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A DELETION MUTATION OF THE CONNEXIN 26 (*GJB2*) GENE IN A TURKISH PATIENT WITH VOHWINKEL SYNDROME

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Summary: *A deletion mutation of the connexin 26 (gjb2) gene in a Turkish patient with Vohwinkel syndrome:* Vohwinkel syndrome (VS), also known as keratoderma hereditaria mutilans, is a rare keratinization genetic disorder characterized by palmoplantar keratoderma, skeletal dysmorphisms and varying degrees of sensorineural deafness. Its mode of inheritance is autosomal-dominant, with mutations in loricrin and connexin 26 (*GJB2*) genes that manifest during infancy and become more evident during adulthood. We herein report a case of VS in a 23-year-old female exhibiting sensorineural hearing loss, palmar keratoderma and homozygous deletion mutation delE120 (c.358-360delGAG) in the *GJB2* gene. VS, is a rare genetic disorder, should be considered in patients with palmoplantar keratoderma and hearing loss and should be investigated connexin 26 (GJB2) gene mutation.

Key-words: Connexin 26 – Deafness – Keratoderma – Vohwinkel syndrome.

INTRODUCTION

Vohwinkel syndrome (VS), also known as keratoderma hereditaria mutilans, represents a rare genodermatosis consisting of palmoplantar keratoderma and manifesting as hyperkeratosis of the palms and soles. This infrequently occurring autosomal dominant syndrome was first described by Vohwinkel in 1929. Classical VS is characterized by a triad of symptoms consisting of diffuse palmoplantar keratoderma with a honeycomb-like appearance, star-shaped hyperkeratotic plaques on the dorsa of the hands and a fibrous constriction band, appearing at later stages on the digits, which can lead to autoamputation (2). Clinically, VS manifests during infancy or early childhood. The keratoderma may spread, with linear or starfish-like keratosis, to extensor surfaces such as the dorsa of the hands and feet, knees and elbows, and occasionally the knuckles. Trans gradient margins may also be present (2, 12). Other symptoms associated with VS include alopecia, sensorineural hearing loss (mild-to-moderate), myopathy, ichthyosiform dermatoses, skeletal dysmorphisms and nail abnormalities. Deaf mutism

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and high-tone acoustic impairment may also occur (3, 7). We herein describe a case of VS that presented with marginal palmar keratoderma, bilateral sensorineural hearing loss and thoracal scoliosis.

CASE REPORT

A 23-year-old female patient was admitted to our dermatology clinic complaining of hardening of the palms for > 10 years. She had previously been treated with topical salicylic acid and steroid ointment, urea and other emollients, and she reported moderate, congenital sensorineural hearing impairment. Symptom onset occurred during early childhood. The patient reported no similar dermatologic or hearing complaints present in her sister or other family members. Dermatological examination revealed yellowish thickening of both palms and a linear hyperkeratotic margin causing flexion contracture of the fourth and fifth fingers of the right hand (Fig. 1). There was no xerosis, ichthyosiform dermatoses or constricting fibrous band in the palmoplantar area. Moderate hearing loss was detected in physical examination. The results of ocular and musculoskeletal examinations were normal. Thoracal scoliosis was detected on X-ray. Audiometric analysis, conducted by the otolaryngology clinic, revealed bilateral, mild sensorineural hearing loss. A biopsy was performed. Any important evidence, except hyperkeratotic signs, was not determined in pathological examination of the dermatological samples. The audiograms for her parents were normal. The patient was referred to the Department of Medical Genetics. A detailed family history was obtained and the pedigree of patient's family was drawn. Her parents are related. Informed consent

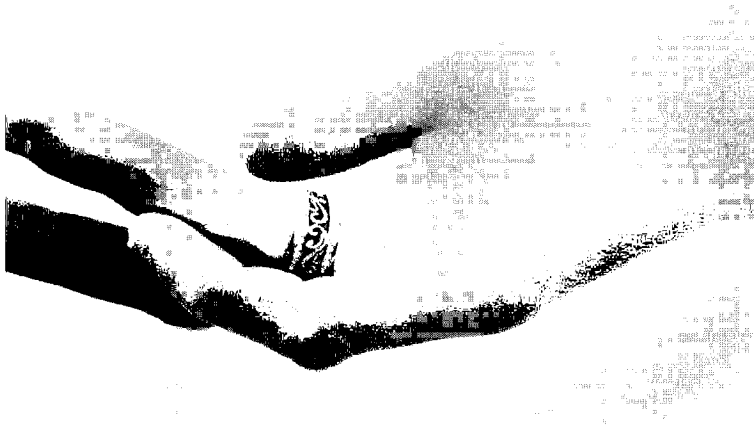

Figure 1:
Yellowish thickening of the right palm and a linear hyperkeratotic margin causing flexion contracture of the fourth and fifth fingers of the right hand.

was obtained from the patient. Peripheral blood was collected from the patient. DNA extraction was performed through salt precipitation method. Coding exons of the *GJB2* gene was reproduced via suitable primers by polymerase chain reaction. *GJB2* Gene Sequencing Analysis was performed through automated DNA sequencing analysis. We detected a homozygous deletion mutation delE120 (c.358-360delGAG) in the *GJB2* gene (GenBank accession number XM_007169) (Fig. 2). Non-directive genetic counselling was given about the result of this genetic analyses and inheritance of VS. Although we suggested to parents performing genetic analysis, they did not accept.

