NETHERTON SYNDROME – A SMALL SERIES STUDY. IS THERE A CORRELATION BETWEEN ATOPY MANIFESTATIONS AND THE PRESENCE OF MULTIPLE HAIR SHAFT DYSTROPHIES?

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Abstract

Background: Netherton syndrome (NS) is a rare autosomal recessive disorder characterized by the triad of congenital ichthyosis, hair shaft dystrophy and severe atopic diathesis. The specific hair shaft defects include trichorrhexis invaginata, trichorrhexis nodosa and pili torti. Trichorrhexis invaginata is considered to be pathognomonic of NS and its presence confirms the diagnosis.

Methods: We aimed to observe through scanning electron microscopy the prevalence of these structural hair shaft defects among the eight cases diagnosed with NS in our clinic over a 10-year period. The examination included samples of scalp hair, eyebrows, eyelashes and pubic hair. Several clinical, biological, neuropsychological, ophthalmological, digestive and histopathological tests were also performed, including allergy testing.

Results: Trichorrhexis invaginata was evident in all cases. Trichorrhexis nodosa hair pathology represented 62.5% and pili torti 50%. When a patient presented more than one atopic manifestation (juvenile atopic dermatitis, asthma, atopic cheilitis), the hair shaft dystrophies were multiple and included not only the major abnormalities (trichorrhexis invaginata, trichorrhexis nodosa, pili torti), but also longitudinal and transversal fractures of the hair shaft, breaks, fissures and splits.

Conclusions: We noticed a possible correlation between atopy manifestations and the presence of multiple hair shaft dystrophies. The occurrence of trichorrhexis invaginata is necessary to make a diagnosis of NS but its presence is inconstant and it becomes evident after the first year of life and sometimes completely regresses in adulthood.

Keywords:
- genodermatoses
- atopic dermatitis
- ichthyosis
- hair disorders

Introduction

Netherton syndrome is a rare autosomal recessive disorder characterized by the triad of congenital ichthyosis, hair shaft dystrophy and severe atopic diathesis (1). The Netherton syndrome gene, named SPINK5 (serine protease inhibitor Kazal-type 5), has been identified on chromosome 5q32 and encodes a serine protease inhibitor called LEKTI (lymphoepithelial Kazal-type related inhibitor). The loss of LEKTI results in premature activation of stratum corneum trypsin/chymotryptic enzymes, which leads to proteolysis of desmosomes and adhesion molecules (2, 3). The incidence of NS has been estimated to 1 in 200 000

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and the condition is also thought to be the cause of up to 18% of congenital erythrodermas (4).

The clinical course often begins at birth. Infants with NS are born with congenital ichthyosiform erythroderma or these skin findings can develop within the first few weeks postpartum (1). Some affected infants are born with a tight, clear sheath covering their skin, called a collodion membrane. These infants can also have an associated failure-to-thrive and hypertensive dehydration, likely secondary to excess fluid loss from a defective skin barrier (5). Complications such as bronchopneumonia or sepsis rarely occur (6). Nails and teeth are not affected in NS. The initial erythroderma usually evolves into ichthyosis linearis circumflexa ILC) over time; ILC is not present in patients at all times and may vary with seasonal climate changes. An extreme erythroderma can be observed with infection or excitement. Atopic diathesis can include eczema-like eruptions, pruritus, atopic dermatitis, atopic cheilitis, angioedema, urticaria, asthma, allergic rhinitis, elevated serum IgE, and hypereosinophilia (1).

Other possible symptoms are: mental deficiency, neurological deficits, delayed growth and body development, short stature, heat intolerance, recurrent infections, hypogammaglobulinemia or hypergammaglobulinemia (7) and interstitial aminoaciduria (8, 9). The diagnosis of NS is definitely established by demonstration of trichorrhexis invaginata (TI) through light and/or scanning electron microscopy (10). Other hair anomalies such as pili torti, trichorrhexis nodosa (TN), trichoschisis, trichoptilosis can be found but are not specific of NS (11).

Trichorrhexis invaginata (“bamboo hair”) is a focal defect of the hair shaft that produces development of torsion nodules and invaginated nodules. The hair shaft nodules caused by this defect are sometimes visible to the naked eye. These hair defects can be found in scalp, eyebrow, eyelash, axillary or pubic hairs (12). Grossly, scalp hair is described to be sparse and brittle. Ito et al. (13) have reported the hair shaft abnormality to be secondary to intermittent incomplete formation of disulfide bonds in the keratogenous zone. The consequence is the subsequent invagination of the fully keratinized distal hair shaft into the softer, incompletely keratinized proximal segment. If hair is pulled distally from this focal defect, a golf-tee-like deformity is left. Hence, any hairs examined should be cut, rather than plucked (9). Trichorrhexis invaginata causes patchy hair thinning, but rarely complete alopecia. Hair growth often improves with age, and can sometimes completely resolve.

