

# Papillon-Lefèvre Syndrome: Case Report and Genetic Analysis

## SUMMARY

**Background/Aim:** Papillon Lefèvre syndrome is a rare autosomal recessive genodermatosis. The characteristic findings of the disease are early loss of primary and permanent teeth and palmoplantar keratoderma. Notwithstanding that many etiologic factors like genetic mutations, bacterial agents, immunologic changes have been identified, the pathogenesis has not been fully understood. Although dentists play an important role in the diagnosis and treatment of Papillon Lefèvre syndrome, it is appropriate to treat the disease with a multidisciplinary approach. **Case Report:** In this case report, the clinical, radiological and genetic examination of the patient with Papillon Lefèvre syndrome who has a homozygous mutation in the CTSC gene will be presented. **Conclusions:** Dentists should have knowledge about treatment management of these patients. Teeth can be preserved longer with early diagnosis and appropriate treatment of the disease.

**Key words:** Papillon Lefèvre, Cathepsin C, Gene Mutation

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**CASE REPORT (CR)**

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## Introduction

The syndrome was first described by Papillon and Lefèvre in 1924<sup>1</sup>. The disease is characterized by diffuse palmoplantar keratoderma and prematurely starting aggressive periodontitis affecting both dentitions. It has an autosomal recessive inheritance pattern. The patients have cathepsin C(CTSC) gene mutation<sup>2</sup>. The symptoms that may accompany are hyperhidrosis, arachnodactylia, intracranial calcification, tendency to infection and mental retardation<sup>3,4</sup>. The incidence of the disease has been reported to be 1 to 4 in a million. The incidence is higher in societies where consanguineous marriages are common. Girls and boys are affected equally by the disease<sup>5</sup>.

Cutaneous lesions usually begin to appear along with oral findings between 6 months to 4 years of age. Cutaneous lesions have been considered to develop due to the disorders of ectodermal and mesodermal components<sup>6</sup>. Cutaneous lesions are seen in Papillon Lefevre syndrome since CTCS gene is expressed in epithelial tissues. Hyperkeratosis and erythema are present in palms and soles. Keratinization may spread to the dorsum of hands and feet. Hyperkeratotic plaques developed might be associated with hyperhidrosis of the hands and feet and may

end up with foulodor<sup>6</sup>. The lesions may appear as patches or deep fissures with different colors and appearances. Eyelids, cheeks, knees and labial commissure might also be involved<sup>7</sup>. The patients report that their complaints increase in cold weather<sup>8</sup>. Horizontal growth and fissure formation might be seen in nails in advanced cases.

Vertical bone loss in first molars is seen in localized forms of PLS as radiographic findings, while this bone loss may include all teeth in the generalized form. "Floating in air" image might develop in radiography since bone support of the teeth is completely lost in very advanced stages<sup>8</sup>.

Some cases are reported to have microdonti, root eruption and deterioration in root formation although there is no change in the form and time of tooth eruption of primary teeth<sup>10,11</sup>. Upon eruption of primary teeth, an inflammatory picture begins in gingiva. Gingiva is hyperemic and edematous. Flow of pus from periodontal pockets is seen. After premature loss of primary teeth, gingiva returns to normal. The process repeats in conjunction with the eruption of permanent teeth. The patients with Papillon Lefèvre syndrome usually remain toothless at age of 14-15. Alveolar bone resorption is observed in radiographic assessment<sup>12</sup>. Wisdom teeth are usually not affected by the disease.

## Case Report

A 19-year-old male patient was referred to Department of Oral and Maxillofacial Surgery of Dentistry Faculty, Abant Izzet Baysal University to be evaluated for implant indications before prosthetic rehabilitation. In the clinical examination, palmoplantar hyperkeratosis (Figure 1), loss of all teeth except wisdom teeth, maxillary and mandibular growth retardation were observed. Mental functions of the patient were not affected. In the radiographic examination, resorption in the alveolar crests was detected (Figure 2). Wisdom teeth were not affected by the disease. In the anamnesis of the patient, it was stated that he was informed by a physician that he had a genetic disorder but no detailed examination was performed. He reported that his teeth had been extracted due to loosening at the age of 12 and started using prosthesis. He has been using the same prosthesis for seven years. No family member was affected by the disease. There was no consanguinity between the parents of the patient. Hematologic examination revealed no anomalies. In the genetic analysis of the patient, it was confirmed that he was carrying p.Gly139Arg (c.415 G>A) mutation which was found in exon 3 of CTSC gene homozygously. It is known that the mutation in the patient causes Papillon Lefèvre syndrome<sup>13</sup>. The diagnosis became definite as a result of clinical, hematological and genetic studies.



Figure 1. Palmoplantar hyperkeratosis

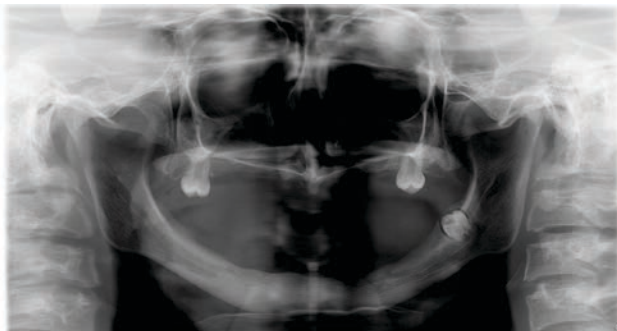


Figure 2. Radiographic view shows maxillary and mandibular alveolar crest resorption

Due to constant use of the same prosthesis during growth and development period and being toothless, there was inadequate development of jaws in horizontal and vertical planes. The vertical dimension decreased and the denture face appearance occurred in the patient. The success rate and cost of implant therapy were explained and the patient was notified that additional surgical procedures may be required. Renewal of the prosthesis was offered to the patient as the second treatment option. The patient rejected implant therapy since it has high cost and is an invasive treatment and he wanted his prosthesis to be renewed.

