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RESEARCH ARTICLE

Netherton Syndrome in Combination with Iron-deficiency Anemia

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Abstract

Netherton syndrome (NS) is a rare severe autosomal recessive disorder of cornification characterized by a triad of symptoms: congenital ichthyosiform erythroderma, trichorrhexis invaginata and an atopic diathesis with elevated immunoglobulin E (IgE). Skin surface recovered in the background of IDA correction with iron preparations and vitamin and mineral complexes. Family history: patient has a 55-year-old uncle with ichthyosis vulgaris and her 4-year-old daughter suffers atopic dermatitis. The patient was treated with systemic steroids (prednisolone solution 90mg per day IV days 1-5; 60 mg per day, days 6-11; 30 mg per day, days 12-15) with marked improvement of the skin lesions in 1, 5 weeks. At the time of discharge from the hospital almost complete regression of eruptions and desquamation was observed, there were some residual effects in the form of post-inflammatory erythema. We present a case of a 29-year-old woman with Netherton syndrome, primarily diagnosed with atopic dermatitis. The iron-deficiency anemia concurrent with gastro-intestinal tract disorder was also observed. Topical corticosteroid therapy showed no clinical improvement. Combined in-depth clinical assessment and genetic testing resulted in NS diagnosis with subsequent successful systemic therapy-intestinal tract. Trichoscopy examination of the scalp hair demonstrated trichorrhexis nodosa, one of the typical NS signs. Initial parameters. HGB: 95.0g/l (normal range 120-140g/l), RBC: 3.45□10^{12}/l; (normal range 3.7-4.7□10^{12}/l), Hypochromia: ++ Color indicator: 0.64 (normal range 0.85-1.15), Eosinophils 13%; (normal range 0-5) and serum IgE level of 156 IU/ml (normal range 20-100 IU/ml). Quality blood indicators after treatment are within normal limits or close: HGB level has increased, eosinophils number has decreased, which indicates an almost complete inflammatory process cessation in the body. The main change vital for the body, which the physiological blood indicators depend on, is an increase in iron content (almost 1.5 times). Indicators of toxic substances, such as uric acid, decreased. Each of the patients with Netherton's syndrome requires a strictly individual approach. Emphasis on the advisability of prescribing systemic glucocorticosteroids is also essential, as well as the dosage of aromatic retinoids. In this case, the dosage and prescription of drugs of this type depends on the disease severity, in particular on the pathology's manifestations on the skin surface. Genetically caused disease (Netherton syndrome) proceeded against the background of acquired disease (anemia). Our strategy has shown effectiveness, caused by systemic steroids.

Key words: *Netherton syndrome, Trichorrhexis invaginata, Ichthyosiform erythroderma, SPINK 5, Iron-deficiency anemia.*

Introduction

The skin performs a number of vital functions, which include providing a barrier between the external and the internal body environments. This function is possible in connection with skin keratinization [1]. Keratinization refers to the keratinizing process from basal epidermocytes at the beginning to nuclear-free horny scales. In the formed stratum corneum, there is a structure consisting of two main components-keratinocyte cells themselves, as well as intercellular substance [2].

The latter includes cholesterol, free fatty acids, and ceramides. The formation of intercellular substance is associated with lamellar granules, which are located in the granular layer of the epidermis. During normal functioning of the body, keratinization is regulated by the phyllagrin protein (PLH), which, in turn, is formed from the precursor, prophyllagrin. Thanks to phyllagrin, differentiated filaments aggregation occurs into a single unit - the cytoskeleton [3].

As a result, corneocytes form - the post-cell formations, with a high protein content and organelles absence. Gene responsible for coding phyllagrin is localized on the long arm of the first chromosome (1q21) [4]. In case of mutation occur, the result is reflected in the phenotype - the barrier function of the skin is disrupted and the penetration of various allergens into the body becomes possible. The consequence is the activation of the body's immune system. This mutation was discovered in 2006 and four of its modifications associated with phyllagrin known today are: R501X, 2282de14, R2447X and S3247X [5].

Several diseases are known to result due to this mutation and appear as a result of a violation of the barrier function of the skin. The most famous of these are atopic dermatitis, vulgar ichthyosis, and Netherton's syndrome [6]. Atopic dermatitis is characterized by itching and pain. This disease initiates at an early age. One of the signs is dry skin. The modern concept of the causes of atopic dermatitis includes a genetically determined metabolic disturbance leading to dry skin [7].

The mutations are associated with phyllagrin [8].During the phyllagrin hydrolysis, deamination of the key amino acids occurs. The by-products resulting from the hydrolysis reaction are referred to as the so-called natural moisturizing factor (NMF), determining the normal moisture condition of the skin. In addition, there are variations in the polymorphism of another gene, SPINK5, which determine the inhibition of LEKTI serine proteases [9].