Pili torti is characterized by hair shafts twisted around their axis with 180°. Fractures occur within the twists, being the weakest point. Trichorrhexis nodosa is microscopically emphasized by the appearance of frayed cortical fibers faced against each other like two paintbrushes; it is of traumatic origin and can affect hairs weakened by congenital or acquired diseases. Trichoschisis is characterized by a transverse fracture of the hair shaft. The low cysteine (sulfur) of hair is postulated to account for cuticular and cortical weakness. Trichoptilosis causes longitudinal fractures or fraying of the distal end of the hair.

Diagnosis of NS can be difficult for some reasons due to lack of family history, unspecific histologic changes and variable skin lesions and hair abnormalities (14).

The aim of our study was to examine retrospectively the possible correlation between atopic manifestations and the presence of multiple hair shaft dystrophies in eight cases diagnosed with NS in Dermatology Clinic of Timisoara over a 10-year period.

Material and methods

This study included eight patients diagnosed with NS in our clinic over a 10 year-period. Relevant clinical data of these patients were retrospectively collected. Diagnosis was based on the triad of congenital ichthyosis, atopic manifestations and hair shaft anomalies and was confirmed by the presence of trichorrhexis invaginata in optical microscopy. The data collected comprised clinical features such as age at onset, cutaneous manifestations, atopic manifestations, macroscopic hair features, personal and/or familial history of allergy/atopy, optical microscopy of hair shaft, chromatography of serum and urine aminoacids, neuropsychiatric and ophthalmologic assessment, allergy testing, tests for urinary tract infection and parasitic digestive infection.

The hairs collected from scalp hair, eyebrow and pubic hair, were first observed through light microscopy to confirm the presence of an abnormality and then analyzed by scanning electron microscopy (SEM). The studies were performed on samples fixed on copper supports. The surface was examined by using an Environmental Scanning Electron Microscope (ESEM) type Quanta 200, operating at 20kV with secondary electrons in Low vacuum mode.

Results

The median age at diagnosis was 1.8 (0.4–9). Patients were predominantly females (62.5%). The main manifestations at diagnosis were ichthyosis linearis circumflexa (75%), ichthyosis vulgaris (25%), juvenile atopic dermatitis (100%), asthma (25%) and atopic cheilitis (37.5%). Macroscopic and repeated optical microscopic examination of hair shafts at diagnosis revealed trichorrhexis invaginata (100%), trichorrhexis nodosa (62.5%) and pili torti (50%) (Table 1).

Other important data included chromatography of serum and urine aminoacids with low levels of aspartic acid (25%), high levels of alanine and tyrosine (37.5%); neuropsychiatric assessment with low IQ (37.5%), anxiety (25%), emotional lability...
Clinical study

Table 1. Main manifestations at diagnosis and hair shaft anomalies

<table>
<thead>
<tr>
<th>Initials, gender, age at onset</th>
<th>Hair shaft anomalies</th>
<th>Cutaneous manifestations</th>
<th>Atopic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.A., F., 0-6 months</td>
<td>Trichorrhexis invaginata, trichorrhexis nodosa</td>
<td>Ichthyosis linearis circumflexa</td>
<td>Juvenile atopic dermatitis</td>
</tr>
<tr>
<td>I.V., F., 9 years</td>
<td>Trichorrhexis invaginata, trichorrhexis nodosa, pili torti</td>
<td>Ichthyosis linearis circumflexa</td>
<td>Juvenile atopic dermatitis, asthma</td>
</tr>
<tr>
<td>I.F.V., F., 2 years</td>
<td>Trichorrhexis invaginata, trichorrhexis nodosa, pili torti</td>
<td>Ichthyosis linearis circumflexa</td>
<td>Juvenile atopic dermatitis, asthma, atopic cheilitis</td>
</tr>
<tr>
<td>T.M., F., 0-6 months</td>
<td>Trichorrhexis invaginata, trichorrhexis nodosa</td>
<td>Ichthyosis vulgaris</td>
<td>Juvenile atopic dermatitis</td>
</tr>
<tr>
<td>L.C., M., 0-6 months</td>
<td>Trichorrhexis invaginata</td>
<td>Ichthyosis linearis circumflexa</td>
<td>Juvenile atopic dermatitis</td>
</tr>
<tr>
<td>B.E., F., 0-6 months</td>
<td>Trichorrhexis invaginata trichorrhexis nodosa</td>
<td>Ichthyosis vulgaris</td>
<td>Juvenile atopic dermatitis</td>
</tr>
<tr>
<td>L.P., M., 0-6 months</td>
<td>Trichorrhexis invaginata, pili torti</td>
<td>Ichthyosis linearis circumflexa</td>
<td>Juvenile atopic dermatitis, atopic cheilitis</td>
</tr>
<tr>
<td>G.S., M., 0-4 months</td>
<td>Trichorrhexis invaginata, pili torti</td>
<td>Ichthyosis linearis circumflexa</td>
<td>Juvenile atopic dermatitis, atopic cheilitis</td>
</tr>
</tbody>
</table>

