Could Congenital Insensitivity to Pain with Anhidrosis Be Misdiagnosed as Papillon–Lefèvre Syndrome?

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Abstract

Keywords

- ▶ early loss of teeth
- ▶ congenital insensitivity to pain with anhidrosis
- ▶ Papillon–Lefèvre syndrome

Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive disorder characterized by early loss of teeth with hyperkeratosis of the palms and soles. Congenital insensitivity to pain with anhidrosis (CIPA) is a disorder of decreased pain sensation, decreased sweating, recurrent infections, and fever. Here, we report a 5-year-old girl born to consanguineous parents with a family history of a similarly affected sibling. The girl presented with early loss of teeth and palmoplantar hyperkeratosis, hence, provisionally diagnosed as PLS. Further clinical examination and detailed history taking shifted the diagnosis to CIPA. CIPA could be misdiagnosed as PLS. Congenital insensitivity to pain with anhidrosis, although rare, should be considered in the differential diagnosis of PLS.

Introduction

Papillon–Lefèvre syndrome (PLS, OMIM 245000), is a condition of severely destructive and rapidly progressive periodontal disease and hyperkeratosis of the palms and soles.¹ It is an autosomal recessive disorder with greater frequency among consanguineous offspring. A loss-of-function mutation affecting the cathepsin-C gene *CTSC* on chromosome 11q14.1-q14.3 has been associated with PLS.² The prevalence of the disease is 1 to 4 per million.³ Recurrent skin infections and liver abscesses are frequently reported.^{4–6} Mild mental retardation and intracranial calcifications were also reported.¹

Congenital insensitivity to pain with anhidrosis (CIPA) (OMIM, 256800), is an extremely rare autosomal recessive disorder⁷ with an incidence of 1 in 125 million newborns.⁸ CIPA is characterized by congenital insensitivity to pain with intact tactile perception, lack of thermal sensitivity, proprioception, and vibratory sensation.⁹ Patients have recurrent episodes of infections, mental retardation, self-mutilation, anhidrosis, failure to thrive, and recurrent episodes of fever

secondary to anhidrosis.¹⁰ The disorder is caused by a mutation in the *NTRK1* gene “neurotrophic tyrosine kinase receptor, type 1” located on chromosome 1q21–22. This *NTRK1* gene is responsible for a protein formation that is essential for the development and survival of nerve cells, especially sensory neurons.¹¹

Through this report, we highlight that CIPA could present with clinical and radiographic features that mimic those main characteristic features of PLS, which might result in misdiagnosis of CIPA.

Case Report

A 5-year-old girl presented at the Oro-Dental Genetics Outpatients' Clinic, National Research Centre. The parents complained of their child's teeth becoming loose and exfoliate spontaneously. She was one of the two affected siblings of a double consanguineous couple, born to full term with an unremarkable perinatal period. She had a history of recurrent attacks of fever. She was noted to have a long face, hairy forehead and eyebrows, trichomegaly, broad nose, and

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Fig. 1 (A) Loss of lower teeth, intraoral ulcers, and scars on the tongue and alveolar mucosa, (B) perioral scars, (C, D) mild hyperkeratosis of the palms and soles. (E) Panoramic radiograph showing the absence of nearly all of the lower permanent set of teeth, (F) radiograph showing mild thumb acro-osteolysis.

hypotonia. Intraoral examination revealed loss of all erupted lower teeth, thin atrophic lower alveolar ridge, atrophic ulcerated tongue, and enamel hypoplasia (►Fig. 1A). Extra-oral examination showed multiple scars in the perioral region (►Fig. 1B), fingers and legs in addition to slight palmoplantar hyperkeratosis (►Fig. 1C, D). The clinical evaluation also revealed bilateral hyperextensibility of upper limbs and left genu valgum. She had no motor developmental delay; however, she suffered mild mental subnormality. Panoramic radiography confirmed the loss of all erupted lower teeth (►Fig. 1E) and hand X-rays revealed mild acro-osteolysis (►Fig. 1F).

The studied case was provisionally diagnosed as Haim-Munk syndrome (HMS; OMIM 245010), the allelic variant of PLS. The diagnosis was based on clinical and radiographic manifestations as early loss of teeth combined with palmoplantar hyperkeratosis and acro-osteolysis. However, this diagnosis did not explain the survival of the upper set of teeth with no signs of periodontal disease characteristic for PLS. Further history taking revealed tongue ulcers as well as habits of lip and finger biting. Suspicions were then directed toward one of the self-mutilation syndromes. Moreover, the girl had experienced absent reactions toward noxious and painful stimuli, anhidrosis, recurrent fever, hip dislocation at the age of 1 month and fractured right tibia followed by

secondary osteomyelitis at the age of 2.5 years. All of the above unexpectedly shifted the diagnosis to CIPA.

Discussion

PLS and CIPA are two disorders with considerably different clinical courses and pathogenesis.^{2,12} The reported case was initially diagnosed as HMS, the allelic variant of PLS, based on the presence of spontaneous early loss of teeth according to her parent's words, palmoplantar hyperkeratosis, and acro-osteolysis.¹³ However, later investigations revealed misdiagnosis and diagnosis of CIPA was then adopted.

Symptoms of periodontitis of PLS appear as teeth erupt leading to premature loss of the deciduous dentition. Once the primary dentition exfoliates, the gingiva regains its normal appearance. However, the eruption of permanent teeth retrigger periodontitis and results in partial or complete loss of teeth at a very young age.¹² On the other hand, early loss of teeth associated with CIPA has a cause which is completely apart from any dental component. Patients of CIPA have sensory and autonomic dysfunction with profound insensitivity to pain resulting in self-mutilation, and auto-amputation.¹⁴ Autoextraction was the most common cause of early loss of teeth in patients with CIPA as reported by Amano et al.¹⁵ In their report of 24 cases of CIPA, Bodner et al

pointed out that some of the patients had their mandibular incisors been extracted immediately following their eruption to prevent further trauma.¹⁶ This explained why the periodontium of the upper teeth in the studied case lacked classic manifestations of periodontitis. The patient used to self-mutilate her lower teeth rather than her upper ones. Self-mutilation practiced by the patient explained her atrophic and ulcerated tongue as well.

Keratoderma, the main feature in PLS, can present in the first 3 months of life, although palmoplantar hyperkeratosis first appears in the years 1 to 4.¹ Our case presented some palmoplantar hyperkeratosis which also misled to the initial diagnosis of PLS. Meanwhile, it was reported that many individuals with CIPA have thick, leathery skin on the palms and soles and areas of hypotrichosis on the scalp.¹⁷ Anhidrosis associated with CIPA contributes to the skin calloused appearance with lichenification of palms and dystrophic nails.¹⁸ Also, patients with CIPA have definite problems in healing of ectodermal structures (skin and bone) although they have no immunological problems.¹⁹

Finally, the reported case showed some degree of radiographic acro-osteolysis, a common feature in HMS, as a result of self-mutilation of her digits, which greatly participated to the misdiagnosis as HMS.

Conclusion

Congenital insensitivity to pain with anhidrosis and PLS and its allelic variant, HMS may have strikingly similar features of early loss of teeth, palmoplantar hyperkeratosis, and acro-osteolysis. Congenital insensitivity to pain with anhidrosis could be misdiagnosed as PLS or HMS and hence should be considered in the differential diagnosis of these two syndromes.

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Conflict of Interest

None.

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