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Case report

Netherton's syndrome: a case report

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Abstract Netherton's syndrome is a rare, autosomal recessive disorder of keratinization characterized by trichorrhexis invaginata, ichthyosis linearis circumflexa and atopic diathesis. There is also failure to thrive. Recently the genetic defect has been identified as a mutation in SPINK5 gene on chromosome 5q31-q32. A case of this rare disorder with classical presentation in a 16-year-old boy is reported here. He had had congenital erythroderma, failure to thrive, ichthyosis linearis circumflexa, trichorrhexis invaginata, epilepsy, spastic gait, and raised IgE levels. A brief review o the literature is presented as well.

Key words
Netherton's syndrome, ichthyosis linearis circumflexa, trichorrhexis invaginata

Introduction

Netherton's syndrome (NS), also known as Còmel-Netherton syndrome, ichthyosis linearis circumflexa, is the commonest of the multisystem ichthyosiform syndromes and characterized by ichthyosiform dermatosis (ichthyosis linearis circumflexa [ILC]) with variable erythroderma, hair-shaft defects i.e. trichorrhexis invginata, atopic features and failure to thrive. It is inherited in autosomal recessive pattern with an estimated incidence of 1 in 100,000.[1]

Touraine and Solente in 1937 were the first to note the association between hair-shaft defects (bamboo node) and ichthyosiform erythroderma. Later, Còmel coined the term ichthyosis linearis circumflexa in 1949 to describe a rash in a young Italian woman without referring to the hair-shaft defects; however, Rille (Frühwald) had previously described the distinctive features of ILC by 1922.[1]

In 1958, Netherton reported a young girl with generalized scaly dermatitis and fragile nodular hair-shaft deformities that he termed trichorrhexis nodosa (bamboo hair). Later, this was more appropriately renamed as trichorrhexis invaginata for a ball-and-socket-type hair-shaft deformity at the suggestion of Wilkinson *et al*.[2]

In 1974, Mevorah *et al.*[3] established the clinical/statistical relationship between ILC and NS. All cases of ILC in which the hair changes have been carefully sought have been found to show them. The atopic diathesis occurs in approximately 75% of patients with NS. Hurwitz *et al.*[4] questioned the variability of NS and postulated that it is not a single entity but a heterogeneous one.

Case report

A 16-year-old boy presented to the Department of Dermatology, Lahore Medical College, Lahore who was referred to Department of Dermatology, Mayo

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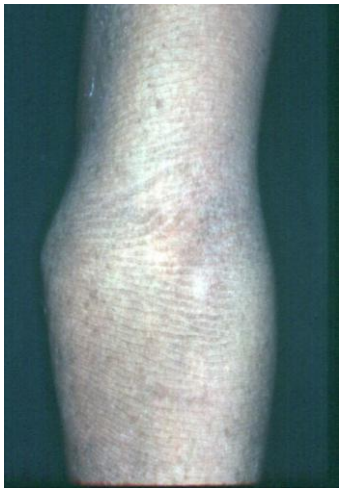