In a number of cases, atopic dermatitis development can be determined by differences between two proteases belonging to the kallikrein family [10]. The main function of kallikrein is the destruction of root desmosomal proteins. The latter are involved in the corneocytes cohesion located in the stratum corneum [11].

Another reason for skin barrier function violation is a low level of lipid concentration or an imbalance in their composition. An example of such a violation of the quantitative and qualitative composition is the lack of ceramide content, as well as the absence of their specific components [12]. Another factor may be exposure to dust mite proteases, as well as *Staphylococcus aureus*. All of the factors lead to microflora allergens penetration and absorption through the skin.

Vulgar ichthyosis occurs with a frequency of 1:300 and is hereditarily determined (semidominant). A consequence of genetic conditioning is that people monozygotic for ichthyosis suffer more from its manifestations than heterozygotes. Retention type of hyperkeratosis occurs. At the cellular level, there's a decrease or complete disappearance of the granular layer [13].At the time of birth, no external signs of ichthyosis can be distinguished.

The diagnosis is possible with the help of specialists after three months or even later (for example, dry skin) - up to two years. The main three signs are peeling of the skin, coarsening and the formation of pronounced folds on the skin of the palms of the hands and feet, as well as the presence of follicular hyperkeratosis. The scales localization with hyperkeratosis differs. So, there are hyperkeratotic scales on the extensor surfaces of the limbs, namely the front and side of the legs, characterized by large size, dark color, difficult to separate from the skin surface [14].

The remaining body areas with ichthyosis can be covered with scales of another type - small in size and gray in color. Hyperkeratosis associated with hair follicles is identified on the shoulders and hips front and side surfaces. At the same time, changes in the heels and palms skin papillary pattern occur, which can be diagnosed as the ichthyosis first signal [15]. A characteristic ichthyosis manifestation is its relationship with the seasons of the year. In summer, at sea or in areas with high humidity and temperature, the skin dryness decreases, while in winter it increases [16]. Patients are diagnosed with vulgar ichthyosis on the basis of the presence of this disease in relatives, as well as on the basis of morphological and histological signs.

Other a disease with which vulgar ichthyosis is often associated is atopic dermatitis, bronchial asthma, and allergic rhinitis [17].NS is a rare but severe autosomal recessive disease characterized by the triad of pathologic features: skin disease as icthichtioiform erythroderma, hair abnormality ichthyosis linearis circumflexa, and manifestations which mimics atopic dermatitis.

Misdiagnosis of atopic dermatitis is typical since patients' present skin lesions similar to AD. NS is a disorder, which is caused by mutations in the serine protease inhibitor (SPINK5) gene located in chromosome 5q31-32 and encoded lymphoepithelial Kazal-type-related inhibitor (LEKTI [18]. The mutations in this gene result in increased activity of epidermal proteases leading to desquamation of the stratum corneum and impairment of the skin barrier. This condition affects one in 100,000 to 200,000 live births [19].

The clinical characteristics of this syndrome are the triad of congenital ichthyosiform erythroderma/ ichthyosis linearis circumflexa, trichorrhexis invaginata ("bamboo hair" or "ball-and-socket" hair shaft deformity), and an atopic diathesis. A mild delay in growth and development is also common [20]. Recent reports have shown that an eosinophilic esophagitis and colonic mucosal eosinophilia are probable NS common features [21].Congenital ichthyosiform erythroderma often presents at birth or shortly after and develops over time into an ichthyosis linearis circumflexa, which is described by serpiginous migratory polycyclic eruptions with double-edged peripheral scaling.

The hair is typically sparse, brittle and lusterless and the best way to observe it is trichoscopy or trichogram [22, 23]. Some patients may have trichoclasia nodosa and pili torti. Atopic manifestations include asthma, atopic dermatitis, urticaria, allergic rhinitis, anaphylactic reactions to food, elevated IgE levels and plasma hypereosinophilia [24]. NS patients are also at increased risk for recurrent infections, especially bacterial infections of the skin as the result of compromised skin barrier [25].

Netherton's syndrome is a rare disease that has been observed sporadically. It is usually combined with ichthyosis, atopy, and hairline disorders at the structural level [26]. Generalized erythroderma can be observed already at birth. In terms of clinical signs manifestation, NS may be erroneously diagnosed as lamellar ichthyosis, as well as congenital ichthyosiform erythroderma [27].