## Discussion

Although the etiology of Papillon Lefèvre syndrome is not fully understood, the syndrome has been associated with cathepsin C gene mutation, various microbial agents and immunologic factors<sup>14</sup>.

Dipeptide peptidase 1, also known as cathepsin C, is a lysosomal cysteine protease and is encoded by the cathepsin C gene which is located on the 11q14.1-q14.3 chromosome. Seventy-five different mutations related to the CTSC gene have been described<sup>15</sup>. Among the mutations, 75% are homozygous and among the homozygous mutations, 50% are lost mutation, 25% are meaningless mutation, 23% are frameshift mutation and 2% are other type mutations<sup>16</sup>. Mutation of c.415 G>A, seen in this presented case was defined first by Zhang *et al.* as heterozygous in a PLS patient with Caucasian origin<sup>13</sup>. Cases carrying homozygous c.415 G>A mutation have also been reported<sup>17,18</sup>. CTSC, CTSG and elastase functions are almost completely lost in homozygous mutations<sup>17</sup>.

Cathepsin C plays an important role in the activation of cytotoxic T lymphocytes, natural killer cells, mast cells and serine proteases in neutrophils<sup>19</sup>. It also functions in collagen type I, III, IV and fibronectin degradation<sup>20</sup>. In Papillon Lefèvre syndrome, as a result of the inactivation of serine proteases in inflammatory cells due to mutations in the CTCS gene, impairment occurs in the immune system<sup>14</sup>. The periodontal disease and the tendency to infection are caused by the impairment of neutrophil, T lymphocyte and B lymphocyte functions<sup>21,22</sup>. The first immune dysfunction developing in PLS is the impairment of the cytotoxic functions of natural killer cells<sup>8</sup>.

*Aggregatibacter Actinomycetemcomitans*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Prevotella intermedia* are the bacteria which are present in high numbers in periodontal pockets of the patients with Papillon Lefèvre syndrome and therefore they are held responsible for the pathogenesis of the disease<sup>23</sup>. High levels of immunoglobulin against *Aggregatibacter Actinomycetemcomitans* have been

observed in individuals affected by the disease<sup>8</sup>. In Papillon Lefèvre syndrome, there is a decrease in the neutrophil response to *Staphylococcus spp.* and *Aggregatibacter Actinomycetemcomitans*<sup>8</sup>. Herpes viruses in addition to the pathogenic bacteria including *Aggregatibacter Actinomycetemcomitans* and also impairment of the host immune response are considered to play role in periodontitis developing in patients with Papillon Lefevre syndrome<sup>24</sup>.

There is no specific histopathological finding associated with Papillon Lefevre syndrome. Hyperkeratosis, acanthosis, hypergranulosis or psoriasiform hyperplasia might be seen in gingival epithelium<sup>8</sup>. Intense inflammatory infiltration in patients with PLS is observed in the subepithelial connective tissues of the periodontal tissues. Dominant cells of this inflammation are the plasma cells<sup>25</sup>.

Dental treatment of patients with Papillon Lefevre is challenging for both the patient and the dentist since the prognosis is poor and outcome is unpredictable. The main goal of the periodontal treatment in Papillon Lefèvre syndrome is to optimize oral hygiene and keep the teeth in the mouth as long as possible. For this purpose, oral hygiene education is given, scaling and root planning is performed and oral rinse with 0.2% chlorhexidine is recommended. Antibiotics may be used in the presence of active periodontitis. The most commonly used antibiotics for this purpose are erythromycin and tetracycline. There are also studies reporting that amoxicillin metronidazole or amoxicillin clavulanic acid combinations result in success<sup>26</sup>. Some investigators defend the idea that cleaning the oral cavity from pathogen bacteria and then the tooth eruption of the permanent teeth uninfluenced from the infection increases the duration of permanent teeth stay in mouth<sup>8,27</sup>. For the treatment of cutaneous lesions, retinoids, salicylic acid and steroid are applied. Use of retinoid was reported to increase alveolar bone height and periodontal attachment level, reduce periodontitis formation and improve cutaneous lesions<sup>28-30</sup>.

There are studies reporting that the use of dental implants result in success for prosthetic rehabilitation of PLS patients<sup>31,32</sup>. Senel *et al.* followed a PLS patient, to whom they applied implant therapy, for 3 years and reported successful results<sup>32</sup>.

The role of the dentist is very important in the diagnosis and treatment of PLS. Duration of stay of the teeth in mouth can be prolonged when the disease is treated appropriately. This situation is important for the preservation of maxillary and mandibular bone height. Unfortunately, it was late for these treatment options when the patient was admitted to us. The most appropriate treatment options were presented to the patient and the decision was left to him. He was informed about his disease and possible complications were explained.

## Conclusions

Dentists should have knowledge about treatment management of these patients. Teeth can be preserved longer with early diagnosis and appropriate treatment of the disease.

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