Figure 1 Flexural lichenification of left antecubital fossa

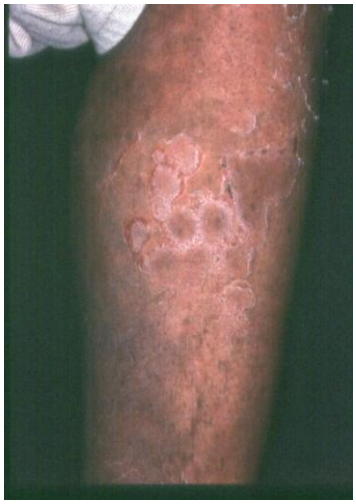

Figure 2 Typical double-edged, serpiginous scales of ILC

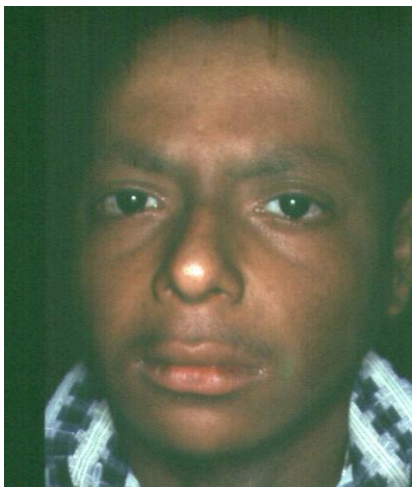

Figure 3 Erythrodermic face with sparse eyebrows

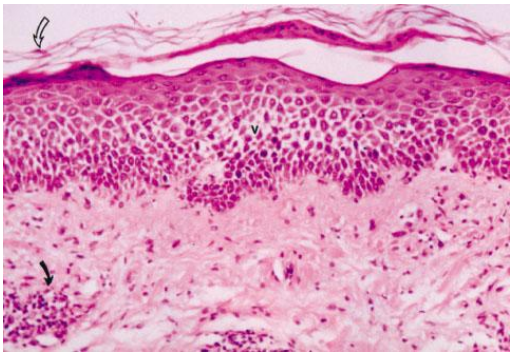

Figure 4 Histoathology of ILC showing spongiosis and exocytosis

Hospital, Lahore for further investigations of his cutaneous eruption. He had had erythroderma since birth. He was born after an uneventful pregnancy to consanguineous couple. The patient showed delayed milestones since birth and also developed epileptic fits at the age of 9 years. There was no history of similar illness in the family. No personal or family history of atopy was found.

Physical examination revealed a young boy of average height and built. The rash appeared to be an eczematous, with a flexural accentuation (**Figure 1**). A characteristic serpiginous migratory annular/polycyclic rash with double-edged scale was also present on the limbs (**Figure 2**). The patient had sparse, abnormal scalp hair which was short, lusterless, and brittle. Madarosis was present, as well (**Figure 3**).

Examination of nervous system revealed mental retardation (IQ of 75%), clumsy movements, resting dystonic movements, and spastic gait. Both fundi were normal. He also had pectus excavatum (pigeon-shaped chest). Rest of the systemic examination was normal.

Light microscopic examination of the hair from scalp and eyebrows revealed a ball-and-socket hair-shaft deformity typical of

trichorrhexis invaginata. Histopathological examination of a specimen taken from a lesion of ILC revealed atopic dermatitis like changes with spongiosis and exocytosis (**Figure 4**). His serum IgE level was 1400 IU/l (normal up to 200 IU/l).

The patient was given topical keratolytics and investigated for systemic retinoid therapy.

Discussion

Typical hair shaft defect, erythroderma with flexural accentuation, ichthyosis linearis circumflexa, neurological abnormalities and raised IgE levels in our patient lead to the diagnosis of NS. The histopathological findings were also compatible.

Children with NS, as in our case, develop congenital erythroderma, which is evident at birth or during the first weeks of life. It may not be pronounced in some neonates who are affected. Collodion baby is usually not feature. Pruritus is usually quite troublesome. Clinically, the rash is more eczematous or psoriasiform rather than ichthyosis-like. It may improve with time.[1] **Table 1** summarizes different features of NS.

ILC is a characteristic serpiginous migratory annular/polycyclic rash with double-edged scale. It is pathognomonic for NS. It usually occurs after age of 2 years and is fairly short-lived, lasting from a few weeks (followed by clearance for months) to years. ILC appears to last longer in adults than in children. Migratory lesions of ILC may be caused by a dermal influx of inflammatory cells that undergo phagocytosis and digestion by keratinocytes, resulting in disruption of keratinization.[1,2]

Failure to thrive is often profound in the first year of life. This condition is accompanied by diarrhea and symptoms of malabsorption. Jejunal villous atrophy that spontaneously resolved at age 10 months has been reported in 1 patient with NS. In another French study, 3 out of 5 children had jejunal villous atrophy.[6] This malabsorption is essentially dermopathic enteropathy, which is a recognized problem with congenital and some acquired erythrodermas. It is not specific to NS. By the second year of life, most children start to thrive, though most remain below the 25th percentile for height and weight.

