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A PEER LOOK ON PAPILLON-LEFÈVRE SYNDROME: A REVIEW

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ABSTRACT

Papillon-Lefèvre syndrome (PLS) is a very rare syndrome of autosomal recessive inheritance characterized by palmar-plantar hyperkeratosis and early onset periodontitis, leading to premature loss of both primary and permanent dentitions. Various etiopathogenic factors are associated with the syndrome, but a recent report has suggested that the condition is linked to x mutations of the cathepsin C gene. The dental treatment comprised oral prophylaxis, scaling and root planning, antibiotic therapy, instructions on oral hygiene, restorations, extraction of hopelessly affected teeth, and prosthetic rehabilitation. The purpose of this paper is to demonstrate clinical as well as radiological features of Papillion Lefevre Syndrome.

INTRODUCTION

Papillon lefevre is a rare genodermal condition characterized firstly by two French Physicians Papillon and Lefevre in 1924, in a brother and sister suffering from palmoplantar hyperkeratosis associated with early onset periodontitis and pre mature loss of deciduous as well as permanent dentition [1]. Gorlin et al [2] in 1964 have added the third component of dural calcification for making diagnosis of this syndrome. It has a prevalence of 1-4 cases per million in general population and the carrier frequency appears to be 2-4 per thousand populations with no sexual predominance. A genetic predisposition with greater frequency of occurrence in consanguineous offspring has been reported. It may be attributed to high rate of consanguineous marriages in Arab communities. But no predilection for gender or race has been documented. It is a rare, autosomal recessive disorder occurring between the first and fifth years of life.

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Phenotypically, the parents were healthy and there was no family history of the disease, suggesting an autosomal recessive pattern of inheritance. It is characterized by palmoplantar keratoderma (thickening of the stratum corneum of the skin on the palms of the hands and soles of the feet) and periodontitis followed by the premature shedding of both primary and permanent teeth. Usually these plaques get worsen in winters and had associated fissured lesions. In the field of dentistry, the most significant finding is early onset periodontitis which usually get started at the age of 3-4 years.

In addition, some patients manifest hyperhidrosis, the growth of fine body hair and the development of dirty colored skin on the affected parts. Calcifications of the falx cerebri of the dura mater, as well as other areas of the brain have been reported. There is usually gingival enlargement, gingival ulceration and the formation of deep periodontal pockets but in some cases, there is no inflammatory reaction and only the periodontium of the secondary teeth is affected [3].

Pathogenesis

The pathogenesis of Papillon Lefevre syndrome is still controversial. The skin lesions are thought to be because of disturbances in ectodermal and mesodermal components but there is no reason to explain the rapid loss of all the deciduous as well as permanent teeth in the order of their eruption. Two new aspects for the pathogenesis of PLS have been discovered. First, some patients suffering from PLS exhibit cellular immune defect with decreased chemotactic and phagocytic function of neutrophils and other granulocytes. Various immunologic defects have been described. A decreased peripheral T lymphocyte subpopulation (CD3 + CD4 +), noted in our patient, has been described [4]. Defective production of superoxide radicals by polymorphonuclear leukocytes (burst test), has been described in PLS patient. Defective chemotaxis of polymorphonuclear leukocytes is also a commonly described abnormality. Evidence has suggested that PLS patients have decreased chemotatic and phagocytic functions of neutrophil leucocytes, or a cellular immune defect involving decreased phyto-haemaglutinin response by T lymphocytes. Products of the Gram negative organisms isolated from PLS patients' periodontal pockets may directly or indirectly contribute to leucocyte dysfunction, and there may be genetic component in the white cell dysfunction. Second, some pathogenic micro-organisms as porphyromonas gingivalis, capnocytophaga gingivalis, actinobacillus actinomycetemcomitans, pepto streptococcus micros, fusobacterium nucleatum, and spirochetes have been implicated as the causative agents for periodontal problems in PLS. The gingiva is inflamed; bleed on slight provocation leading to rapid destruction of underlying periodontium. This rapidly progressing periodontitis is usually unresponsive to traditional periodontal treatment modalities [5].

It has been suggested that the presence of periodontal pathogens alone is not sufficient for the expression of PLS, and other factors, such as host response, play an important role in the pathogenesis of the disease process. Several authors have suggested an abnormal neutrophils dysfunction with PLS3 to explain the pathogenesis, whereas others have reported cases where they appeared within normal limits. It has been suggested that the development of periodontal disease in PLS patients might be associated with a specific profile of suspected subgingival pathogens coupled with some still unknown nature of altered and reduced immune defence [6]. In a number of case reports, Actinobacillus actinomy cetemcomitans has been observed in subgingival plaque samples from periodontal pockets in cases with PLS [7,8]. The development and eruption of the deciduous teeth occur normally but shedding occurs prematurely mostly by the age of 3-4 years. After the shedding the gingivae appears to be normal and condition again worsens with the eruption of the permanent teeth. The patient usually shed off all his or her permanent teeth by the age of 13-16 years. Later on third molars undergo the same fate. Because of resorption of underlying alveolar bone, teeth appear as floating in air in radiographs. Recently, the gene for PLS has been mapped to 11q14-q21.In 1999, Hart et al [9] identified a germline missense and truncating mutations in the gene encoding cathepsin C (or dipeptidyl aminopeptidase I), a lysosomal cysteine proteinase that plays an important role in intracellular degradation of proteins in families with PLS. Cathepsin C is an enzyme that processes and activates several granule serine proteases critical to immune and inflammatory responses of myeloid and lymphoid cells. Although the etiology of PLS remains relatively obscure, Hattab et al [10] classified the etiology into three types: immunologic, microbiologic, and genetic factors. From an immunologic point of view, an impaired neutrophil chemotaxis, phagocytosis and bactericidal activities accompanied by a decrease in cell migration was noted.

