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Case Report

A long-term survivor of ITGA3-related infantile lethal nephrotic syndrome with epidermolysis bullosa

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ABSTRACT

Infantile lethal nephrotic syndrome with epidermolysis bullosa (ILNEB) syndrome is an autosomal recessive genodermatosis caused by biallelic variants in ITGA3 (integrin subunit alpha 3; 17q21.33), disrupting α3β1 integrin-mediated adhesion in epithelial basement membranes. Canonical features-progressive interstitial lung disease (ILD), congenital/infantile nephrotic syndrome (CNS/INS), and junctional epidermolysis bullosa (JEB)-manifest neonatally with >95% mortality by age 2 years across 22 reported cases. A 9-year-old female from consanguineous pedigree presented with chronic respiratory insufficiency, stunting, mechanobullous dermatosis, and nephrotic-range proteinuria (4.95 g/1.73 m²/day). Multimodal diagnostics, including histopathology and trio-exome sequencing, confirmed homozygous in ITGA3 exon 8, diagnostic of ILNEB. Despite multisystem involvement, multidisciplinary palliation yielded sustained remission. This index case of protracted survival delineates ITGA3-related phenotypic heterogeneity, advocates genomic ascertainment in paediatric ILD-CNS-JEB triads, and posits supportive therapies as longevity modifiers.

Keywords: ILNEB syndrome, ITGA3, Junctional epidermolysis bullosa, Congenital nephrotic syndrome, Interstitial lung disease, Genotype-phenotype correlation

INTRODUCTION

Infantile lethal ILD with nephrotic syndrome and epidermolysis bullosa (ILNEB) is a rare inherited genodermatosis caused by pathogenic variants in the ITGA3 gene. The ITGA3 gene encodes integrin α3, a transmembrane protein necessary for epithelial cell adhesion and basement membrane stability.[1] The disorder is typically described by a triad of early-onset ILD, congenital nephrotic syndrome, and JEB, which indicate multisystem involvement of the skin, lungs, and kidneys.[2] Most affected infants develop symptoms within the first few months of life, commonly presenting with significant breathing difficulty, worsening kidney involvement, and fragile skin that blisters easily.[3] The course of the disease follows an aggressive course, leading to severe complications and death during infancy or early childhood.[4] As a result, survival beyond a year age is exceptionally uncommon, and information on longer-term outcomes remains very limited.[5]

In this report, we describe an unusual case of genetically confirmed ILNEB syndrome in a child who survived beyond infancy.

This case illustrates an atypical clinical trajectory and contributes additional insight into the phenotypic range and prognosis of this otherwise fatal disorder.

CASE REPORT

The proband, a female of South Indian Tamil descent, was delivered vaginally at 39+2 weeks gestation (birth weight 2.98 kg [-0.5 SD]; length 49 cm; occipitofrontal circumference 34 cm). Apgar scores were 9/10/10 with no resuscitation required. Antenatal ultrasounds were normal, and no parental consanguinity was present, although distant relatives in the extended family had a consanguineous union. The family pedigree lacks similar phenotypes across three generations. Developmental milestones included smiling at 6 weeks, sitting at 7 months, and walking at 15 months, delayed by recurrent infections, with normal cognition (WPPSI-IV full-scale IQ 92 at age 8).

She remained well until 11 months, when post-viral bronchiolitis heralded recurrent pneumonia, with up to eight episodes per year between ages 1 and 3. A Mantoux test induration of 15 mm prompted a 6-month antitubercular regimen without microbiologic confirmation. Between ages 2-4, frothy urine, periorbital oedema, and trauma-induced blisters emerged, leading to nail loss and trunk scarring. From ages 5-9, exertional dyspnoea (modified Medical Research Council grade 2), productive nocturnal cough, epiphora, and growth stunting predominated. No seizures occurred, and consanguineous siblings remained unaffected.

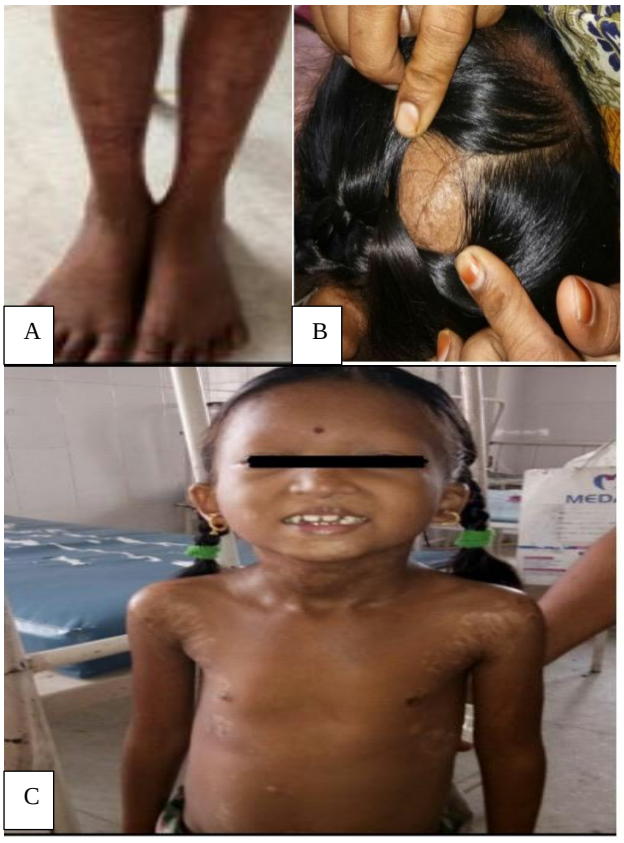

Figure 1: (A) Lower limb cutaneous findings, (B) Scalp involvement and (C) Facial and perioral features.

