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FIRST CASE REPORT OF PAPILLON-LEFÈVRE SYNDROME FROM GEORGIA

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პაპილონ-ლეფევრის სინდრომის პირველი შემთხვევა საქართველოდან

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის მოლეკულური და სამედიცინო გენეტიკის დეპარტამენტი, თბილისი, საქართველო

რეზიუმე

პაპილონ-ლეფევრეს სინდრომი (PLS) ძალიან იშვიათი აუტოსომურ-რეცესიული დაავადებაა, რომელიც პალმოპლანტარული ჰიპერკერატოზითა და მძიმე, ადრეულ ასაკში გამოვლინებული პერიოდონტიტით ვლინდება, რაც ორივე, სარძევე და მუდმივი კბილების ნაადრევ დაკარგვას იწვევს. PLS-ის ეტიოლოგიის კომპლექსურია და მოიცავს გენეტიკურ, იმუნოლოგიურ და მიკრობიოლოგიურ ფაქტორებს. მუტაციები 11q14-q21 გენში, რომელიც სხვადასხვა ანთებით და იმუნოლოგიურ პროცეს მონაწილე გენს - კათეფსინ C-ს მოიცავს, წარმოადგენს წამყვან გენეტიკურ დეფექტს, რომელიც PLS-ს იწვევს. PLS-ის მკურნალობა კომპლექსურია და მოითხოვს მულტიდისციპლინურ მიდგომას. წარმოდგენილ სტატიაში ჩვენ აღვწერთ PLS-ის პირველ შემთხვევას საქართველოდან, აქამდე აღუწერელ ვარიანტს CTSC გენში და ყურადღებას გავამახვილებთ მთლიანი ეგზომის სექვენსირების (WES) მნიშვნელობაზე საბოლოო დიაგნოზის დასმაში.

Introduction

Papillon-Lefèvre syndrome (PLS) is an exceedingly rare genetic condition with around 250 reported cases in the literature [1]. It's characterized by palmoplantar hyperkeratosis and severe prepubertal periodontitis, which results in premature loss of both deciduous and permanent teeth. PLS is inherited in an autosomal recessive condition and results from mutations of the *CTSC* gene that regulates production of lysosomal protease cathepsin C. The exact etiology of disease is still not fully elucidated, and it seems that environmental, genetic, and immunologic factors influence its onset [2]. Cathepsin C is expressed at high levels in immunogenic responses that activate serine proteases, as well as in epithelial tissue [3]. This could explain the main clinical features of PLS that include an increased risk of infectious diseases, progressive periodontitis, gingivostomatitis and palmoplantar keratoderma. Here, we report the first case of PLS described in Georgia.

Case Report

We describe a case of 10-year-old otherwise healthy girl who presented to the Givi Zhvania Pediatric Academic Clinic at Tbilisi State Medical University, Georgia with a chief complaint of loosening of permanent teeth, loss of mandibular central incisor and diffuse mild transgradient palmoplantar keratosis and erythema. The condition started at the age of 7 with a periodontal disease. She was born with a hemangioma on the upper lateral arm which was surgically treated. She was a second child in non-consanguineous family. The parents and other family members were not affected. Pregnancy and delivery were normal. Her birth height was 51 cm, and his weight was 3000 gr. Treatment included various antiseptic oral rinses and topical steroid medications for palmoplantar keratosis previously diagnosed as psoriasis with a little improvement. Intraoral examination showed loosening of permanent teeth and loss of mandibular central incisor (Fig. 1). Dermatologic examination revealed diffuse erythema and mild hyperkeratosis of palms and soles (Fig. 2). Dental panoramic radiograph displayed several floating teeth with generalized horizontal and vertical bone loss (Fig. 3). Physical and cognitive development was normal. Reminder of the physical examination was unremarkable. Routine hematological and biochemical tests were normal. Whole exome sequencing (WES) was performed, which revealed two variants in *CTSC* gene: a previously described c.415G>A p. (Gly139Arg) and a novel c.1220T>A p. (Val407Asp) variants. The patient was prescribed topical tretinoin 0.1% cream once a day and emollients which resulted in complete clearing of palmoplantar hyperkeratosis within one month, treatment with retinoid

discontinued and the effect is long-lasting (6 months posttreatment). The enforcement of oral hygiene habits was advocated, and she was referred to dental care team for the management of periodontal disease.