The further NS course looks like a linear circumflex ichthyosis [28].The appearance of erythematous plaques migrating throughout the body of a polycyclic and serpiginous type. Peeling is present on the periphery of the plaques. As regards hairline defects, as a rule, they are detected microscopically and at birth can simply not be recognized [4]. The hair length in patients with Netherton's syndrome, as a rule, ranges up to 5 cm. Thus, the hair structure is disturbed at the micro and macro levels.

In general, diseases caused by genetics, that is, congenital, are extremely important from the point of view of medicine and sociology. Each birth of a child with such diseases is a tragedy for the family, as well as a warning to society. Anemia is caused by a reduced hemoglobin content (less than 120 g per 1 liter for women and less than 130 g per 1 liter for men), which is a consequence of a decrease in the number of red blood cells in the blood. In contrast to the other diseases, iron-deficiency anemia is widespread in the world and recognized as a problem disease in more than 100 countries.

In total, every seventh inhabitant of the Earth can be diagnosed with this issue (i.e. more than 1 billion people), especially common among women and children. A consequence of iron deficiency anemia is mortality among children and mothers. The clinical picture of iron deficiency anemia is muscle weakness, as well as changes of mucous membrane integrity, and a decrease in immunity.

Additionally, there is a weakening of the elasticity and permeability of the skin, delamination and breaking of hair and nails [29]. In the article we describe a 29-year-old female NS patient with iron-deficiency anemia with no diagnosis set, who was treated unsuccessfully for 2 years as atopic dermatitis. The aim of this work is to study a unique case of a combination of a fairly common disease (iron-deficiency anemia) associated with disorders at the physiological level and a genetically caused disease (Netherton syndrome).

In this case, one disease was superimposed on another, which necessitated an integrated approach to therapy. When collecting data and analysing the material, all ethical and moral standards are met. The study was carried out with the written consent of the patient undergoing therapy. The authors declare no conflict of interest.

Methods

Materials

Clinical Observation

Patient M., 29 y. o., was admitted to the clinic of skin and venereal diseases named after V. A. Rakhmanova with complaints of a common skin rash, fever up to 37.2C, chills. Subjective sensations: itching and soreness. Concomitant diseases: mild IDA. Heredity: burdened by this disease.

Medical History

Patient considers herself ill for two years. The disease is associated with congenital ichthyosis. According to the mother, she was born with ichthyosiform erythroderma. The patient underwent hormone therapy for a month with a positive effect. On the part of the skin process, erythroderma regressed with age. Skin rashes were noticed for the first time in May 2016 on the neck, on both elbow joints and in the inguinal region in the form of bright red spots, accompanied by an increase in body temperature to 37.2 °C.

In November 2016, she first applied to the clinic at the place of residence. Analyzes identified the severe IDA (iron deficiency anemia), iron drug sorbifer durules (the active substance is iron sulfate and ascorbic acid) was prescribed for 2.5 months. Iron therapy showed an improvement. The recommended iron medication is ferritin (the active substance is an iron-containing protein) inside for 3 months. After taking ferritin, positive dynamics were observed. In 2018, in the spring, patient noted a rash in the same places as in 2016.

In September of the same year, she applied to a dermatologist in a private clinic where following treatment was prescribed: Diet, Zirtec (active ingredient - cetirizine dihydrochloride) 1 tablet per night, externally: face + neck ointment, advantan (methylprednisolone aceponate) morning and evening for up to 2 weeks, on the folds of Beloderm ointment (betamethasone) and in the evening on the foci of redness.

Against the background of the therapy, the patient's worsened; the rash progressed to partial erythroderma. Following patient applied to a dermatologist, who was diagnosed with atopic dermatitis, ichthyosis, mild manifestations.

Drug therapy was prescribed: sodium thiosulfate sol. IV 30% 10 ml + 0.9 sodium chloride sol.

10 ml every other day - 10 injections; IV or IM calcium gluconate sol. 10% 10 ml every other day -10 injections, ebastine (ebastine) 10 mg, chloropyramine (chloropyramine) 2 ml IM, externally: hydrocortisone ointment once daily, underm cream (lanolin, nipagin, nipazole). No effect acquired. An allergy diagnostic was also recommended, no deviations detected: Ig (E) -45 IU/ml (N). 17.10.2018, due to the treatment's inefficiency, she applied to a dermatologist.

Diagnosis: Ichthyosiform erythroderma, atopic dermatitis, exacerbation of ichthyosis. Medication: Prednisone (prednisone sodium phosphate) 60 mg (2 amp) IM. Given the severity, condition and ineffectiveness of the therapy, inpatient treatment is recommended. Due to the ineffectiveness of treatment, she applied to our clinic. Family history: patient's 55-year-old uncle has ichthyosis vulgaris and her 4-year-old daughter has atopic dermatitis.

