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Case Report

Adrenal Hypofunction in a Patient with Netherton Syndrome, Septo-Optic Dysplasia and Joubert Syndrome

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Abstract

Netherton Syndrome (NS) is caused by a mutation in the *SPINK5* presenting with ichthyosiform erythroderma, atopy and hair abnormalities. NS can be difficult to diagnose and could be frequently mistaken with atopic or seborrheic dermatitis that fails to respond to topical steroids, this can predispose to deliberate use of topical steroids in these patients. The defective stratum corneum in NS increases absorption of any topical medication including corticosteroids predisposing to exogenous Cushing Syndrome. We present the case of a 2 week old female infant with congenital hydrocephalus and Septo-Optic dysplasia (SOD) that was managed with topical steroids for presumed severe seborrheic dermatitis. At 2 months she presented with emesis and cushingoid facies. She was evaluated for panhypopituitarism showing low serum cortisol < 0.2 µg/dl with normal pituitary function. Cosyntropin stimulation test confirmed adrenal hypofunction. Dermatologic evaluation showed skin biopsy and hair exam findings pathognomonic of NS. Genetic testing confirmed diagnosis of NS. Topical steroids were titrated-and Hypothalamic Pituitary Adrenal (HPA) axis fully recovered at 12 months of age. NS should be suspected in cases of seborrheic dermatitis refractory to topical steroids and its cautious use is advised since avid absorption in a disrupted skin barrier may lead to suppression of HPA axis.

Keywords: *Netherton Syndrome; Septo-Optic Dysplasia; Adrenal Insufficiency; Joubert Syndrome; Congenital Ichthyosiform*

Abbreviations

NS: Netherton Syndrome; SOD: Septo-Optic Dysplasia; JS: Joubert Syndrome; AI: Adrenal Insufficiency; ROH: Regions of Homozygosity; HPA: Hypothalamic Pituitary Adrenal; ACTH: Adrenocorticotropic Hormone; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; TSH: Thyroid-Stimulating Hormone; IGF-1: Insulin-Like Growth Factor-1; RAST: Radioallergosorbent Test

Introduction

Netherton Syndrome (NS) is a rare, autosomal recessive form of ichthyosis presenting with atopic diathesis, congenital ichthyosiform erythroderma and "bamboo hair" or trichorrhexis invaginata. This is due to mutations in the *SPINK5* gene, which encodes the serine protease inhibitor, lymphoepithelial Kazal-type-related inhibitor (LEKTI). Dysfunction of LEKTI leads to increased activity of serine proteases (Kallikreins - KLK5, KLK7 and KLK14) in the stratum corneum involved in desquamation and epidermal remodeling. Disruption of the skin barrier in NS can manifest with severe life-threatening complications, such as skin infection, atopic dermatitis, severe allergies and hypernatremic dehydration accounting for a 16% mortality rate [2]. Treatment of NS with topical steroid is challenging due to increased

systemic absorption. Multiple cases of exogenous Cushing Syndrome and Hypothalamic Pituitary Adrenal (HPA) axis suppression resulting from topical steroid therapy have been reported in NS. We report a unique case of an infant with NS, Septo-optic dysplasia (SOD) and Joubert Syndrome (JS) who developed HPA axis suppression. The diagnostic dilemma was to establish whether the cause of adrenal insufficiency was exogenous and/or endogenous HPA axis suppression.

Case Presentation

A late preterm female infant with prenatally diagnosed hydrocephalus and absent septum pellucidum presented at 2 months of age with emesis and dehydration and was admitted to the hospital. Prior to admission she had been treated by her pediatrician for severe seborrheic dermatitis with topical emollients since birth and with several trials of daily topical steroids (hydrocortisone 1 and 2.5%, fluocinonide 0.05%, mometasone 0.1%, triamcinolone 0.025%, and mometasone 0.1%) since 2 weeks of age without any improvement. Family history relevant for consanguineous parents (first cousins) and multiple paternal first degree members having ichthyosis linearis circumflex which is a skin lesion suggestive of NS. On examination she was awake and alert, her length in 5th percentile (Z Score-1.617), weight in 14th percentile (Z Score-1.073) and head circumference in the 98th percentile (Z Score-1.4). She had tachycardia with normal blood pressure, full anterior fontanelle, frontal bossing, moderate dehydration, global developmental delay, cushingoid facies, severe erythema and seborrheic scaling on scalp, trunk and intertriginous creases with superimposed infection (Figure 1).