The immune mediated mechanisms such as lymphocytic response to pathogens, helper/suppressor T cells ratio and monocytic function were also impaired in this syndrome. Microbiologically, the presence of virulent gram negative anaerobic pathogens (Actinobacillus actinomycetomcomitans) in the periodontal pockets and periodontal plaques are noted which might act as trigger factors. Previous case reports and studies have reported that A. actinomycetomcomitans plays an important role in the pathogenesis and progression of the rapid periodontal breakdown seen in PLS [7,8]. In addition to the organism, the presence of leukotoxins, collagenase, endotoxin, epitheliotoxin and fibroblast inhibiting factors suggest that PLS is mediated bacteriologically. Recently genetic factors, have gained importance in the pathogenesis of PLS due to advancements in the field of genetic engineering. The inactivation of the cathepsin C gene is recently noted as the primary factor that is responsible for the abnormalities in skin development and periodontal disease progression. An interesting point about the cathepsin C gene is that mutations in this gene also results in two closely related conditions: i) Haim-Munk syndrome and ii) aggressive periodontitis. The cathepsin C gene is expressed in the epithelial regions and in various immune cells including polymorpho nuclear leucocytes, macrophages and their precursors. Microbially gram negative microbial polysaccharides are recognized as the primary factors in the etiology of periodontitis in Papillon-lefevre Syndrome. Actinobacillus actinomycetemcommitans constituted more than 50% of colony forming units [11].

DISCUSSION

The degree of dermatologic involvement may not be related to the level of periodontal infection. Nail changes such as transverse grooving and fissuring are apparent in advanced cases. The dental features of Papillon-lefevre syndrome are the looseness, hyper mobility, drifting, migration and exfoliation of teeth

without signs of root resorption.

Primary teeth are exfoliated or extracted and child becomes completely edentulous by the age of 4-5 years with gingiva returning to normal healthy state. Same cycle begins with the eruption of permanent teeth and by the age of 13-15 years if not intervened all permanent teeth is lost [12]. Chewing is very painful because of the mobility of teeth. Fetid mouth odour and regional lymphadenopathy are observed commonly. Radiographic examination reveals severe loss of alveolar bone and teeth appear to be"floating in air". Patients typically have an underlying disease associated with functional or quantitative neutrophil abnormalities, and 50% are immunocompromised. Increase susceptibility to infections was reported in 20 per cent patients due to dysfunction of leucocytes and neutrophils. Pyogenic liver abscess is increasingly recognized as a complication PLS associated with impairment of immune system [13].

Management

Papillon Lefevre syndrome can drastically affect the psychology of patient especially young children because of social and esthetical problems. Hence, early dental evaluation and parental counseling as a part of preventive dental treatment is needed. A multidisciplinary approach is needed for providing a complete psychological rehabilitation to improve the prognosis and quality of life. Palmoplantar keratoderma is usually treated with topical emollients. Salicylic acid and urea can be added to enhance their effect. Systemic retinoids have proven to be effective. The concern that retinoid treatment in PLS may increase the risk of pyogenic liver abscess, is probably unfounded, as this may occur in patients not receiving retinoids. The periodontitis is usually difficult to control. Reported effective treatment includes extraction of the primary teeth combined with oral antibiotics and professional teeth cleaning [14].

Etretinate and acitretin have been though claimed to modulate the course of periodontitis and preserve the teeth, frequently do not succeed in preserving the permanent teeth. Prophylactic antibiotics use has not been studied, and there are no clear guidelines. Frequent periodontal cleaning, oral hygiene instructions and antibiotic therapy only delay the shedding of teeth. Early extraction of teeth has been advocated to prevent bone loss. Moreover, this allows solid base for subsequent use of artificial dentures [15]. Etretinate, isotretinoin and acitretin have all been successful in improving the cutaneous as well as gingival lesions. However, normal dentition is observed with retinoids only, when given before the onset of permanent teeth at 5 years of age. Prosthetic replacement in Papillon lefevre syndrome is age specific, specialty job involving initial replacement with complete or partial dentures with future consideration for implant supported prosthesis. Because the etiology and pathogenesis of PLS periodontitis is directly related to high levels of Actinobacillus actinomycetemcomitans, the use of an antibiotic that acts specifically on this pathogen has been claimed to be important for a successful treatment. Some authors have recommended the elimination of periodontal pathogenic flora through premature extraction of all primary teeth combined with antibiotic coverage in an attempt to minimize the possibility of infection of the unerupted permanent dentition. Selecting the ideal treatment is not as clear-cut when the patient seeks dental care in the mixed dentition stage or later. In these patients, the treatment plan may include either extraction of all erupted teeth followed by a period of antibiotic coverage or extraction of only the hopelessly affected teeth combined with periodontal therapy for the remaining teeth with antibiotic coverage [16].

