Keratinization Disorders and Genetic Aspects in Palmar and Plantar Keratodermas

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ABSTRACT Palmoplantar keratoderma (PPK) is a heterogeneous group of hereditary and acquired disorders characterized by abnormal thickening of the palms and soles. There are three clinical patterns: diffuse, focal, and punctuate. Palmoplantar keratodermas can be divided into the following functional subgroups: disturbed gene functions in structural proteins (keratins), cornified envelope (loricrin, transglutaminase), cohesion (plakophilin, desmoplakin, desmoglein 1), cell-to-cell communication (connexins) and transmembrane signal transduction (cathepsin C). Unna-Thost disease is the most common variety of hereditary PPK. Mutations in keratin 1 have been reported in Unna-Thost disease. We report 12 cases in which Unna-Thost disease was diagnosed. Genealogical study demonstrated that the genodermatosis was a familial disease inherited as an autosomal dominant disorder. Dermatological examination revealed yellowish hyperkeratosis on the palms and soles. Oral mucosa, teeth, and nails remained unchanged. Histopathological examination of the biopsy sample taken from the soles of the patients showed orthokeratotic keratosis, hypergranulosis, and acanthosis without epidermolysis.

KEY WORDS: palmoplantar keratoderma, keratin 1, autosomal dominant, genodermatosis

INTRODUCTION Palmoplantar keratoderma (keratosis palmoplantaris) is the term which denotes a heterogeneous group of local, genetically conditioned skin thickening. The disease process involves excessive orthohyperkeratotic thickening, while parakeratosis rarely applies to the palms and soles.

In some cases, there is crossing (transgrediens) of lesions on the spinal regions of the palms and soles as well as other surrounding of limb skin, and sometimes even the trunk. In other forms, the progression of symptoms (progrediens) throughout life is characteristic of the disease. In some patterns, the lesions on the palms and soles are accompanied with disorders in other organs (1-3).

CLASSIFICATION The classification of hereditary palmoplantar keratoderma is difficult due to the presence of many types and individual differences in terms of symptoms intensification in the initial period and in the period of
full disease progression, differences in the nomenclature, and a great number of cases described. More and more often one can also find reports on new palmoplantar keratoderma disorders in the literature where the clinical picture or the results of molecular and genetic examinations do not make it possible to classify the disease in terms of the present disorders.

The classification of Lucker et al. as of 1994 (4) takes the following into account:
- characteristic morphology of lesions and their location;
- presence or absence of additional symptoms;
- way of inheritance;
and also:
- presence of lesions on skin areas other than the palms and soles, the beginning of keratoderma, intensification of the disease process throughout the patient’s life, and histopathological examination results.

Most sources say that the most common type of hereditary palmoplantar keratoderma is keratoma palmare et plantare hereditarium Unna-Thost (KPPH). Since retrospective examinations indicated that most cases of Unna-Thost disease were actually Vorner type syndrome, this is why, at present, some authors state that it is the Vorner syndrome that is the most frequent type of palmoplantar keratoderma (5). Both types may be distinguished only based on the histopathological picture (6).

Palmoplantar keratoderma Unna-Thost

Keratoma palmare et plantare Unna-Thost was described by Thost in 1880 under the name ichthyosis palmaris et plantaris cornea and in 1883 by Unna as keratoma palmare et plantare hereditarium. Nowadays in the literature, this type is also defined as limited diffuse palmoplantar keratoderma of Unna-Thost (keratoma palmoplantaris diffusa, circumscripta Unna-Thost) (3).

This genodermatosis occurs in a familiar setting; it is an autosomal dominant disorder. The genetic defect refers to cytokeratin 1 (5). Mutation in V1 end domain of keratin 1 has been defined (7). The KPPH incidence ranges from 1:200 – 1:400 000, depending on the ethnic group (8). In Slovenia, the disease incidence with regard to KPPH amounts to 3.3/100000 of inhabitants, while in Croatia it is 1.7/100000 inhabitants (9). In an epidemiological examination carried out in 1997 in southern India, the incidence was determined to be 1:2000. The disease occurred more often in men; the ratio of men to women was 4:2:1 (10).