All patients at some stage in their disease develop allergy to foodstuffs, especially nuts. Most have an atopic predisposition, with a strong family history of asthma, eczema, and hay fever.[1]

Amongst hair features, trichorrhexis invaginata (TI) or bamboo node is the mosst characteristic feature.[1] It is a ball-and-socket hair-shaft deformity caused by invagination of the distal hair shaft into the cup formed by the proximal hair shaft. This invagination occurs at the site of an intermittent keratinizing defect of the hair cortex resulting from incomplete conversion of the sulfhydryl-SH group onto S-S disulfide bonds in the protein of the cortical fibers. This defect leads to cortical softness, bulging of external root sheath, and the bamboo deformity. All patients have sparse, abnormal hair. The hair is short, spiky, lusterless, and brittle. Scalp hair grows for a few centimeters before breaking. This finding is particularly evident at the areas of friction, especially the occiput and the temples. The eyebrows also have sparse, broken hair. Older patients may lose their eyebrows and eyelashes altogether. Some patients

Table 1 Features of Netherton's syndrome [1, 5]

General
Failure to thrive
Hyper-/hypothermia
Dehydration
Cutaneous
Erythroderma
Ichthyosis linearis circumflexa
Hair
Trichorrhexis invaginata
Trichorrhexis nodosa
Helical hair [15]
Sparse scalp, body hair
Madarosis
Traumatic alopecia
Atopic features
Personal or family history of atopy
Raised IgE levels
Urticaria/angioedema
Food allergy to fish or nuts
GIT
Diarrhea
Jejunal villous atrophy
Immunodeficiency
Increased bacteria/viral infections
Neutrophil defects
Lymphocytes defects
Raised C3, C4 levels
CNS
Cerebral infarction [16]

also show fragility of the reduced body hair. A few older children have normal-looking hair that is microscopically defective. Identifying the bamboo node on the hair shaft by unaided visual inspection is practically impossible.[2]

NS should be at the top of the differential diagnosis list in a newborn with erythroderma and abnormal-looking scalp hair. It can be misdiagnosed as nonbullous congenital ichthyosiform erythroderma, generalized seborrheic dermatitis, immunodeficiency syndromes and acrodermatitis enteropathica.[7] Most of these are misdiagnosed as Leiner disease, which is a descriptive term for congenital erythroderma, failure to thrive, and diarrhea, and not a specific disease entity.

Neonates with NS may develop complications of generalized erythroderma e.g. temperature instability and cutaneous and systemic infections, increased transepidermal water loss due to corneocyte barrier function and occasionally, hypernatremic dehydration. Failure to thrive and diarrhea may also occur. Other inconsistent immunologic abnormalities have been reported e.g. transient neutrophil function defects, impaired cellular and immune responses, and raised complement levels (C3 and C4).[1,2]

The gene responsible of the disease was mapped to chromosome 5q31-q32.[8] This gene, called SPINK5, encodes a 15 domain serine protease inhibitor (LEKT1) predominantly expressed in epithelial and lymphoid tissues, and plays a critical role in epidermal barrier function and immunity. The same locus is associated with predisposition to atopy in general. Coding polymorphism in SPINK5 exons 3 and 4 have been reported to be associated with atopy, asthma and topic dermatitis.[9]

Topical retinoid therapy almost always adversely affects patients with NS.[10] NS has been attributed to impaired transcription of relevant retinoic acid receptor genes affecting differentiation. Other treatments used include, ammonium lactate,[11] tacrolimus[12,13] and photochemotherapy.[14]

The disease tends to improve with age, but the course can be punctuated by intermittent exacerbations.

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