Mc Donald et al. have put forward the following guidelines for the successful management of PLS cases. It includes: i) extraction of all deciduous dentition, ii) construction of complete dentures three months after the removal of primary teeth, iii) prophylactic doses of tetracycline for 10 days immediately after the denture insertion, iv) adjustment of denture bases to allow for the emergence of the permanent dentition followed by another therapeutic dose of the tetracycline . Tetracycline should be administered at a dosage of 250 mg four times daily for one month [17].

Papillon Lefevre Syndrome should be differentiated from Langerhans' Cell Histiocytosis (Histiocyto-sis X), Hypophosphatasia, and Haim Munk Syndrome.

1. Langerhans' Cell Histiocytosis (Histiocytosis X): The presenting signs include pain, swelling, ulceration and loose teeth and alveolar bone loss. Radiographically, the teeth often appear to be "floating in air" surrounded by large radiolucent regions. Mandible is most frequently affected. The presence of alveolar bone loss in young children with precacious exfoliation of primary teeth suggests the possibility of histocytosis X. LCH represents a spectrum of clinical disorders ranging from a highly aggressive and frequently fatal leukemia like disease affecting infants to a solitary lesion of bone. The term eosinophilic granuloma is used when a solitary lesion is found, but multiple lesions may develop later. The cause of LCH is unknown. It may be triggered by an unusual reaction of the immune system to something commonly found in the environment. It is not a known infection or a cancer and, although there may be a more than one patient in certain families, it is usually not hereditary. Around 10-20% of patients, usually infants, die. In other patients there may be long term sequelae due to damage caused by the disease. Not all children require specific treatment [18].

2. Hypo phosphatasia is autosomal recessive disorder characterized by low level of serum alkaline phosphatase.

Teeth are lost without any evidence of inflammation of gingival or periodontal disease. A radiograph shows extensive alveolar bone loss [19].

3. Haim and Munk syndrome is a condition with congenital palmoplantar keratosis, progressive early onset of periodontal destruction, recurrent pyogenic skin infections, acro-osteolysis, atrophic changes of the nails, arachnodactyly, and a peculiar radiographic de-formity of the fingers consisting of tapered, pointed phalangeal ends.

4. Feer's syndrome When there is premature loss of deciduous and/or permanent teeth, one should also consider Acrodynia which is also known as Feer's syndrome. This condition is usually caused by mercury intoxication. Here one may observe a red desquamative process involving both the extremities. But in addition there are erythocyanosis, muscle pain, insomnia, sweating, tachycardia and psychic disturbances. The teeth erupt prematurely, have dystrophic enamel, and are shed prematurely. Acrodynia is seen in children between the ages of six months and four years [20].

5. Hypophospotasia Another condition of interest in differential diagnosis is Hypophosphatasia. In addition to the clinical features of knock-knee, bowing of femur and tibia and enlarged wrists. The teeth are prematurely shed and are hypoplastic. Diagnosis can be made on basis of increased amounts of phosphoethanolamine in the urine [21].

6. Takahara's syndrome Another condition characterized by progressive gangrenous lesions involving the gingiva and alveolar bone, resulting in exfoliation of the teeth is Acatalasemia or Takahara's syndrome. This is also transmitted as an autosomal recessive trait but has rarely been observed outside Japan.

7. In cyclic neutropenia severe periodontal disease may also be present but palmoplantar hyperkeratosis is absent. Other condition to be considered in differential diagnosis of Papillon-Lefevre syndrome are palmoplantar hyperkeratosis of Unna Thost, mal de Meleda, Howel-Evans syndrome, keratosis punctata, keratoderma hereditarium mutilans (Vohwinkel's syndrome), and Greither's syndrome. However while these entities are associated with palmoplantar hyperkeratosis but there is no periodontopathy [22].

Figure 1. Showing hyperkeratosis of palmar surface Courtesy: J Clin Exp Dent. 2010; 2(1):e43-6.

Figure 2. Showing hyperkeratosis of plantar surface Courtesy: J Clin Exp Dent. 2010; 2(1):e43-6.

CONCLUSION

The dental professional is mostly first one to detect the periodontal manifestations of patients suffering from PLS. A thorough knowledge of all the symptoms and signs of this syndrome as well other conditions having similar manifestations may help the dentist to make a diagnosis of the syndrome at an early stage.

Hence dentist can prevent the loss of permanent teeth by early institution of oral retinoinds during the eruption of permanent teeth. Even if the patient comes at later stages, dentist can administer prompt periodontal treatment regimens to preserve disease free teeth with early extraction of affected teeth to prevent the alveolar bone loss.

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