Commentary

Of palms, soles, and gums

Of not quite venerable status, Papillon-Lefèvre syndrome was first described in 1924. That was a year after I was born and one never likes to think of oneself as venerable. However, as a graduate fellow in pathology at Columbia Presbyterian Hospital, New York, USA in the late 1940s, my initial exposure to the general concept of syndromes had only just occurred (acanthosis nigricans and gastric adenocarcinoma). Although I had high hopes that other oral syndromes existed for me to identify (the idea of discovering a new one did not enter my mind at the time), I remember talking about my new found interest to almost everyone I encountered at Columbia University Dental School, my hope being that they would show me a new one. In late 1949, Dr Sam Rosenthal, Chair of Pediatric Dentistry, knowing of my interests, asked me to see a child who was experiencing exfoliation of his entire dentition. The child clearly did not have mercury intoxication.

I noticed that his palms and soles were thick and calloused. Not finding an obvious explanation, I wondered whether this patient had one of those syndromes. Knowing nothing about binary combinations, I set out to do my first library search, hampered by my inchoate knowledge of German and French. Pure chance led me to very brief notes by Corson[1] and Woods and Wallace.[2] With a little help, I tracked down the paper of Wannenmacher.[3] All routes led back to Papillon and Lefèvre.[4]

Before finishing my fellowship, I presented my evidence to Dr Rosenthal and he published one of the first examples of the syndrome in a dental journal.[5]

Papillon-Lefèvre syndrome is a very rare (1-4/million) autosomal recessive disorder characterised by diffuse, red, scaly palms and soles which appear from 2 to 4 years of age. The hyperkeratosis of the palms is quite well demarcated, extending to the edges, over the thenar eminences, and to the volar wrists. The soles are more severely involved, the process frequently extending to the Achilles tendon. Occasionally, the elbows, knees, external malleoli, and tibial tuberosities are involved.

The development and eruption of the deciduous teeth proceed normally but, about the time of appearance of the palmar and plantar lesions, the gingiva swell, bleed, and become boggy. Inexorable periodontal disease ensues until all deciduous teeth are shed by the age of 4 years. The mouth heals and appears normal until the secondary teeth erupt, when the process is repeated. Most secondary teeth are lost by 14 years. There was considerable debate but no resolution regarding a general increased susceptibility to infections.[6]

Haim and Munk[7] in 1965 and others subsequently reported a somewhat similar disorder in inbred Jewish families from Cochin, India on the Malabar Coast who migrated to Israel. In addition to congenital palmoplantar hyperkeratosis, there were progressive periodontal destruction, pes planus, recurrent pyogenic skin infections, arachnodactyly, and unique, tapered, pointed phalangeal ends, and a claw-like volar curve. In contrast to Papillon-Lefèvre syndrome, the skin manifestations are more severe and extensive and there is later onset. The periodontium is less severely affected. We suggested that the Haim-Munk and Papillon-Lefèvre syndromes were allelic.[6]

In 1997-98, three independent groups[8–10] mapped the gene for Papillon-Lefèvre syndrome to 11q14-q21. Last year, Hart *et al*[11] identified germline missense and truncating mutations in the gene encoding cathepsin C (or dipeptidyl aminopeptidase I), a lysosomal cysteine proteinase which plays an important role in intracellular degradation of proteins, in families with Papillon-Lefèvre syndrome. These results were also found by an independent group.[12] In this issue, Hart *et al*[13] show that Haim-Munk syndrome is allelic to Papillon-Lefèvre syndrome. More tantalising, however, is the identification of a germline missense mutation in a highly conserved residue in the cathepsin C gene in familial prepubertal site specific periodontitis.[14] Since periodontitis is a common problem among the general population, affecting perhaps 30%, these findings might have public health implications.

Our dentists and dental hygienists have always preached to us that periodontal disease is a result of microbial onslaught and poor oral hygiene. The genetic aetiology of Papillon-Lefèvre syndrome, Haim-Munk syndrome, prepubertal periodontitis, and other syndromes have suggested that there is a genetic basis for susceptibility to these microbes. The susceptibility gene for Papillon-Lefèvre syndrome, Haim-Munk syndrome, and prepubertal periodontitis is cathepsin C. Cathepsin C is an enzyme which processes and activates several granule serine proteases critical to immune and inflammatory responses of myeloid and lymphoid cells. Loss of function mutations in the gene in these three disorders should, therefore, result in an altered immune response to infection. This would explain both the oral and dermatological phenotypic spectrum of the three syndromes. The series of ground breaking work by Hart and colleagues lends new meaning to the much used adage "by the skin of one's teeth"!

For me, it has been a long 50 year voyage, but a fascinating one.

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