

Netherton Syndrome Associated with Growth Hormone Deficiency

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Abstract: Netherton syndrome (NS) is a rare autosomal recessive disorder characterized by ichthyosiform scaling, hair abnormalities, and variable atopic features. Mutations in the serine protease inhibitor Kazal type 5 (*SPINK5*) gene leading to lymphoepithelial Kazal-type-related inhibitor (LEKTI) deficiency cause NS. Growth retardation is a classic feature of NS, but growth hormone (GH) deficiency with subsequent response to GH therapy is not documented in the literature. It is proposed that a lack of inhibition of proteases due to a deficiency of LEKTI in the pituitary gland leads to the overprocessing of human GH in NS. Herein we report three patients with NS who had growth retardation associated with GH deficiency and responded well to GH therapy.

Netherton syndrome (NS) is a rare autosomal recessive disorder characterized by ichthyosiform scaling, hair abnormalities, and variable atopic features (1). The gene for NS has been identified on chromosome 5q32, named serine protease inhibitor Kazal type 5 (*SPINK5*), and encodes an inhibitor of serine proteases called lymphoepithelial Kazal-type-related inhibitor (LEKTI) (2,3). Growth retardation is a classic feature of NS, but, to the best of our knowledge, growth hormone (GH) deficiency is not documented in the literature.

We present three patients with NS who had growth retardation due to GH deficiency that responded well to GH therapy.

CASE REPORTS

Patients 1 and 2 (Twins)

Six-year-old identical twin sisters presented to our department with short stature. They were born appropriate for gestational age at 36 weeks after an

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uneventful pregnancy to healthy unrelated parents. Shortly after birth they both developed ichthyosis and were found to be allergic to various foods. They had short, dry scalp hair and sparse eyebrows. Microscopic examination of their hair and eyebrows showed trichorrhexis invaginata. The diagnosis of NS was confirmed according to a DNA analysis. A homozygous mutation c581_82delGT in exon 7 of the *SPINK5* gene was found in both patients (GeneDx, Gaithersburg, MD) (4).

At initial presentation to our unit, they were severely short, their bone ages were delayed, and both had low height velocity (Table 1). They were not taking corticosteroids or other medications that could suppress their growth. GH stimulation tests were conducted and inadequate responses were noted (Table 1) (5). Prolactin levels were also low (Table 1). Thyroid hormone and early morning cortisol levels were normal (Table 1). Magnetic resonance imaging (MRI) of the sella was normal. GH therapy was started when they were 6.4 years old. They responded well, and after 2 years of GH therapy their height standard deviation scores increased to -1.1 and -0.74 while they were still prepubertal (Table 2). Their skin lesions also improved after GH treatment. The ichthyosis and redness were ameliorated and the pruritus improved (Fig. 1A, B).

Considering the combined pituitary hormone (GH and prolactin) deficiency in our patients and the proximity of the NS gene, the pituitary-specific

paired-like homeodomain transcription factor (*PROPI*, Online Mendelian Inheritance in Man 601538) gene was studied. Screenings were conducted for *PROPI* mutations using multiplex ligation-dependent probe amplification to identify any gross deletion, followed by DNA sequencing for other small variations and mutations, but no abnormalities were found.

Patient 3

A 12.25-year-old boy with a diagnosis of NS was referred to our department for evaluation of short stature. He was born appropriate for gestational age at full term after a normal pregnancy to nonconsanguineous parents with no known family history of skin disorders. His medical history was significant for generalized erythematous skin lesions beginning at the age of 1 month. He was found to be allergic to various foods and was treated for severe atopic dermatitis with no clinical response. He had sparse hair on the scalp, sparse eyebrows and eyelashes, and scaly red skin involving almost the whole body. Light microscopic examinations of eyebrow and scalp hair were all remarkable for the characteristic trichorrhexis invaginata consistent with the clinical diagnosis of NS. DNA analysis revealed a heterozygous mutation IVS14+4 A>T in the *SPINK5* gene (GeneDx).