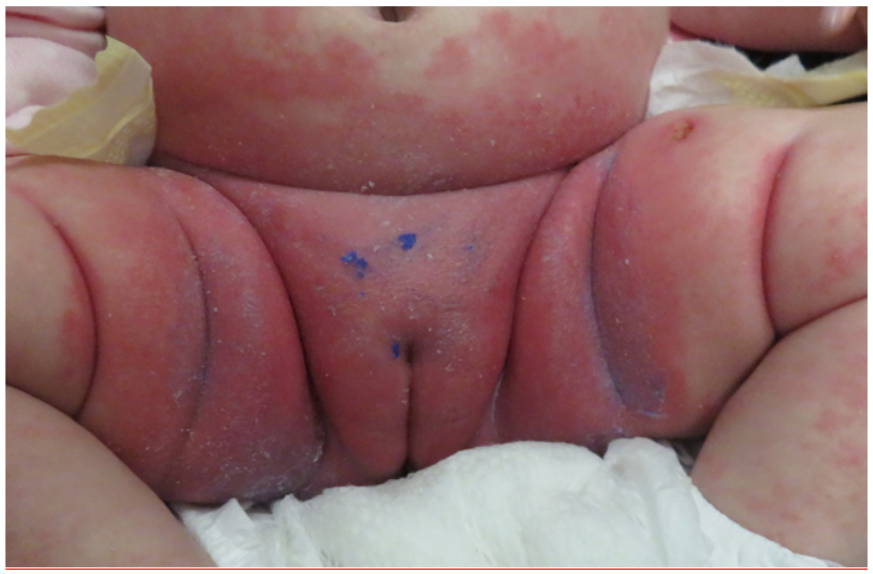

Figure 1: *Severe erythema and seborrheic crusting seen at initial presentation.*

During the admission given the history of prenatal hydrocephalus and SOD, a further evaluation was performed to assess the intracranial pressure and pituitary function. Brain MRI showed ventriculomegaly, SOD with intact optic nerves and chiasm, partial fusion of cerebellar hemisphere, hypoplastic vermis and elongation of cerebellar peduncles, suggestive of Joubert syndrome without signs of elevated intracranial pressure or progressive cranial enlargement. Blood work revealed hyperkalemia (potassium 6.0 meq/dL), normal serum sodium (139 meq/dL), hypoglycemia (52 mg/dL) and low serum cortisol (0.2 mcg/dL). Serum TSH (2.45 mIU/L), IGF-1 (100 ng/

ml), LH (1.59 U/L), FSH (4.8 U/L) and Prolactin (62.7 ng/mL) were normal. In light of low cortisol an ACTH stimulation test with 125 µg was performed showing basal plasma ACTH of 28 pg/ml, serum cortisol of < 0.5 ug/dL (0 minute) and 2.2 ug/dL (60 minutes) which was diagnostic for adrenal insufficiency (AI). Since the plasma ACTH level was normal central AI was ruled out and it was determined that most likely the prolonged use of topical steroids had caused exogenous suppression of HPA axis**.** Therapeutically, daily mid potency topical steroid therapy was changed to intermittent low potency therapy (hydrocortisone 2.5%) to allow for HPA axis recovery. Stress doses of hydrocortisone was recommended as needed for fever, illness or surgical procedures. Patient was managed with intravenous fluid therapy and was discharged home after resolution of the emesis and dehydration.

On outpatient follow up, a skin biopsy was done which revealed epidermal hyperplasia with scaling suggestive of NS. The patient continued to carefully use low potency topical steroids (2.5% Hydrocortisone ointment) intermittently along with topical emollients, with improvement of skin lesions over 9 months. In addition, the superimposed infections necessitated treatment with mupirocin 2%, ketoconazole 1 and 2%, gentamicin 0.1%, nystatin 1,000,000 units per gram as well as frequent bleach baths and gentian violet therapy. Treatment with topical tacrolimus was recommended, however could not be initiated due to unaffordability and insurance barriers. A microscopic hair exam showed the characteristic bamboo hair abnormality, trichorrhexis Invaginata, which is pathognomonic for NS (Figure 2). At 4, 5 and 9 months of age, random serum cortisol remained low at 5, 1.9 and 3.9 ug/dL respectively. Plasma ACTH levels measured alongside cortisol at 4 and 9 months of age were 12 pg/mL and 11 pg/mL respectively hence stress dose Hydrocortisone was still recommended as needed. At 9 months of age patient presented severe allergic reaction to eggs and to peanuts at 15 months manifested by angioedema, generalized urticaria, and respiratory distress which responded well to epinephrine and anti-histaminic therapy. Radioallergosorbent test (RAST) showed elevated serum IgE levels specific to eggs (12.80 kU/L, class IV, very high level of allergen) and to peanuts (2.72, class III, high level of allergen). At 12 months of age an ACTH stimulation test revealed a baseline plasma ACTH level of 52 pg/mL, serum cortisol 23.5 ug/dL (0 minute), 29 ug/dL (60 minutes) showing full recovery of HPA axis (Table 1). Patient has been feeding and growing appropriately for age and skin lesions have improved.