Methods

According to the characteristic cutaneous findings (ichthyosiform erythroderma with double-bordered) and to the results of trichoscopy (trichorrhexis nodosa) and laboratory tests (eosinophilia and elevated serum IgE level) the patient was diagnosed with NS. The patient was treated with systemic steroids (prednisolone solution (active substance-prednisone sodium phosphate) 90mg per day IV, days 1-5; 60 mg per day, days 6-11; 30 mg per day, days 12-15 + sodium chloride solution -0.9% -200 ml IV) with marked improvement of the skin lesions in 1.5 weeks.

Further, corrective therapy was performed. The following drugs were prescribed to stop the progression of symptoms: Venofer (iron hydroxide complex III with sucrose) 200ml + 0.9% -200 ml sodium chloride sol. No. 3, antihistamines: Ketotifen (ketotifen hydrofumarate) 1mg x 1-tab 2x daily, Chloropyramine (antihistamine, a derivative of ethylenediamine) 1 ml IM at night. To correct the deterioration of the functioning of the gastrointestinal tract, gastroprotectants were prescribed: Omeprazole (active

ingredient-omeprazole) 20 mg once daily, Amitriptyline (active ingredient-amitriptyline) 25 mg, ¼ tab 2x a day. To reduce dermatological rashes, the Unna cream was locally prescribed (the active substance is lanolin).

Trichoscopy was performed to confirm the diagnosis of possible Netherton syndrome. During therapy in a hospital, a laboratory general and biochemical blood test, a general urinalysis, a coagulogram, an immunological study, and exchange plasmapheresis were prescribed. Since the patient is diagnosed with iron deficiency anemia, monitoring the physiological state of the blood seems to us an important condition for successful therapy. A blood test was performed on days 7 and 12 of therapy.

At the end of therapy, the patient was consulted by genetics and transfusiologist. At the time of discharge from the hospital almost complete regression of eruptions and desquamation was observed, there were some residual effects in the form of post-inflammatory erythema.

Results

Clinical Observations

On the 7th day of ambulatory treatment there is a slight positive dynamic of the skin state, decrease in subjective sensations in the form of soreness. On the 12th day, an active regression of rashes is observed. Finally, at the time of discharge, a rashes regression almost completed, residual effects were present in the form of post-inflammatory erythema and peeling regression. This made it possible to assert the correctness of the chosen therapy tactics.

Trichoscopy Examination

Trichoscopy examination of the scalp hair demonstrated trichorrhexis nodosa, one of the typical signs of NS.

Coagulogram

Coagulogram from 26.10.2018: % prothrombin after Quick: 96%; APTT: 0.89 Ratio; TEG (K): 1`20``; TEG (MA): 59; TEG (R): 5`00``; Coagulogram from 06.11.2018:% prothrombin after Quick: 111%; APTT: 0.83 Ratio; TEG (K): 1`50``; TEG (MA): 42; TEG (R): 5`40``; Fibrinogen: 2.29 g/l;

Comparison of the coagulogram data showed an increase in prothrombin %, a decrease in APTT, and an increase in the TEG (K) ratio.

An immunological study from 30.10.2018 showed the presence of antibodies to double-stranded DNA: 4.67 IU/ml.

Urinalysis 26.10.2018: Bacteria: small amount; Protein: 0; Bilirubin in the urine: Negative; Glucose: Positive; Mushrooms: not detected; Ketone bodies I.M.: Negative; Renal Epithelial Cells: Not Detected; Amount: --- ; Blood: - ; White blood cells: 1-2; Microscopy: Microscopy; Nitrites: -; Flat Epithelium: Moderately; Transparency: Cloudy; Reaction pH: 6.0; Mucus: Moderately; Specific Gravity: 1014; Urobilinogen: +3 (140 µmol/l); Urine color: straw yellow; Hyaline cylinders: not detected; Granular cylinders: not detected. The main parameters fall within the normal range.