Figure 1 A and B: Intraoral photograph showing missing in lower arch.

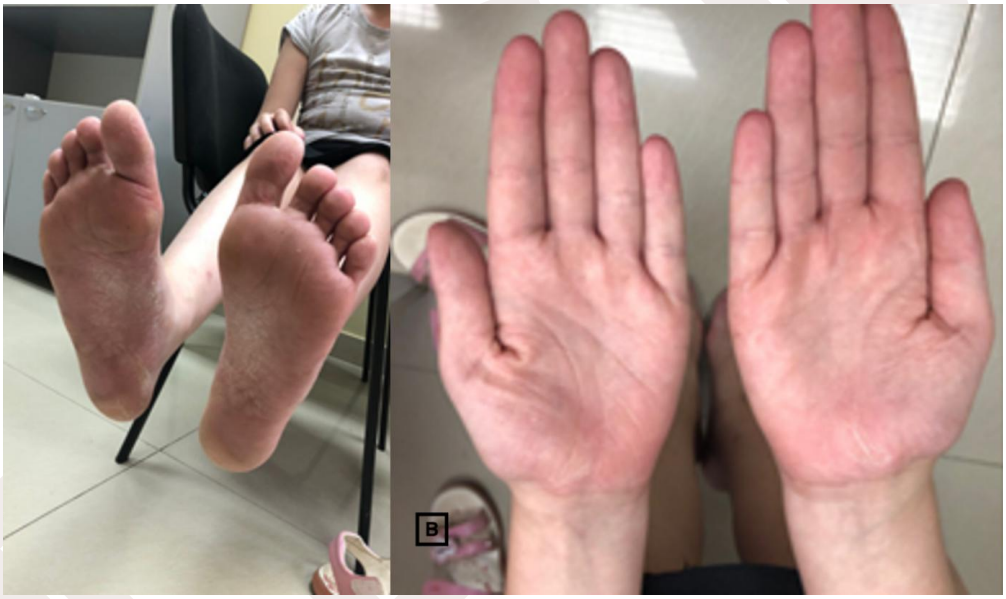

Figure 2 A and B: Diffuse erythema and mild hyperkeratosis of palms and soles.

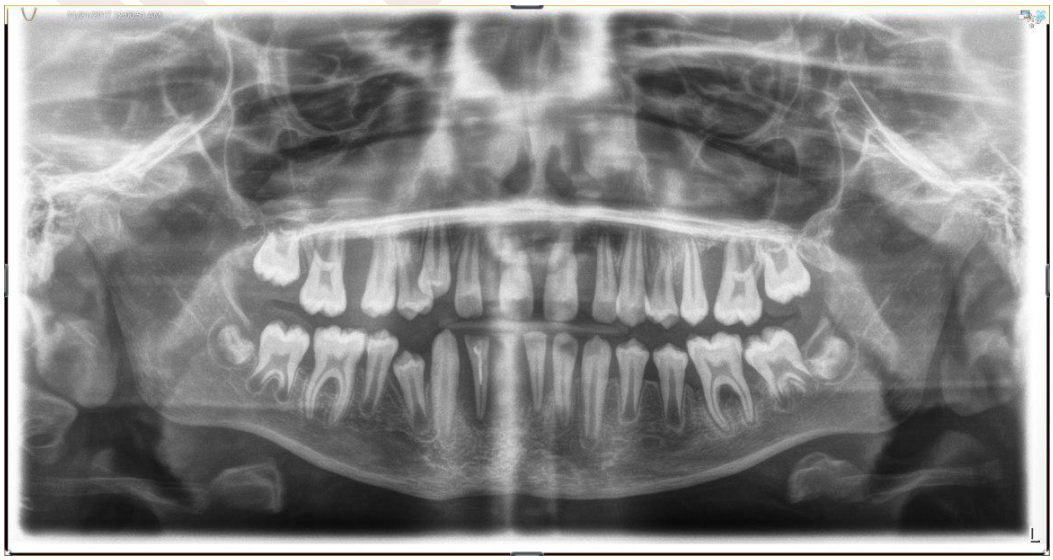

Figure 3: Panoramic radiograph of the dental arch.