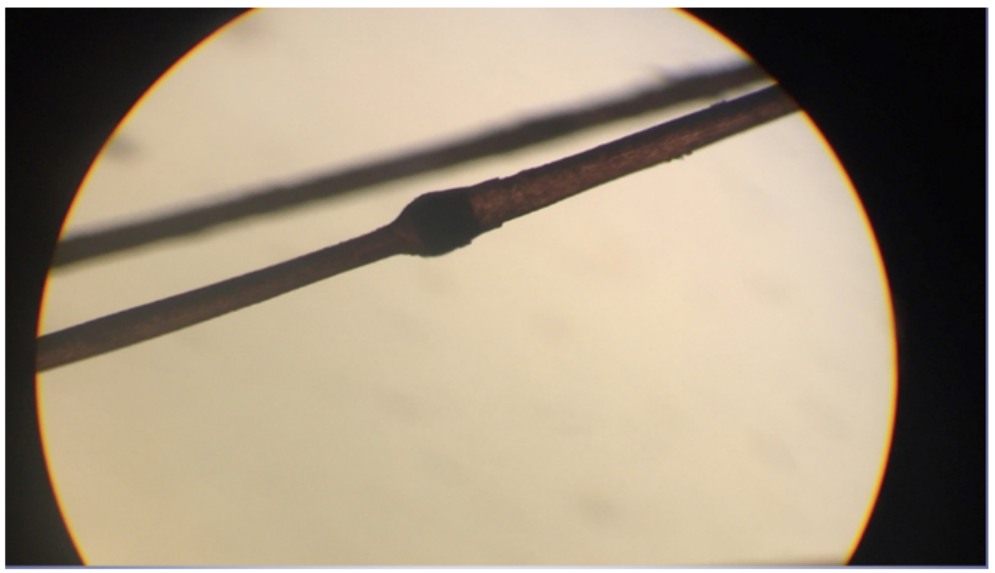

Figure 2: *Trichorrhexis Invaginata: A characteristic bamboo hair abnormality, pathognomonic of Netherton Syndrome.*

Age (months)	ACTH (pg/ml)	Cortisol (ug/dl) 0 minutes	Cortisol (ug/dL) 60 minutes
2	-	< 0.2	-
3*	28	< 0.5	2.2
4	12	5.0	-
5	-	1.9	-
9	11	3.9	-
12*	52	23.5	29

Table 1: *Serial serum ACTH and cortisol levels.*
**ACTH stimulation test performed with 125 ug of Cosyntropin intravenously.*
Abbreviation: ACTH: Adrenocorticotropic Hormone.

In light of paternal history of consanguinity and global developmental delay in a syndromic patient, a microarray analysis was conducted revealing regions of homozygosity (ROH) in 14 chromosomes, all of which were > 5 Mb in length. These ROH included genes implicated in NS, SOD and Joubert's Syndrome (Table 2). Chromosome 5 containing the SPINK5 gene showed a ROH of 16 Mbs. Chromosome 3 and 14 containing the SOX2 and OTX2 genes responsible for SOD showed 62.8 and 15.4 Mb ROHs respectively. Chromosome 1, 2, 4, 8, 11, 14 and 17 showed ROH ranging from 5 - 30 Mb in the areas containing genes for Joubert's syndrome. The combined length of the homozygous regions was approximately 395 Mb. Exome analysis showed homozygosity for a pathogenic variant in SPINK5 confirming NS.

