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Early Intervention in STAT3 Dominant-Negative Disease

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Keywords

Hyper IgE syndrome; Job's syndrome; STAT3 dominant negative; STAT3DN

Introduction

STAT3DN disease causes an autosomal dominant Hyper IgE syndrome (AD-HIES; Job's syndrome) characterized by elevated immunoglobin E (IgE), recurrent lung and skin infections, eczematous dermatitis, mucocutaneous candidiasis, and skeletal, connective tissue, and vascular abnormalities. Since genetic etiology identification in 2007[1,2], diagnosis of infants with a family history of STAT3DN can be confirmed in newborns or prenatally. Although antibiotic prophylaxis targeting *Staphylococcus aureus* is known to decrease infectious complications in STAT3DN[3,4], the impact of early diagnosis and treatment specifically in infants with antimicrobials and antiseptics is unexamined. We retrospectively reviewed medical histories of 18 STAT3DN pediatric patients to compare the clinical course for those with and without a family history of STAT3DN.

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Methods

Eighteen STAT3DN pediatric patients born in 2008 or later were identified in our National Institute of Allergy and Infectious Diseases IRB-approved natural history study; guardian consent, with assent when appropriate, was obtained for all patients. Demographics, clinical features, laboratory results, and treatments were compared between those with and without (probands) a family history of STAT3DN. Patient data were analyzed and reported for descriptive statistics. For continuous variables, means and/or medians were determined and *t*-tests were performed. For categorical data, chi-squared tests were performed. P-values < 0.05 denoted significance.

Results (Table 1)

Eight patients with STAT3DN family history (median age 9 years; range 4-14) and 10 probands (median age 13 years; range 5-14) were identified (Table 1). The time of genetic diagnosis in those with family history were *in utero* (n = 1), within the first 2 months (n=6), and at 2 years (n=1). Probands were diagnosed at a median age of 2 years (range 1-6 years). Patients with a family history had lower median HIES scores as compared to probands (32 vs. 61 points respectively; p = 0.001)[5]. Mean peak serum IgE and peripheral eosinophilia were comparable in patients with or without a family history. Extended lymphocyte phenotyping at comparable ages were not available.

Patients with family history started antiseptic washes (commonly chlorhexidine) at a younger age than probands (mean 0.2 vs. 4.7 years, p = 0.001). Dilute bleach baths were initiated at a mean of 2 years for 4 patients with family history, while 100% of probands started this therapy at a mean age of 4.4 years (p = 0.01). All initiated prophylactic antibiotics, commonly trimethoprim/sulfamethoxazole (TMP/SMX); those with family history started earlier than probands (mean 0.4 vs. 3.0 years respectively, p = 0.00005). Four probands received chronic antifungals for mold infections; mold infections were not observed in those with family history, but one initiated itraconazole prophylaxis. Immunoglobulin replacement was prescribed less frequently in patients with family history (13% vs. 60%, p = 0.04). Dupilumab was prescribed for eczema at comparable rates between those with and those without a family history (25% vs 30%).

Patients with family history had significantly fewer hospitalizations (mean 0.9 vs 6.3 times for probands, p = 0.02) and fewer bacterial pneumonias (13% vs 90%, p = 0.001). The majority of infection-related hospitalizations for both groups were at ages 6 years or younger. Three of eight patients with family history had hospitalizations outside the newborn period for viral bronchiolitis (2), cellulitis (1), and bacterial pneumonia (1). Nine of ten probands had a total of 16 hospitalizations for infection, including sepsis (1), hemoptysis (1), pneumonia (bacterial and *Aspergillus*, 5), prolonged bronchopleural fistula after lung resection (2) and pneumatocele-related pneumothorax (1), *Fusarium* skin infection (2), severe thrush (1), skin abscess (2), and mastoiditis with epidural abscess (1). Mechanical ventilation for pneumonia was required for two probands (newborn and at 4 years) versus one newborn with family history. One proband underwent hematopoietic stem

cell transplantion at 7 years after recurrent severe infections and pneumatocele development despite optimal prophylaxis.