Discussion

Papillon-Lefèvre syndrome (PLS), also known as hyperkeratosis palmoplantaris with periodontosis or keratoris palmoplantaris with periodontopathia, is a rare ectodermal dysplasia characterized by palmoplantar keratoderma with early-onset periodontitis. It was first described by French physicians

M. M. Papillon and Paul Lefèvre in 1924 [4]. The prevalence is estimated between 1/250,000 and 1/1,000,000 individuals with no sex or racial differences. The onset of the symptoms starts early during childhood and typically becomes apparent from approximately one to five years of age. PLS is an autosomal recessive genetic disorder that is caused by a mutation in the *CTSC* gene encoding lysosomal exo-cysteine protease cathepsin C [5]. Cathepsin C appears to be a critical coordinator for activation of several serine proteases in immune and inflammatory cells. It also regulates the formation of the enveloped corneocytes [6]. Clinically PLS is characterized by symmetric palmoplantar hyperkeratosis and severe, early-onset periodontitis, leading to the premature loss of teeth. Cases with mild and/or late-onset periodontal disease have been reported occasionally. Other manifestations include increased susceptibility to skin and systemic infections, hyperhidrosis, follicular hyperkeratosis, nail dystrophy, mild mental retardation, or dural calcifications [7]. PLS affects psychological, social, and esthetic well-being of the patient and requires multidisciplinary approach to improve the quality of life. Dental team involvement is needed for the treatment of periodontal disease and prevention of its complications. A dermatologist can manage the skin manifestations. Emollients, salicylic acid, urea, and topical steroids are used. Retinoids can also be used, and it showed excellent results in our patient.

The presented case is significant in various ways. First, there was a diagnostic delay and multiple physician visits before the final diagnosis of PLS was made highlighting the importance to include the PLS in differential diagnosis in every patient with palmoplantar hyperkeratosis and periodontitis. Diseases with oral features as seen in PLS periodontitis are acrodynia, hypophosphatasia, severe congenital neutropenia, histiocytosis X, cyclic neutropenia, and Takahara syndrome. Dermatologic conditions with similar features of PLS but not associated with periodontopathy are Unna Thost syndrome, Mal de Meleda, Howel-Evans syndrome, Vörner's syndrome, Vohwinkel's syndrome, and Greither's syndrome [8]. Second, WES offers clear diagnostic benefits for patients with rare disease and impact management, and genetic counseling options. Inability to identify potential therapies, failure to detect the risk of recurrence in later pregnancies, and failure to provide anticipatory counseling and prognosis are all consequences of a lack of diagnosis for patients and their families. WES approaches have greatly facilitated the discovery of candidate genes or gene variants and it is increasingly applied to genetic testing for undiagnosed patients [9]. Third, our patient has a novel previously undescribed c.1220T>A p. (Val407Asp) variant in *CTSC* gene, expanding the mutation spectrum of this rare condition. Finally, the presented case shows that retinoids can offer benefits for patients with PLS.

Conclusion

Hyperkeratosis of the palms and soles and generalized severe periodontitis characterize Papillon-Lefèvre syndrome. A mutation in the gene that codes for CTSC causes this autosomal recessive genetic disease. Furthermore, unless genetic testing is performed, the diagnosis of PLS may delayed for years. To improve the quality of patients' lives and improve results, early detection and adequate management by a multidisciplinary team is critical.

Conflict of interest statement - The authors declare that they have no conflict of interest.

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SUMMARY

Papillon-Lefévre syndrome (PLS) is a highly rare autosomal recessive condition characterized by palmoplantar hyperkeratosis and severe early-onset widespread periodontitis, resulting in the premature loss of both primary and permanent teeth. PLS has a complex etiology, with genetic, immunological, and microbiological factors being the main causes. Mutations in the gene 11q14-q21, which codes for cathepsin C, an enzyme implicated in a range of inflammatory and immunological processes, are the leading genetic abnormalities that cause PLS. Treatment of PLS is challenging and requires a multidisciplinary approach. Here, we report the first case of PLS described in Georgia, describe a novel previously undescribed variant in the *CTSC* gene, and highlight the importance of whole exome sequencing (WES) in making a definitive diagnosis.

Keywords: Papillon-Lefévre, PLS, CTSC, WES, Georgia