS are a heterogeneous group of disorders characterized by abnormal formation of collagen or molecules related to collagen synthesis, abnormalities in the matrix glycoprotein tenascin, and probably fibronectin. Oral mucosal fragility with delayed healing but without scar formation, early periodontal disease, because of easily traumatized gingiva, subluxation of the temporomandibular joint, and 50% of patients will be able to touch their nose with the tongue. Dental abnormalities include hypoplastic enamel and dentin, high cusps with deep occlusal fissures, deformed roots with pulp stones, and multiple odontogenic keratocysts.

This review is a compilation of literature evidence from standard articles obtained from PubMed, MEDLINE and other
databases on various aspects such as historic nomenclature, definitions, etiology, clinical features and focusing on genetic basis of these diseases. Apart from, the routine online data bases a specific web link - OMIM http://omim.org/was used to access data on genetic disorders. This web link has been providing immediate access to current information on human genes and genetic diseases for more than 25 years.

Observations made from this review are that:

i. There exists no standard classification system to group all the disorders under the title “Genodermatoses.” However, many authors have mentioned a few disorders suitable for the same header

ii. There exists fewer data on Indian epidemiology of genodermatoses. Data pertaining to malignant transformation occurring in some of the genodermatoses has to be updated

iii. Abundant data are available in the literature on various aspects of genodermatoses such as prenatal diagnosis, molecular basis, and etiopathology which general population is not aware of

iv. The primary reason for patients to seek medical help is due to associated esthetic problems or functional compromise, but not being aware of adverse effects, oral or systemic effects or on the familial/genetic pattern of disease.

The formation of standard registries for noting on various aspects of these genetic disorders is needed for formation and implementation of common guidelines/consensus for diagnosis and management of these disorders is needed at the moment.

Genodermatoses are usually associated with high morbidity and poor quality of life because of the incurable nature of the disease. Some are associated with increased mortality. Lesions are noted primarily on the skin and secondarily involve the oral cavity. Dental management mainly aims at improving the overall oral health. In general, dental treatments include topical steroids for oral ulcers and blisters, oral prophylaxis and oral hygiene instructions to maintain good oral hygiene, prophylactic plastic and fissure sealant application for those with high caries index, antifungal therapy for angular cheilitis, prosthetic rehabilitation, and orthodontic management for correction of malocclusion.

**Conclusion**

The available research in genetics related to genodermatoses has been narrowed to the western population; very few reports have been published from Indian studies. There is now better understanding of the genetic basis of genodermatoses with tremendous progress in their molecular diagnosis. Definitive diagnosis of most of the genodermatoses is difficult in resource-poor countries such as India; hence, clinical acumen of the physician with appropriate diagnostic algorithm for each group of disorder is helpful means to reach a provisional diagnosis; however, management is symptomatic in most of the cases. Genetic counseling and prenatal diagnostic facilities bring a ray of hope to affected families. With advancement in the fetal diagnostic technique, definitive prenatal diagnosis of several genetic disorders has become easier. At present, successful gene therapy is available for only a few disorders. The technology required to correct the defective gene formation is yet to be developed fully. Further active research in this field will bring new hopes for effective management of these incurable disorders.

**References**