Unna-Thost keratoderma begins in the first five years of life. In the second year of life, the symptoms are present in most patients.

Excessive thickening is of a confluent nature and appears on the whole surface of the palms and soles; this is why it is referred to as diffuse while the presence of the lesions is at the same time limited to these locations (3).

At first, the symptoms of excessive thickening appear at the edges of the palms and soles, mostly in the places of increased mechanical pressure. A blue and red band is visible on the edges of lesions, which usually resolves spontaneously within several years (3,11).

During full progression, the lesions usually appear symmetrically and cover the whole surface of the palms and soles, moving on to the side regions of the locations with a clear demarcation from the healthy skin. Palm and sole epidermis is thickened, hard, of yellowish or wax-yellow color, and smooth-surfaced or separated with furrows and cracks. The characteristic feature of the disease is also excessively sweaty palms and soles, what may cause maceration of epidermis and lead to painful cracks and secondary bacterial or mycotic infections (12,13).

Lesions most often do not have the tendency to spread to spinal areas, however, some symptoms of excessive thickening may be found on the finger ridges above the metacarpophalangeal joints, as well as on the elbows and knees (1-3).

Nail plates may sometimes have trophic changes; they may be thickened and lifted upwards as a consequence of subungual keratosis. Hair is regular (14,15).

Histopathological imaging shows overgrowth of the horny layer (stratum corneum) with features of orthohyperkeratosis, to a lesser extent also other layers with the features of granulosis, acanthosis, and papillomatosis. In the dermis, there may be some inflammatory infiltrations present around the blood vessels. Blood vessels and appendages remain unchanged (16).

The disease is diagnosed based on:
1. The characteristic clinical picture with the presence of symptoms of excessive, diffuse keratosis limited to the palms and soles without symptoms in other regions or lesions in other organs.
2. Family history indicating features of autosomal dominant inheritance with presence of lesions in parents and in subsequent generations (3).

Unna-Thost keratoderma treatment:

In the 60s, treatment was attempted by administering vitamin A to the patients, and later also great doses of vitamin B12 in conjunction with oral
magnesium preparations. However no essential improvement of the clinical condition after treatment was observed. Local administration of preparations which contained retinoids in 1975 gave promising therapeutic results (17).

At present, the treatment of Unna-Thost keratoderma involves local application of keratolytic agents (10-20% salicylic acid ointment, 30-50% urea ointment, 5-10% urea ointment with the addition of 5-10% salicylic acid or 5% lactic acid) interchangeably with preparations containing retinoids or steroids (18). Active vitamin D was also applied due to its anti-hyperproliferating properties and in support in differentiation of the epidermis cells (19). Such a type of keratosis sometimes requires general administration of retinoids; however, they cause heavy side effects. Long-term therapy with acitretin is not recommended as lesions recur after the end of the therapy (20).

Menni et al. (3) observed improvement after administration of biotin preparation in a patient who was diagnosed with decreased levels of the vitamin in the blood serum.

Quite promising are the trials to implement PUVA-bath therapy due to anti-proliferation and immunomodulating properties (21).

More and more often, the advantageous influence of alpha-hydroxy acids on keratinization is described. They are applied in order to accelerate the horny layer peeling and improvement of skin appearance. AHA and especially glycolic acid in a concentration which does not exceed 20% reduce the corneocyte cohesion in the lower layers of the stratum corneum, which initiates peeling and thinning of the stratum corneum. The peeling reaches the lowest level of the stratum corneum and is characteristic only for this group of compounds. It is not accompanied with skin irritation or keratolysis, as it takes place while stratum corneum peeling with salicylic acid, which is known to belong to beta-hydroxy acids (22-25).

It is sometimes possible to remove the horny deposits surgically (26) or by means of dermabrasion (27), which brings relief to patients and allows for better penetration for the preparations applied locally.