Biochemical analysis of blood from 26.10.2018: Fe saturation %: 9.6%; ALT: 20 units/l; Albumin: 43.8 g/l; Antistreptolysin O: 175 units/ml; AST: 22 units/l; Total protein: 66.3 g/l; Total bilirubin: 11.8 µmol/l; GGT: 15 units/l; Glucose: 4.7 mmol/l; Fe: 7.4 µmol/l; AC (calc.): 2.06; Creatinine: 74.8 µmol/l; HDL: 1.21 mmol/l; LDL: 2.06 mmol/l; VLDLP: 0.43 mmol/l; Uric acid: 230 µmol/l; Rheumatoid factor: 0 units/ml; Transferrin: 3.05 g/l; Triglycerides: 0.94 mmol/l; Cholesterol: 3.7 mmol/l; Alkaline phosphatase: 131 units/l. Biochemical analysis of blood from 06.11.2018: Fe saturation %: 26.64%; ALT: 24 units/l; Albumin: 41.8 g/l; AST: 23 U/l; Total protein: 61.7 g/l; Bilirubin total: 16.5 µmol/l; GGT: 14 units/l; Glucose: 4.2 mmol/l; Iron: 17.5 µmol/l; Creatinine: 72.8 µmol/l; VLDLP: 0.61mmol/l; Uric acid: 199 µmol/l; Transferrin: 2.60 g/l; Triglycerides: 1.35 mmol/l; Cholesterol: 5.29 mmol/l; Alkaline phosphatase: 105 units.

Comparing biochemical blood tests at the beginning of therapy and at the end, a decrease in glucose levels, an increase in total bilirubin (due to a reaction to intensive drug therapy) was noted.

The main changes, on which the physiological characteristics of the blood depend, which are vital for the body, are an increase in the iron content (almost 1.5x). Indicators of toxic substances, such as uric acid, decreased. At the same time, the concentration of lipids and

their derivatives increased - VLDL, cholesterol and triglycerides. In the general analysis of blood: from 26.10.2018. HGB: 95.0 g/l; (in N 120-140 g/l) RBC: 3.45 10*12/l; (in N 3.7-4.7 10*12/l) Hypochromia: ++ Color indicator: 0.64; (0.85-1.15) Eosinophils: 13%; (in N 0-5%) Complete blood count from 06 .1 1 .2018: HCT: 37.30%; HGB: 109.0g/l; MCH: 22.90 pg; MCHC: 292.00 g/l; MCV: 78.40fl; PLT: 301 10*9/L; RBC: 4.76 10*12/L; RDW: 24.70%; WBC: 12.60 10*9/L; Anisocytosis: ++; Basophils: 0%; Basophils%: 0.30%; Blasts: 0%; Hypochromia: ++; ; Lymphocytes: 22%; Lymphocytes #: 2.8 10*9/L; Lymphocytes%: 20.9%; Myelocytes: 0%; Monocytes: 6%; Monocytes #: 0.9 10*9/L; Monocytes%: 6.3%; Neutrophils #: 9.5 10*9/L; Neutrophils%: 69.9%; Unclassified%: 0.9%; Normoblasts: 0; Band stab: 1%; Plasmatic cells: 0%; ; Prolymphocytes: 0%; Promyelocytes: 0%; Segmented: 69%; ESR West: 6; Color indicator: 0.64; Eosinophils: 2%; Eosinophils #: 0.2 10*9/L; Eosinophils%: 1.7%; Youth: 0%; High-quality blood counts have also undergone changes for the better, within or close to normal: hemoglobin level has increased, the number of eosinophils has decreased, which indicates an almost complete cessation of the inflammatory process in the body.

Consultations of Genetics and Transfusiologist

The patient's parents are obligate heterozygotes. They usually do not have symptoms of the disease and carry a mutation in the SPINK5 gene. Sib (half-brother) of the patient has a 50% chance of being an asymptomatic carrier. Children of the patient have a 25% chance of being affected by heart failure, a 50% chance of being asymptomatic carriers. In rare cases, when the reproductive partner is a carrier of the SPINK5 mutation, the offspring has a 50% risk of heart failure and a 50% risk of being a carrier. Genetic testing is recommended to determine the SPINK5 mutation.

Transfusiologist consultation. Conclusion: Iron deficiency anemia of moderate severity. Currently, intravenous administration of iron preparations in a therapeutic dose is recommended (Venofer 200 mg per 200 ml of a solution of sodium chloride-in/drip, with a biological test, every other day No. 3). CBC and serum iron metabolism control, and re-consultation.

Recommendations

Observations by a dermatologist and hematologist at the place of residence. To identify the etiological factor of anemia-endoscopy and colonoscopy, examination by a gynecologist. Conducting a genetic analysis to determine the mutation of the SPINK-5 gene to confirm the diagnosis. Continuation of IDA corrective therapy. Locally: moisturizers (lotion, emulsion, creams) and their constant use 3-4 times a day.

Discussion

The skin has a complex structure resembling solid elements (corneocytes) immersed in a liquid solution (lipid portion). This model most accurately reflects the structure of the skin stratum corneum, where the barrier function violation begins [30]. Phyllagrin breakdown reactions play a key role in moisturizing the skin.