At presentation (age 9 years 2 months), examination revealed a cachectic child (weight 13.4 kg [<-3.5 SD]; height 104.2 cm [<-3 SD]; BMI 12.4 kg/m²; mid-upper arm circumference 14 cm). Vital signs included heart rate 98 bpm, respiratory rate 28/min, oxygen saturation 94% on room air, and blood pressure 90/60 mmHg. Respiratory findings comprised fine velcro-like crepitations at bilateral bases with reduced air entry. Dermatologic survey showed cicatricial scalp alopecia affecting 20% surface area, hypopigmented atrophic scars on trunk (15%) and limbs (10%), anonychia of toenails, and perioral milia. Ocular exam disclosed bilateral madarosis, punctal atresia, symblepharon, and mild corneal haze. Trace ascites was noted without organomegaly; Tanner staging was 1.

Diagnostic assessment

Initial laboratory evaluation showed mild leucocytosis accompanied by peripheral eosinophilia. Blood glucose levels, liver enzymes, thyroid function, renal parameters, and serum electrolytes were within normal ranges. The lipid profile was abnormal, revealing elevated total cholesterol and triglyceride levels with a concomitant reduction in high-density lipoprotein cholesterol.

Urine examination demonstrated marked proteinuria (+++), with the presence of microalbuminuria. Quantitative assessment confirmed nephrotic-range protein loss, with a 24-hour urinary protein excretion of 4.947 g/dL. Abdominal ultrasonography revealed asymmetry of the kidneys.

Further evaluation with renal imaging showed a smaller right kidney measuring 6.3 cm and an enlarged left kidney measuring 8.6 cm, along with reduced corticomedullary differentiation and increased cortical echogenicity. A cortical cyst measuring 1.5 cm was noted at the upper pole, and the overall findings were suggestive of grade II renal parenchymal disease. Renal biopsy was not pursued because of the increased procedural risk associated with asymmetric renal anatomy.

Histopathological examination of a skin biopsy, including light microscopy and immunofluorescence studies, demonstrated dermo-epidermal separation, consistent with JEB. High-resolution computed tomography of the chest, supported by lung biopsy findings, revealed features characteristic of ILD. Cardiac evaluation, including electrocardiography and echocardiography, showed no structural or functional abnormalities.

In view of the combined presence of ILD, nephrotic-range proteinuria, and JEB, an underlying genetic disorder was strongly suspected. Molecular genetic analysis confirmed a pathogenic deletion mutation, c.1173_1174del, in exon 8 of the ITGA3 gene, thereby establishing the diagnosis of ILNEB.

Management and follow-up

There are no disease-specific management protocols for ILNEB syndrome. The patient was managed with a multidisciplinary supportive approach. Corticosteroids were administered for ILD and nephrotic syndrome. Antibiotics were used as needed for recurrent respiratory and skin infections. Comprehensive supportive care, including nutritional rehabilitation, skin care, and respiratory monitoring, was provided.

The patient and her family were extensively counselled regarding the disease course, prognosis, and potential complications, including worsening respiratory distress, oliguria, renal failure, and overall clinical deterioration. Ongoing follow-up is being conducted under the supervision of a paediatrician, dermatologist, nephrologist, pulmonologist, psychiatrist, and geneticist.

DISCUSSION

ILNEB syndrome is an exceptionally rare disorder resulting from loss-of-function mutations in ITGA3, which plays a crucial role in epithelial cell adhesion in the skin, lungs, and kidneys. Previously reported cases uniformly demonstrated severe disease with onset in infancy and death within the first 19 months due to multisystem failure.[5-7] The present case is unique in that the child has survived into late childhood with a comparatively milder clinical phenotype.

The survival of this patient suggests phenotypic variability and possible genotype-phenotype correlations within ITGA3-related disorders. Early diagnosis, vigilant supportive care, and multidisciplinary management may contribute to prolonged survival and improved quality of life in selected cases.

CONCLUSION

This report presents a unique instance of ILNEB syndrome, validated through ITGA3 mutation analysis. The case expands the known clinical manifestations of the condition and underscores the necessity of considering ILNEB syndrome in paediatric patients exhibiting the triad of ILD, nephrotic syndrome, and junctional epidermolysis bullosa. Prompt identification and the implementation of coordinated supportive care are crucial for achieving the best possible outcomes.

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