Desmoplakin mutation in neonatal erythroderma

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INTRODUCTION

A novel *Desmoplakin* (*DSP*) heterozygous mutation, c.1756C>T, p.(His586Tyr), was found in an infant with ichthyosiform erythroderma, recurrent sepsis and skin infections, failure to thrive, constant vomiting and brain abnormalities. A similar phenotype named SAM-syndrome (Severe dermatitis, multiple Allergies and Metabolic wasting) was has been reported in five cases with *DSG1* mutations and one case with a neighboring *DSP* mutation c.1757C>T, p.(His586Pro)^{1,2,3}. Our patient presented with some novel features e.g. brain abnormalities and recurrent severe HSV stomatitis

METHODS

Immunohistochemistry on skin biopsies with LEKTI, Filaggrin, DSP and electron microscopy (EM) were done to study epidermal function and structure.

Detailed phenotypic, vast immunological and metabolic analyses and radiologic imaging were conducted.

Ichthyosis and immunodeficiency gene panels and whole exome sequencing (WES) were performed to detect the genetic cause.

A literature review of previously reported *DSP* and *DSG1* patients with a similar phenotype with congenital erythroderma was done.

OBJECTIVES

1. Evaluate the phenotypic effect of a novel *DSP* mutation.
2. Compare phenotypes with the one other *DSP* heterozygous mutation patient and five patients with homozygous *DSG1* mutations with similar phenotypes.

RESULTS

An otherwise healthy boy presented at 2 weeks age with a seborrheic like eczema, which progressed into an ichthyosiform erythroderma with recurrent enterococcal and staphylococcal sepsis, skin infections, severe failure to thrive, constant vomiting and developmental delay.

MRI showed brain abnormalities and he suffered from recurrent HSV stomatitis. He had persistent thrombocytosis, hypoalbuminemia, hypernatremia and elevated IgE levels without eosinophilia. A non-IgE mediated cow's milk allergy was diagnosed. Vast immunologic and metabolic analyses were normal.

Skin biopsy showed a psoriformic reaction with absent filaggrin but normal LEKTI staining. WES revealed a *de novo* heterozygous *DSP* missense variant c.1756C>T, p.(His586Tyr) predicted deleterious by *in silico* tools SIFT and MutationTaster. Loss of DSP was seen in skin samples and electron microscopy revealed significant loss of intercellular cohesiveness and decreased numbers of desmosomes and absent tonofilaments perinuclearly. IVIG and acitretin treatment and optimizing enteral nutrition alleviated scaling, erythema and itch and induced hair regrowth.

DSP mutation patients suffered from recurrent sepsis. Otherwise clinical features were similar with *DSP* and *DSG1* mutations.

Reference	Here	1	2	2	2	3	3	
Gene	<i>DSP</i>		<i>DSG1</i>					
Mutation	c.1756C>T	c.1757A>C	c.49-1G>A	c.49-1G>A	c.1861delG	c.1892-1delG	c.1892-1delG	
Age	13 months	6 years	7 years	3 years	9 months	7 years	13 years	
Congenital ichthyosis	+	+	+	+	+	+	+	7/7
PPK	-	+	+	+	-	+	+	5/7
Hypotrichosis	+	+	+	+	+	-	-	5/7
Curly hair	-	-	-	-	-	+	+	2/7
Multiple allergies	-	+	+	+	+	+	N/A	5/7
Recurrent infections	+	+	+	+	+	+	-	6/7
Recurrent sepsis	+	+	-	-	-	-	-	2/7
Failure to thrive	+	+	+	+	+	+	-	6/7
Gastrointestinal problems	+	+	+	+	-	-	N/A	4/7
Developmental delay	+	+	+	+	+	N/A	-	5/7
IgE IU/ml elevated	985	611	10,900	266	1,438	>25,000	N/A	6/7
Hypoalbuminemia	+	N/A	+	+	+	N/A	N/A	4/7
Hypernatremia	+	N/A	+	+	N/A	N/A	N/A	3/7

CONCLUSIONS

DSP mutations should be considered in erythrodermic infants, with recurrent sepsis and infections, developmental delay and failure to thrive. *DSP* and *DSG1* mutations can cause a similar phenotype and lead to severe skin barrier defects resulting in a Netherton syndrome like phenotype.

REFERENCES

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