In this case, a solution of a complex composition is formed, which in addition to water includes polycarboxylic acids, as well as hygroscopic amino acids, urea, metal ions, etc. All these substances bind water inside corneocytes. Thus, the normal water balance in the stratum corneum is maintained [12]. As mentioned above, Netherton's syndrome is directly related to gene mutations, namely the SPINK5 gene [31].

This mutation at the physiological level leads to increased proteolysis of desmosomes, as well as to desquamation of the stratum corneum. Hypersensitivity of the skin to allergens, observed with atopic dermatitis, as well as with a concomitant violation of the barrier function of the skin, is ultimately a consequence of disturbances in the regulation of the proteolysis process [5].

An increase in transcutaneous absorption leads to an increased chance of enhanced systemic toxicity. This feature should always be considered when prescribing pharmacotherapy to the external integument, for example, tacrolimus is not used in patients with Netherton's syndrome. Cases are known when Cushing's syndrome developed during topical corticosteroid therapy [32].

More than 40 mutations are known associated with the gene encoding phyllagrin. The consequences of these mutations at the phenotypic level are at least dry skin.

That is, a low concentration of phyllagrin may be a direct precursor to the development of atopic dermatitis. 10-20% of people from the European population have 1-2 mutations out of five typical for Europeans.

The consequence of this is the widespread prevalence of dry skin among the European population [31, 1].NS is commonly misdiagnosed as atopic dermatitis because of atopic skin lesions and elevated serum IgE levels. Also, misdiagnosis happens when the symptoms are atypical or absent. In the presence of characteristic cutaneous findings, hair shaft deformity, atopic diathesis and positive family history, the diagnosis is rather straightforward.

In our case her mother's brother aged 55, has ichthyosis vulgaris and her 4-year-old daughter has atopic dermatitis. Currently, there is no cure for NS. Topical treatments with topical calcineurin inhibitors, topical retinoids, narrowband ultraviolet B phototherapy, psoralen and ultraviolet irradiation, combined with oral acitretin are the treatment options which have been used with varying success [33, 34].

Intravenous immunoglobulin and anti-TNF-α have been shown to be effective in treating severe illnesses [35]. Further study of the underlying reasons of the pathological cutaneous process will help to find a more effective treatment. The main focus of treatment strategies for diseases associated with impaired barrier function of the skin is its recovery, as well as the normalization of immunogenetic abnormalities [10].

Taken together and in general terms, a strategy aimed at long-term therapy of Netherton syndrome, atopic dermatitis, and also vulgar ichthyosis should be associated with the application of moisturizers [32]. The composition of the drugs should include lipids, namely ceramides, cholesterol and free fatty acids.

When treating patients with NS, strictly individual approach is required for each of them. Thus, it is necessary to emphasis the advisability of prescribing systemic glucocorticosteroids, as well as the dosage of aromatic retinoids [27]. In this case, the dosage and prescription of drugs of this type depends on the severity of the ongoing disease, in particular on the manifestations of pathologies on the skin surface.

According to some reports, the prerequisite for successful therapy is the appointment of emollients and root protectors. Other studies have shown high efficacy from the combination of drug therapy and acupuncture [29]. The patient was prescribed a combination of drugs: 30% sodium thiosulfate solution (isotonic solution), 3 times a day, intravenously, orally, potassium permanganate, 1 tablespoon 3 times a day and vitamin B6 at a dosage of 5 mg also 3 times a day, and one aevita dragee (vitamins A and E) per day.

Together with pharmacotherapy, a 5% dermatol ointment was applied to the skin, as well as a moisturizer for children and Advantan ointment (methylprednisolone aceponate). At the same time, acupuncture sessions were performed.

The patient was discharged from the hospital with significant improvements and the need to attend treatment every six months. The second patient received similar therapy. Therapy in the two cases described above took three weeks. This observation is interesting in that this syndrome is an extremely rare nosology and in adult patients it may resemble a clinic of various ichthyoses as well as atopic dermatitis.

For patients with hereditary syndromes, screening and genetic counseling are important for predicting the likelihood of inheritance in offspring. For another, more common disease, also observed in our case, ichthyosis, effective therapy has not yet been found. This is due to a number of reasons, among which is the difficulty of identifying a generally progressive adverse course of the disease.

Conclusions

NS is a rare disease which often misdiagnosed since symptoms may resemble those of congenital erythodermas, atopic dermatitis and some forms of ichthyosis. Another reason for missing NS is that in real life patients often do not get a full assessment of skin and hair. Besides manifestation similar to atopic dermatitis may also contribute to NS misdiagnosis. In the presented case the late diagnosis of NS in consequence of long-term remission for 20 years is rather unusual and attracts attention. Another notable feature of the

current case is the concurrent severe iron-deficiency anemia as a result of the pathology of the gastrointestinal tract due to genetic disease.