When mycotic or bacterial infection is present, the applicable casual treatment is used (20).

While differentiating hereditary Unna-Thost palmar and plantar keratoderma, it is necessary to take into account other types of palmar plantar keratoderma with diffuse lesion character; these are:

- Hereditary epidermolytic palmar plantar keratoderma, Vörner type;
- The feature which differentiates these types is the microscopic image. In Vörner type keratoderma there are intraepidermal epidermolytic blisters in the histopathological picture (15).

The mutation concerns the gene coding keratin 9, the expression of which is greatest in the region of the palms and soles (28).

- Greither type hereditary progressing palm keratoderma is a very rare type with transgredient and progradient features. In comparison with Unna-Thost keratoderma, the symptoms of excessive thickening intensify with age and move to the regions beyond the palms and soles, covering the elbows, knees, forearms, shins, and rarely the trunk (28). The lesions have the tendency to subside above the age of 60 (29).

The mutation is probably related to the gene for connexin 37 (30).

- Meleda disease is palmpoplantar keratoderma with transgrediens of autosomal recessive inheritance. Transgrediens affects the top surfaces of the palms and soles while covering the side regions and wrists, the surroundings of Achilles tendon and ankles, causing a "gloves and socks" appearance, as well as the armpits, groins, neck, elbows, and knees.

The name of the disease comes from the first patients on Meleda island described in the literature (31).

The gene responsible for the presence of the genodermatosis codes SLURP-1, a neuromodulator which participates in the epidermal cells calcium homeostasis which probably restrains the release of tumor necrosis factor (TNF)-alpha by skin macrophages (32).

- Hereditary excessive keratoderma (Vohwinkel syndrome).

This is a very rare type of diffuse palmpoplantar keratoderma also of autosomal dominant inheritance with accompanying lesions in other tissues and organs. The general feature which distinguishes it is the presence of thickened or fibrous skin rings on the knuckles, located most often on the fifth fingers and toes. The distal parts of the fingers and toes below the ring are swollen of blue color and painful to pressure. On the surface of disease foci there are hollows which resemble a honeycomb. Additionally, in many patients the symptoms of excessive keratosis may be accompanied with: ichthyosiform-like dermatosis, frontal fibrosing alopecia, and action hearing impairment in terms of high-pitched tones or deaf-muteness. It was indicated that mutation within the GJB2 gene is responsible both for skin dysfunction and for...
the inner ear function disorder (33).  

• Hereditary excessive palmoplantar keratoderma with periorificial plaques (Olmsted syndrome);  

The disease inheritance has not been explained completely; however defects in keratin 5 and 14 have been mentioned (34).  

The features which distinguish this type of disease involve:  
- Presence on the fingers and toes, which later leads to contractions and/or spontaneous amputation;  
- Keratoderma of sweat glands exits which causes sweat secretion disorders;  
- The symptoms of excessive keratoderma with periorificial plaques;  
- Severe dystrophy of nail plates (8,35).  
- Increased risk of cancer such as squamous cell carcinoma and adenocarcinoma of internal organs (34).  

• Ectodermal dysplasia with preserved function of sweat glands (Clouston syndrome)  

The disease described in French and Canadian populations is related to gene mutation of connexin 30 (13q12). As opposed to Unna-Thost keratoderma, in Clouston syndrome the excessive keratoderma may cover the elbows and knees and no excessive sweating is observed, however dystrophy of nail plates, dystrophy and breaking of hair, and head, eyebrow and armpit alopecia are present, as well as as alopecia on the external sexual organs. Clouston syndrome may be accompanied with disorders in other tissues and organs: small teeth, widespread caries, deafness, dwarfism, photophobia, mental development issues, polydactylism, syndactylism, and arachnodactylism (3).  

• Palmoplantar keratoderma with periodontitis (Papillon-Lefevre syndrome)  

This type differs from Unna-Thost keratoderma in the following characteristics:  
- Autosomal recessive inheritance; the mutation happens in the gene which codes cathepsin C (36).  
- Tendency to transgrediens,  
- Periodontitis which damages both deciduous teeth and permanent teeth [3].  