At initial presentation to our unit he was severely short and his bone age was delayed (Table 1). He was

TABLE 1. Some Clinical and Laboratory Findings of the Patients at Presentation

Characteristic	Patient 1	Patient 2	Patient 3
Age	6	6	12.25
Weight/SDS, kg	14.1/−1.84	14.9/−1.7	52.9/0.57
Height/SDS, cm	101.2/−2.29	101/−2.33	141.3/−1.7
Head circumference/SDS, cm	50.1/−0.48	50.5/−0.22	52.8/−1.29
Body mass index/SDS, kg/m ²	13.8/−1.18	14.6/−0.53	26.7/1.8
Target height/SDS, cm	160.7/−0.35	160.7/−0.35	171.9/−0.66
Bone age, years	3	3	11.5
Free thyroxine, pmol/L (normal range 12–20.6 pmol/L)	13.3	13.9	14.9
Thyroid stimulating hormone, mIU/L (normal range 0.7–4. mIU/L)	2.3	2.81	4.03
Cortisol, µg/dL (normal range 5–25 µg/dL)	7.05	10.9	6.8
IGF-1, ng/mL	96.5 (50–297)*	80 (50–297)*	363 (143–693)*
IGFBP-3, µg/mL	2.7 (1.4–6.1)*	2.86 (1.4–6.1)*	4.77 (2.7–8.9)*
Prolactin, ng/mL (normal range 4.8–23.3 ng/mL)	3.3	3.5	7.3
Peak growth hormone levels, ng/mL			
Insulin tolerance test	5.86	5.14	
Clonidine	4.56	3.26	1.46
L-dopa test			0.23
Mutation	c581_82delGT homozygous mutation	c581_82delGT homozygous mutation	IVS14 + 4 A>T heterozygous mutation

*Numbers inside the parentheses are the normal ranges for their age, gender and puberty stage. SDS, standard deviation score; IGF, insulin-like growth factor; BP, binding protein.

TABLE 2. Some Clinical and Laboratory Findings at Follow-Up

	Patient 1	Patient 2	Patient 3
At the beginning of GH therapy			
Age, years	6.4	6.4	12.6
Height velocity, cm/year	1.03	2.5	1.2
Weight/SDS, kg	14.5/-2.4	14.5/-2.4	49.7/0.26
Height/SDS, cm	101.5/-2.85	102/-2.46	141.7/-1.64
BMI/SDS, kg/m ²	13.9/-0.97	13.9/-0.97	24.9/1.4
GH dose, mg/kg/day	0.025	0.025	0.032
After 1 year of GH therapy			
Age, years	7.4	7.4	13.6
Height velocity, cm/year	8.7	9.8	6
Weight/SDS, kg	18.6/-1.65	19.6/-1.27	47.4/-0.52
Height/SDS, cm	110.2/-2.05	111.8/-1.74	147.7/-1.61
BMI/SDS, kg/m ²	15.4/-0.1	15.7/0.06	21.6/0.42
Bone age, years	4.5	5	12.5
IGF-1, ng/mL	117.3	124.8	167
IGFBP-3, µg/mL	2.58	2.55	2.62
After 2 years of GH therapy			
Age, years	8.4	8.4	
Height velocity, cm/year	11	11	
Weight/SDS, kg	21.1/-1.18	23.1/-0.59	
Height/SDS, cm	121.2/-1.1	122.8/-0.74	
BMI, kg/m ² /SDS	14.5/-0.94	15.3/-0.46	
Bone age, years	5.5	5.5	
IGF-1, ng/mL	113.6	148	
IGFBP-3, µg/mL	3.1	3.4	

GH, growth hormone; SDS, standard deviation score; BMI, body mass index; IGF, insulin-like growth factor; IGFBP, IGF binding protein.

not taking any medication that could compromise his growth. At follow-up, his height velocity remained low. GH stimulation tests were conducted and low responses were obtained (Table 1). Thyroid hormone, prolactin, and early morning cortisol levels were all normal (Table 1). MRI of the sella was normal. GH therapy was started when he was 12.5 years old. After 12 months on GH therapy his height standard deviation increased to -1.61 when he was still prepubertal (Table 2). His skin lesions also improved (Fig. 2A, B).