Thus, the important message of this clinical observation could be an awareness of genetic disorders like NS resulting in early diagnosis and proper treatment. Genetic confirmation of NS with detection of SPINK5 gene mutation is required with appropriate testing. Presence of clinical manifestations in combination with the SPINK5 mutation is an absolute confirmation of the Netherton syndrome.

This observation is interesting because NS is a rare nosology and is often misdiagnosed due to the fact that its symptoms may resemble those of congenital erythroderma, atopic dermatitis and some forms of ichthyosis. Another problem that makes it difficult to diagnose this syndrome is that a patient doesn't always have characteristic skin, hair and atopic manifestations and in this situation, the diagnosis may be wrong.

What attracts attention in the presented case is NS late diagnosis preceded with long-term remission (20 years), along with the presence of severe iron-deficiency anemia as a consequence of the pathology of the gastrointestinal tract due to genetic disease. Therefore, awareness of such rare genetic disorders like NS may assist in early diagnosis and further treatment. It is important to know that the absolute confirmation of NS is the identification of mutation in the SPINK5 gene, which is located in chromosome 5q31-32 associated with presence of clinical manifestations in combination with the mutation of the gene. In our case, the clinical picture of Netherton's syndrome is exacerbated by the negative effect of iron deficiency anemia. Their combined effect leads to an increase in negative effects on the skin and its derivatives. In addition to keratinization and peeling, there is a stratification of nails and hair.

At the physiological level, indicators characteristic of Netherton's syndrome are increased by a reduced hemoglobin content and quantitative indicators of red blood cells. All this leads to the fact that some signs reinforce others. Therefore, in case of refusal of treatment or incorrectly chosen tactics, a fatal outcome is also possible. Genetically caused disease (Netherton's syndrome) proceeded against the background of acquired (anemia). Our strategy has shown effectiveness, which was caused by the choice of systemic steroids.

References

1. Lodén M, Maibach HI (Eds.) (2012) Treatment of dry skin syndrome: the art and science of moisturizers. Springer Science & Business Media.
2. Hara-Chikuma M, Verkman AS (2008) Aquaporin-3 facilitates epidermal cell migration and proliferation during wound healing. Journal of Molecular Medicine, 86(2): 221-231.
3. Coleman III WP (2008) Fitzpatrick's Dermatology in General Medicine. Seventh edition. McGraw Hill.
4. Hubiche T, Ged C, Benard A, LéAUTé-LABRèzE C, McElreavey K, de Verneuil H, Boralevi F (2007) Analysis of SPINK 5, KLK 7 and FLG genotypes in a French atopic dermatitis cohort. Acta dermato-venereologica, 87(6): 499-505.
5. Flohr C, England K, Radulovic S, McLean WHI, Campbell LE, Barker J, Lack G (2010) Filaggrin loss- of- function mutations are associated with early- onset eczema, eczema severity and transepidermal water loss at 3 months of age. British Journal of Dermatology, 163(6): 1333-1336.
6. Weston WL, Lane AT, Morelli JG (2007) Color Textbook of Pediatric Dermatology (370). Elsevier Health Sciences.
7. Bieber Th (2010) Atopic Dermatitis. Ann. Dermatol., 22: 125-137.
8. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, O'Regan GM (2006) Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nature genetics, 38(4): 441.
9. Deraison C, Bonnart C, Lopez F, Besson C, Robinson R, Jayakumar A, Hovnanian A (2007) LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. Molecular biology

of the cell, 18(9): 3607-3619.