Table 2. Aggregate data of our patients with Netherton syndrome at diagnosis

<table>
<thead>
<tr>
<th>Initials, gender</th>
<th>Chromatography of seric and urinary amino acids</th>
<th>Neuropsychiatric manifestations</th>
<th>Ophthalmologic manifestations</th>
<th>Urinary tract infections</th>
<th>Chronic parasitic digestive infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.A., F.</td>
<td>Normal values</td>
<td>IQ</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I.V., F.</td>
<td>Low levels of seric aspartic acid; high levels of seric alanine and tyrosine</td>
<td>IQ, anxiety</td>
<td>Spastic ectropion, macular pigment changes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I.F.V., F.</td>
<td>Low levels of seric aspartic acid; high levels of seric alanine and tyrosine</td>
<td>IQ</td>
<td>Macular pigment changes, hypermetropy, astigmatism</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T.M., F.</td>
<td>High levels of seric alanine; high levels of urinary valine and phenylalanine</td>
<td>Normal IQ, emotional lability</td>
<td>Hypermetrophy</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>L.C., M.</td>
<td>Normal values</td>
<td>Normal</td>
<td>Blepharoconjunctivitis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>B.E.</td>
<td>Trichorrhexis invaginata trichorrhexis nodosa</td>
<td>Normal</td>
<td>Ichthyosis vulgaris</td>
<td>Juvenile atopic dermatitis</td>
<td></td>
</tr>
<tr>
<td>L.P., M.</td>
<td>Normal values</td>
<td>Normal</td>
<td>Blepharoconjunctivitis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>G.S., M.</td>
<td>Not performed</td>
<td>Normal</td>
<td>IQ, emotional lability</td>
<td>Blepharitis, astigmatism, hypermetrophy</td>
<td>+</td>
</tr>
</tbody>
</table>

(25%); ophtalmologic assessment with blepharoconjunctivitis (37.5%), hypermetropy (37.5%), macular pigment changes (25%); urinary tract infections (62.5%); chronic parasitic digestive infections (37.5%). These observations are presented in Table 2.
Scanning electron microscopy of the hair shaft anomalies

Results of SEM evaluation of the hair shafts are presented in the figures below (Figures 1, 2, 3, 4 and 5). The major hair dystrophies (Trichorrhexis invaginata, trichorrhexis nodosa, pili torti) are accompanied by minor modifications such as longitudinal fractures of the hair shaft (trichoptilosis), transversal fractures (trichoschisis), breaks, fissures and splits, as a result of the fragility of intrinsically abnormal hair.

Discussion

In our patients, the disease started to manifest in the first months after birth or in childhood. A dispute over gender predominance exists, with the thought that girls are more commonly affected than boys, but a review of the literature by Smith et al. (7) showed that 20 of 44 cases were males. In our study, females were the predominant subjects; thus, five of eight patients were females: two (I.V. 9 years old and I.F.V. 2 years old) were sisters, while in other two cases there was a family history of ichthyosis vulgaris. Six out of eight patients included in our study presented with ILC as the first clinical sign, whereas the other two patients were characterized by lesions
of ichthyosis vulgaris. Atopic dermatitis was present in all cases, and asthma in two cases. Atopic cheilitis affected three of our patients. Regarding the hair dystrophies, clinical examination revealed: variable length hair, bleached, dull, with hypotrichosis more pronounced in the highest friction area (occipital area). Asatomic manifestations were more than one, likewise the hair shaft distrophies were multiple and included not only the major abnormalities (trichorrhexis invaginata, trichorrhexis nodosa, pili torti) but also longitudinal and transversal fractures of the hair shaft, breaks, fissures and splits, all these being a sign of increased hair shaft fragility. The finding of low serum levels of aspartic acid, high serum levels of alanine and tyrosine and high urine levels of valine and phenylalanine in three of our patients is added to these features. Although more patients need to be studied, we believe that the modified levels of amino acids in the biological fluids of our patients could indicate a biochemical relation between inborn errors and the frequently associated morphological hair dystrophies, by causing an abnormal composition of cortical fibre proteins. Mental retardation has been reported in cases of NS (14), and six of our cases presented with neuropsychiatric manifestations, ranging from emotional lability to low IQ.

Conclusion

Our cases presented the most important NS characteristics described in literature. We focused on the hair shaft abnormalities, for which the diagnosis can be made either through optical microscopy or electron microscopy. Our decision to also use SEM was determined by the fact that this technique offers the possibility of a more precise examination of cuticular scales of hair, having the advantage of allowing detailed observations of scale patterns, permitting considerable magnification. We noticed that when a patient presented more than one atomic manifestation (juvenile atopic dermatitis, asthma, atopic cheilitis), the hair shaft distrophies were multiple and included not only the major abnormalities (trichorrhexis invaginata, trichorrhexis nodosa, pili torti) but also longitudinal and transversal fractures of the hair shaft, breaks, fissures and splits.

The routine usage of SEM in many diseases in which hair surface alterations are common will permit a valuable contribution in the scientific field. Nevertheless, it would be useful in differential diagnosis in diseases affecting hair surface morphology.

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Bibliography