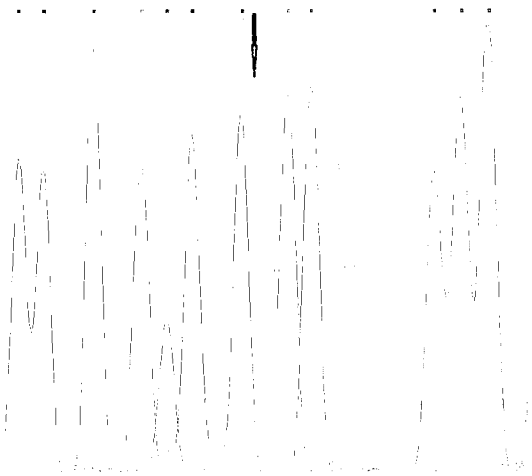

Figure 2:
A homozygous deletion mutation delE120 (c.358-360delGAG) in *Cx26 (GJB2)* gene.

DISCUSSION

In humans, the connexin gene family comprises 21 transmembrane proteins involved in intercellular communication processes (10). Gap junction beta-2 protein (*GJB2*), also known as Connexin 26 (*Cx26*), is a gap junction protein composed of 225 amino acids and localized on chromosome 13. It is involved in intercellular communication and the control of cellular differentiation in stratified, ectodermal-derived epithelium of the cochlea, cornea, palmoplantar epidermis, and sweat glands and ducts (2, 6). Two organs in which connexins and gap junctions are necessary for normal function are the skin and inner ear. Mutations in connexin genes have been linked to human hereditary diseases affecting both the epidermis and cochlea (2, 5, 8). Mutations in *GJB2*, discovered by Richards *et al.* (8), are linked to several hereditary diseases, including non-syndromic deafness and syndromic deafness associated with skin disorders.

Non-syndromic deafness is characterized by sensorineural hearing loss in the absence of other clinical manifestations. Mutations causing deafness may occur in several different connexin genes, but up to 50% of genetic non-syndromic hearing loss is associated with *Cx26* mutations (5, 13). Syndromic hearing loss, which disrupts normal hearing and is caused by dominant mutations in *Cx26* gene, is associated with skin disorders including VS, Bart–Pumphrey syndrome (BPS), palmoplantar keratoderma with deafness (PPK), keratitis–ichthyosis deafness syndrome (KID) and hystrix-like ichthyosis with deafness syndrome (HID) (2). VS, BPS and PPK are characterized by similar phenotypes and involve palmoplantar hyperkeratosis (13). PPK represents a relatively mild form of hearing loss compared with other Cx26 syndromic deafness disorders (2, 5).

VS, representing a rare hereditary disease with approximately 50 cases reported in the literature (and two cases in Turkey) (1, 3), manifests during childhood and becomes more evident during adulthood (4, 11). VS most frequently occurs in Caucasian females (7) and is characterized by an autosomal-dominant pattern of inheritance; however, recessive and sporadic cases have been described occasionally (10). The diagnostic features of VS include starfish-shaped palmoplantar hyperkeratosis, constricting bands on the digits of the hands or feet, starfish-shaped hyperkeratotic lesions and salmon-colored or articular cushion on the dorsum of the hands. Nail dystrophy, alopecia, onychogryphosis and several other neurological abnormalities may also manifest (4, 11). An association between ichthyosis and deafness has been reported; therefore, VS can be classified into ichthyosis-associated (Camisa disease; characterized by loricrin mutation) and deafness-associated variants (2, 4, 9). Keratoderma typically presents during early infancy. Palmoplantar surfaces may exhibit a honeycomb-pattern, and keratoderma may spread, with linear or starfish-like keratosis to extensor surfaces such as the feet, knees, elbows, and occasionally knuckles. Trans gradient margins may also be present (2, 12). A linear hyperkeratotic margin, causing flexion contracture of the fingers, was observed in our patient.

Restriction of pathology to the palms and soles is shared by other syndromic deafness disorders caused by *GJB2* mutations; however, unlike VS, PPK and BPS lack constriction bands and starfish-like keratoses, and the latter disorder is also characterized by nail thickening and brittleness. The absence of ichthyosis and hair follicle defects distinguishes HID and KID from VS; KID also involves extensive keratitis, which in severe cases can lead to blindness (2, 5, 13).

In conclusion, we herein present a case of VS in a 23-year-old female patient exhibiting sensorineural hearing loss, palmar keratoderma and

a homozygous deletion mutation delE120 (c.358-360delGAG) in the *GJB2* gene. This is only the third Vohwinkel Syndrome's case to be reported in Turkey. This syndrome, is rare genetic disorder, should be considered in patient with palmoplantar keratoderma and hearing loss and should be investigated connexin 26 (*GJB2*) gene mutation.

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