The disease symptoms usually intensify during winter (37). Immunodeficiency takes place in about 20% of patients, as well as frequent purulent infections of the skin and internal organs. Liver abscesses are often noted as well (38). Other abnormalities described also included nail dystrophy (39).  

• Hovel-Evans syndrome  

This disease involves mutation of the gene which codes envoplakin (17q25). The syndrome results in excessive keratosis which manifests only during puberty with accompanying esophageal cancer (35). Apart from the esophageal cancer, there is a greater predisposition to the development of skin squamous cell carcinoma, gastric cancer, or lung cancer (40).  

• Huriez syndrome.  

Since 1963 when the syndrome was defined, only a few families with the disease have been described (41). In Huriez syndrome, the excessive keratosis intensifies with age and leads to sclerotic and atrophic lesions within the region of the palms. No Raynaud’s phenomenon is found, while squamous cell carcinoma often develops within the sclerotic lesions, which is explained by the almost total absence of Langerhans cells within the affected skin (42). The process also includes effects on nail plates which undergo furrowing and aplasia (35).  

• Bureau-Barry and Thomas syndrome.  

This keratosis which covers only the palms and soles is accompanied with: overgrowth of phalanx bones in the palms and soles that makes the fingers and toes resemble the shape of drumsticks and nails the shape of a clock glass (35).  

• Sybert syndrome  

There have been 10 cases of this disease described so far. The mutation is still unknown, and incorrect distribution and structure of keratohyalin granules was noted in the literature. Apart from the palmoplantar keratoderma, the following is observed: Achilles tendon involvement, hyperhidrosis of the palms and soles, and pseudoanhum, which sometimes lead to phalanx self-amputation (43).  

• Palmoplantar keratoderma with deafness  

There are 5 families described with an atypical inheritance model. Keratoderma and deafness expression varied within one family, which indicates the great impact of external environment on the disease phenotype. In most cases, the patients were related on the mother’s side, indicating mitochondrial inheritance (44). The occurrence of A7445G point mutations in mitochondrial genomes was confirmed in 4 families with non-epidermolytic palmoplantar keratoderma with deafness (45).  

• Carvajal syndrome  

The characteristic features of the syndrome are:  
- Autosomal recessive inheritance, the mutation being in the gene which codes desmoplakin (6p24)  
- Epidermolyisis within the keratoderma confirmed
in the histopathological examination
- Woolly hair
- Left ventricular cardiomyopathy, which in adulthood leads to circulatory insufficiency, aneurisms, and hypertrophy of the heart muscle (46).
- Haim-Munk syndrome

This is an autosomal recessive disorder characterized by gene mutation for cathepsin C. Apart from diffuse keratoderma, the following can be observed in association with the syndrome: progressing periodontitis, arachnodactyly, acroosteolysis, and bone deformations of the phalanx (18).

Additionally, it has to be remembered that palmoplantar keratoderma is a symptom of generalized, hereditary genodermatoses such as congenital ichthyosis, ichthyosis vulgaris, ichthyosis-like erythroderma, and dyskeratosis congenita. For the purposes of distinguishing Unna-Thost palmoplantar keratoderma it is also necessary to take into account keratoderma acquired in the course of internal organs carcinoma caused by arsenic or found in women in the menopausal period (18).

In the Dermatology Clinic in Bydgoszcz, 12 patients with skin lesions of palmoplantar keratoderma type were examined.

Six (A-F) from among 12 patients belonged to one family, the genealogical tree of which is presented in Figure 1.

**CASE REPORTS**

In this family, skin lesions of keratoma palmoplantare character were present in 11 people over three generations, 6 of which were examined.