Array	Abnormal chromosome/ Gene position	Autosomal Recessive Gene	Location of Disease	Length of the ROH (MB)	Disease
HMZ	5q32-q34	SPINK5	5q32	16	Netherton's Syndrome
HMZ	3q21.2-q27.3	SOX2	3q26.33	62.8	Septo-Optic Dysplasia
	14q21.3-q23.3	OTX2	14q22.3	15.4	
HMZ	1p36.12-p33	CEP104	1p36.32	23	Joubert's Syndrome
	2q12-2q13	NPHP1	2q13	5	
	2q36.3-q37.1	PDE6D	2q37.1	8.8	
	4p16.1-p15.32	CC2D2A	4p15.32	7.9	
	8q22.1-q24.13	TMEM67	8q22.1	30.1	
	11q13.3-q14.2	C2CD3	11q13.4	16.1	
	14q21.3-q23.3	KIAA0586	14q23.1	15.4	
	17p13.1-p11.1	TMEM107	17p13.1	12.3	

HMZ	3p25.3-p25.1			7.2	
	3p24.1-p14.2			29.2	
	4q31.3-q34.1			20	
	7q21.11-q21.2			14.3	
	8q24.21-q24.3			11.08	
	9p24.3-p22.3			14.6	
	11p15.4-p15.1			8.4	
	11p15.1-p14.3			5.1	
	13q14.3-q21.2			8.1	
	13q32.3-q33.2			5.2	
	13q33.2-2q34			9.0	
	17q23.2-q24.2			7.8	
	19q13.42-q13.43			5.0	
	Xp11.4-q21.31			50.0	

Table 2: Microarray regions of homozygosity and associated diseases.
HMZ: Microarray Analysis and Homozygosity.

Discussion

In NS, a mutation in *SPINK 5* results in degradation of the stratum corneum predisposing to infection, percutaneous fluid loss, increased transepidermal absorption of topical medications and risk for systemic absorption [1]. Indeed, Cushing Syndrome and HPA axis suppression following topical steroids has been documented in patients with NS [3-5]. We describe a case of NS with HPA axis suppression following use of topical mid-potency steroids. Our differential diagnosis included exogenous versus endogenous adrenal insufficiency (AI). History of SOD favored ACTH insufficiency (endogenous/central AI) as the likely etiology. However, normal ACTH with intact pituitary function ruled this out. It is likely that the patient's disruption of the skin barrier due to NS allowed for avid absorption of topical steroid, resulting in negative feedback on the CRH/ACTH secretion leading to exogenous adrenal insufficiency. In fact, HPA axis recovered at 12 months secondary to progressive down-titration of topical steroid therapy.

In our patient, microarray analysis showed multiple regions of homozygosity (ROH). The SNP microarray is used to identify copy number variants and regions of homozygosity or loss of heterozygosity [6]. Small random ROH exist in all populations, but rarely present as a contiguous stretch of more than 4 - 5 Mb. When > 5 Mb of contiguous ROHs are present, on multiple chromosomes, it signifies relatedness of the parents or consanguinity [7]. These ROH are not diagnostic of a specific condition, but increase the theoretical risk of an autosomal recessive disorder in the offspring [8]. Exome analysis examines the protein coding sequences of the genome (the exons) and helps identify genetic variants that alter the protein sequences; our patient had a pathogenic variant in SPINK5 confirming NS.

NS also presents with atopic manifestations as LEKTI-deficient epidermis promote unrestricted KLK5 activity triggering expression of proinflammatory and proallergic molecules in NS keratinocytes [9]. Our patient indeed had allergic reaction to peanuts and eggs hence patients with NS should be closely monitored for allergic manifestations.

Treatment of NS is difficult, and emollients are the mainstay of therapy. Other therapies include topical steroids, topical calcineurin inhibitors, oral Etretinate and phototherapy. Topical steroids should be used with caution [10]. Netherton Syndrome may manifest like other skin abnormalities such as severe seborrheic dermatitis, making early diagnosis of this genetic disorder challenging. However, our patient's severe presentation, positive family history and rapid systemic absorption of topical steroids with HPA suppression led to an early clinical diagnosis of NS. Maintaining a high index of suspicion particularly in neonates with poor response to standard therapy and remaining alert to the ensuing consequences of systemic absorption of topical medications in these patients is critical for preventing potential life-threatening sequelae.

Conclusion

Diagnosis of NS in infancy is difficult as it is challenging to differentiate among other causes of inflammatory dermatoses that are typically treated with topical steroids. Prompt identification of NS is crucial as patients with this syndrome have defective stratum corneum that increases absorption of topical steroids, leading to exogenous suppression of the HPA axis.

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