DISCUSSION

The triad of ichthyosis linearis circumflexa, trichorrhexis invaginata, and atopic diathesis characterize NS (1). Trichorrhexis invaginata is the invagination of the distal hair shaft into the expanded proximal hair shaft seen on scanning. This finding is described as a “golf tee” and is characteristic (6). Mutations in the serine protease *SPINK5* gene lead to LEKTI deficiency and cause NS. Genetic testing is usually required to confirm the diagnosis, but mutations can be identi-



Figure 1. The twins (patients 1 and 2) at (A) presentation and (B) follow-up.

fied in two-thirds to three-quarters of patients with clinically suspected NS. In our twin patients, the DNA analysis confirmed the diagnosis of NS and a homozygous mutation was found in the *SPINK5* gene. In patient 3, only a heterozygous mutation in the *SPINK5* gene could be identified, but he has characteristic clinical findings of NS.

Growth retardation is a classic feature of NS. Extensive skin barrier failure leads to growth retardation (7). LEKTI is expressed in normal skin and skin appendages and is important for maintaining epidermal homeostasis. Human tissue kallikreins (KLKs) are colocalized with LEKTI in skin. KLKs are a family of trypsin or chymotrypsin-like secreted serine proteases, and LEKTI suppresses their enzymatic activities. Desquamation of the skin is the result of a tightly regulated multistep proteolytic event, and the balance between KLKs and LEKTI is essential for normal skin barrier function (8); pH critically