Patient A, a 50-year-old woman, a farmer by profession and now a pensioner, had been sick since childhood. In the period of full disease progression, the lesions appear symmetrically, covering the whole surfaces of the soles. The epidermis was thickened, hard, and of wax yellow color. The skin lesions were accompanied with hyperhidrosis of the palms and feet, which caused skin maceration, periodically leading to formation of painful cracks; secondarily it led to the development of bacterial and mycotic infections (Figure 2). Transgrediens occurred in patient A, i.e. moving of the lesions to the side parts of the feet, toes, and heel with clear demarcation of healthy skin, as well as to the finger and toe nail plates that were trophic, thickened, and lifted upwards as a consequence of excessive keratosis. The skin lesions on the palms had the form of single foci of excessive keratosis, clearly separated from the surroundings and located mostly on the thumbs and index fingers of both hands.

Patient B was a 47-year-old man, the brother of patient A, a farmer and now a pensioner, who had been sick since the age of 10. The skin lesions on the soles had the form of thickened epidermis of yellow color; they move to the side surfaces of the feet and toes and were accompanied with clear thickening of nail plates and hyperhidrosis of the feet. On the palms, lesions in the form of foci were clearly separated from the surroundings.

Patient A had 4 sons. Palmoplantar keratoderma was diagnosed in two of them. The older son, 23-year-old patient C, a carpenter by profession, had been sick since the age of 6. In February 2000, the patient was diagnosed with intensified skin lesions of plantar keratoderma which reacted poorly to local treatment. Treatment with Neotigason at the dose of 50 mg/day was applied. After four months of therapy, the local condition was improved. The relapse of the disease was observed after eight months from the end of the therapy with Neotigason.
The second son of patient A – a 14-year-old boy, had like his brother been sick since the age of 6. Because of the shorter family history, skin lesions observed were less intensified and located mostly in the places of mechanical pressure and on the edge of the soles. A blue and red band was visible on the edges of lesions, which usually resolves spontaneously in a couple of years. The patient did not participate in further treatment.

Palmoplantar keratoderma was diagnosed in 3 out of the 5 children of patient B. Patient D was an 18-year-old boy who had been sick since the age of 3. Patient E was an 18-year-old girl who had been sick since the age of 2. In the children, excessive keratosis was found mostly on the soles, with small amount of lesions observed on the hands. A visible redness on the edges of the lesions indicated the early stage of the disease (Figure 3). The children had not been treated before.

The third child of patient B was a 16-year-old boy – patient F, who had been sick since the age of 3. In the boy, local treatment with 70% glycolic acid was applied that led to improvement of the local condition.

Histopathological examination in 12 patients with clinically diagnosed palmoplantar keratoderma confirmed the diagnosis. In all patients, the overgrowth of the horny layer with the features of orthohyperkeratosis was observed; to a lesser degree also of other layers with the features of granulosis, acanthosis, and papillomatosis. There were small inflammatory infiltrations in the corium around the blood vessels. Blood vessels and appendages remained unchanged (Figure 4).

The diffuse morphology of skin lesions was limited only to the palms and soles, without the tendency for transgrediens; positive family history confirmed autosomal dominant inheritance of the disease, and the histopathological picture indicated the diagnosis of hereditary diffuse palmoplantar keratoderma of the Unna-Thost type.

The heterogeneity of palmoplantar keratoderma is expressed through inheritance type, clinical picture, the course of the disease, and in the presence of specific characteristics for the given type of keratoderma and molecular and genetic disorders.

CONCLUSION

Intensive research carried out within the last two decades concerning the structure and function of the epidermis horny layer has provided information about the role of the peeling process in the skin physiology. The classification of keratosis disorders is known, and the ethiopathogenesis of some diseases as well as chromosome loci which are responsible for the occurrence of the disease is now known.

Recognition of the genetic conditionings of defects in the three-dimensional structure and function of the epidermal proteins which cause specific local general keratoderma will contribute to an applicable classification, qualification, and ability to apply the relevant therapeutic method.

References:

3. Urban J. Genodermatozy związane z zaburzonym


18. Solis RR. Vohwinkel’s syndrome in three genera-