10. Darsow U, Wollenberg A, Simon D, Taïeb A, Werfel T, Oranje A, Giusti F (2010) ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. Journal of the European Academy of Dermatology and Venereology, 24(3): 317-328.
11. Goettig P, Magdolen V, Brandstetter H (2010) Natural and synthetic inhibitors of kallikrein-related peptidases (KLKs). Biochimie, 92(11): 1546-1567.
12. Bouwstra JA, Groenink HWW, Kempenaar JA, Romeijn SG, Ponec M (2008) Water distribution and natural moisturizer factor content in human skin equivalents are regulated by environmental relative humidity. Journal of Investigative Dermatology, 128(2): 378-388.
13. Akiyama M (2010) FLG mutations in ichthyosis vulgaris and atopic eczema: spectrum of mutations and population genetics. British Journal of Dermatology, 162(3): 472-477.
14. Kezic S, O'regan GM, Yau N, Sandilands A, Chen H, Campbell LE, Irvine AD (2011) Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. Allergy, 66(7): 934-940.
15. Khoo TL, Halim AS, Saad AM, Dorai AA (2010) The application of glycerol-preserved skin allograft in the treatment of burn injuries: an analysis based on indications. Burns, 36(6): 897-904.
16. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, Arseculeratne G (2006) Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nature genetics, 38(3): 337.
17. Barichello JM, Yamakawa N, Kisyuku M, Handa H, Shibata T, Ishida T, Kiwada H (2008) Combined effect of liposomalization and addition of glycerol on the transdermal delivery of isosorbide 5-nitrate in rat skin. International journal of pharmaceutics, 357(1-2): 199-205.
18. Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, Harper JI (2000) Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nature genetics, 25(2): 141.
19. Wilkinson RD, Curtis GH, Hawk WA (1964) Netherton's disease: Trichorrhexis invaginata (bamboo hair), congenital ichthyosiform erythroderma and the atopic diathesis. A histopathologic study. Archives of dermatology, 89(1): 46-54.
20. Komatsu N, Saijoh K, Jayakumar A, Clayman GL, Tohyama M, Suga Y, Diamandis EP (2008) Correlation between SPINK5 gene mutations and clinical manifestations in Netherton syndrome patients. Journal of Investigative Dermatology, 128(5): 1148-1159.
21. Paluel-Marmont C, Bellon N, Barbet P, Leclerc-Mercier S, Hadj-Rabia S, Dupont C, Bodemer C (2017) Eosinophilic esophagitis and colonic mucosal eosinophilia in Netherton syndrome. Journal of Allergy and Clinical Immunology, 139(6): 2003-2005.
22. Salodkar AD, Choudhary SV, Jadwani G, Singh A (2009) Bamboo Hair in Netherton's Syndrome. Int. J. Trichology., 1(2): 143-144.
23. Bittencourt MDJS, Moure ERD, Pies OTC, Mendes AD, Deprá MM, Mello ALPD (2015) Trichoscopy as a diagnostic tool in trichorrhexis invaginata and Netherton syndrome. Anais brasileiros de dermatologia, 90(1): 114-116.
24. Hannula-Jouppi K, Laasanen SL, Heikkilä H, Tuomiranta M, Tuomi ML, Hilvo S, Ranki A (2014) IgE allergen component-based profiling and atopic manifestations in patients with Netherton syndrome. Journal of Allergy and Clinical Immunology, 134(4): 985-988.
25. Renner ED, Hartl D, Rylaarsdam S, Young ML, Monaco-Shawver L, Kleiner G, Torgerson TR (2009) Comel-Netherton syndrome defined as primary immunodeficiency. Journal of Allergy and Clinical Immunology, 124(3): 536-543.
26. Rawlings AV (2009) Years of stratum corneum and moisturization research. IFSCC Magazine, 12(3): 169-172.
27. Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, McLean WI(2008) Filaggrin mutations, atopic eczema, hay fever, and asthma in children. Journal of Allergy and Clinical Immunology, 121(5): 1203-1209.
28. Hvid M, Vestergaard C, Kemp K, Christensen GB, Deleuran B, Deleuran M (2011) IL-25 in atopic dermatitis: a

possible link between inflammation and skin barrier dysfunction? Journal of Investigative Dermatology, 131(1): 150-157.

29. Hurwitz L (2011) Clinical pediatric dermatology. Fours edition (737). Elsevier saunders.
30. Aberg KM, Man MQ, Gallo RL, Ganz T, Crumrine D, Brown BE, Elias PM (2008) Co-regulation and interdependence of the mammalian epidermal permeability and antimicrobial barriers. Journal of Investigative Dermatology, 128(4): 917-925.
31. Hudson TJ (2006) Skin barrier function and allergic risk. Nature genetics, 38(4): 399.
32. Candi E, Schmidt R, Melino G (2005) The cornified envelope: a model of cell death in the skin. Nature reviews Molecular cell biology, 6(4): 328.
33. Lazaridou E, Apalla Z, Patsatsi A, Trigoni A, Ioannides D (2009) Netherton's syndrome: successful treatment with isotretinoin. Journal of the European Academy of Dermatology and Venereology, 23(2): 210-212.
34. Leung AK, Barankin B, Leong K (2018) An 8-year-old child with delayed diagnosis of Netherton syndrome. Case reports in pediatrics, 2018.
35. Small AM, Cordoro KM (2016) Netherton syndrome mimicking pustular psoriasis: clinical implications and response to intravenous immunoglobulin. Pediatric dermatology, 33(3): e222-e223.