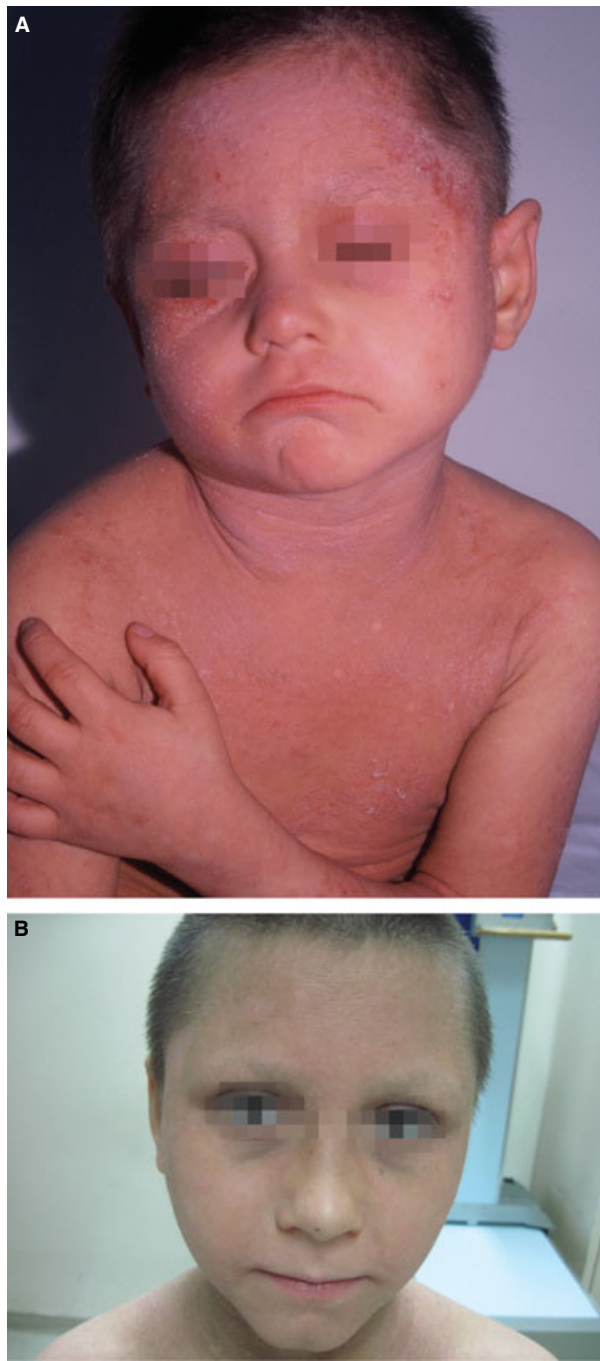


Figure 2. Patient 3 at (A) presentation and (B) follow-up.

modulates this process, and some medications, such as steroids, which are used to treat dermatitis, could suppress linear growth. Our patients had taken some of these medications before their diagnosis of NS, but when they presented to our department, none of them were taking these medications.

It has been proposed that a lack of inhibition of proteases due to a deficiency of LEKTI in the

pituitary gland would lead to the overprocessing of human GH in NS (8), but to the best of our knowledge, GH deficiency is not documented in the literature. Komatsu et al (8) demonstrated that many KLKs are expressed in the human pituitary gland, and their preliminary data suggest that cells that produce GH also produce KLKs. It is thus possible that KLKs proteolytically modify GH before it enters the systemic circulation. They demonstrated that excess KLKs can digest GH into smaller, and probably inactive, fragments and that LEKTI, which was also located in GH-producing cells, can inhibit this process. They stated that GH isoforms are not distinguishable from each other using routine assays in plasma and hypothesized that bioinactive isoforms of GH could be responsible for the growth retardation in NS. We detected GH deficiency in our three patients and achieved a good response to exogenous GH therapy. Because proteolytic processing in the pituitary would not have altered the exogenous GH, this response to GH therapy might further support our theory.

In our twin patients, in addition to GH deficiency, prolactin levels were low at initial presentation. Considering combined pituitary hormone deficiency and the proximity of the NS gene, the *PROPI* gene was studied in our patients, but no abnormalities were found. Previous studies reported that KLKs were associated with prolactin in prolactin-secreting adenomas and prolactin-secreting cells within GH-secreting adenomas of the human anterior pituitary (8–10), and Komatsu et al (8) proposed that KLKs could also proteolytically modify other pituitary hormones such as prolactin.

The skin lesions of our patients also improved with GH therapy. GH therapy has been used in studies to investigate its effects in healing skin lesions. The increase in plasma GH levels in individuals who have been burned leads to improvement in reepithelialization, an increase in granulation tissue and the basal lamina sheath, and a reduction in healing time (11). Skin healing involves cross talk between cells from the epidermis and dermis, with the participation of cytokines, growth factors, and modulation of the extracellular matrix. GH ensures normal growth and development of the skin, stimulating receptors in the dermal cells, principally those in the fibroblasts, using insulinlike growth factor 1 (IGF-1) as a mediator of its actions in the dermis and epidermis, although the direct effects of GH on these cells remain unknown (12). GH can bind to cultured human fibroblasts through GH receptors and elicit a proliferative response. Studies of GH action on avian fibroblasts

have revealed that GH alone can stimulate the production of collagen (13). Immunohistochemical analyses of sections of human skin revealed the presence of GH receptor and GH binding protein in all layers of the epidermis and in the epidermal layers of skin appendages (14). Studies indicate direct effects of the IGF systems in the modulation of epidermal homeostasis. IGF-1 acts on the keratinocytes and melanocytes of the epidermis, modulating various functions such as proliferation, differentiation, migration, and survival (12).

In conclusion, although growth retardation is a classic feature of NS, not all children with NS are growth retarded. Molecular clinical studies are needed to better understand the physiopathology of growth retardation in NS. GH deficiency should be considered in patients with NS who are severely short. As shown, GH therapy can result in taller stature and improvement in skin lesions.

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