Patients with family history had reduced rates of recurrent skin abscesses (13% vs 90%, p = 0.001), recurrent ear infections and/or tympanostomy tube placement (0% vs 60%, p = 0.01), and severe eczema (13% vs 60%, p = 0.04) (Supplemental Figure 1). The only patient with family history with recurrent abscesses and severe eczema did not start therapy (bleach baths and TMP/SMX) until 2 years of age. Chronic mucocutaneous candidiasis (CMC) was frequent in both groups. While parenchymal lung abnormalities (e.g. bronchiectasis and pneumatoceles) did not reach clinical significance (13% in patients with family history vs. 50% in probands, p = 0.09), more significant lung disease and lung surgery (40%) was seen in probands versus none in patients with family history (Figure 1). Fractures and joint hyperextensibility were comparable in those with and without family histories. Young age prohibited analysis of retained primary teeth and scoliosis.

Discussion

With earlier diagnosis and treatment, patients with STAT3DN are living longer with increased potential for childbearing, and as an autosomal dominant disease, there is 50% risk of passing the mutant allele to offspring. Genetic testing has allowed prenatal/newborn diagnosis, facilitating interventions with antiseptics and prophylactic antibiotics. Sixteen years after the genetic identification of STAT3DN, we believe these early interventions significantly reduce infection, hospitalization and surgery rates, positively impacting disease natural history.

Pulmonary complications contribute greatly to STAT3DN morbidity and mortality[3,4,6,7]. Our study found lung surgery performed only in probands and hospitalization outside of the newborn period was predominantly seen in probands, suggesting early interventions has a positive impact on clinical outcomes. Long-term follow-up should determine whether pulmonary morbidity reduction is sustained as patients age, since our overall cohort has a 70% prevalance of parachymmal lung abnormalities. We believe these differences in outcomes are from medical interventions (i.e. antiseptics and prophylactic antimicrobials) at younger ages, although family experience managing HIES may play a role.

We recommend chlorhexidine wash initiation during the newborn period, transitioning to dilute bleach baths in early childhood[8]. We also initiate TMP/SMX around 1-2 months old, with attention to hyperbilirubinemia risk. These measures in newborn and prenatally-diagnosed infants were associated with significantly fewer infections than probands, whose disease was later identified from such infections. Although no patietnts developed *Pneumocystis jirovecii* pneumonia, this risk in STAT3DN infants provides additional rationale for TMP/SMX prophylaxis[9]. More probands received immunoglobin replacement therapy, likely reflecting their more severe course. Affected children with refractory eczema can consider dupilumab[10].

Early diagnosis and intervention were associated with reduced STAT3DN disease severity and improved clinical outcomes. Despite a similar age at comparison, infectious

complications were markedly reduced in those with family history receiving early interventions.

We believe these clinical outcome improvements enhance quality of life, lead to less work and school missed, decrease healthcare costs, and may alter the natural history of STAT3DN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

STAT3DN	Signal transducer and activator of transcription 3 dominant-negative
AD-HIES	Autosomal dominant hyper IgE syndrome
IgE	Immunoglobulin E
DNA	Deoxyribonucleic acid binding domain
SH2	Src-homology 2 domain
TA	Transactivation domain
TMP/SMX	Trimethoprim/sulfamethoxazole
RSV	Respiratory syncytial virus
CMC	Chronic mucocutaneous candidiasis
IgRT	Immunoglobin replacement therapy
VATS	Video-assisted thoracoscopic surgery
HSCT	Hematopoietic stem cell transplantation

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Clinical Implications

Early genetic diagnosis of signal transduction and activation of transcription 3 dominant negative (STAT3DN) disease allows for early intervention, including initiation of antiseptic washes and antimicrobial prophylaxis. These early interventions may reduce long-term infectious, pulmonary, and dermatologic complications.

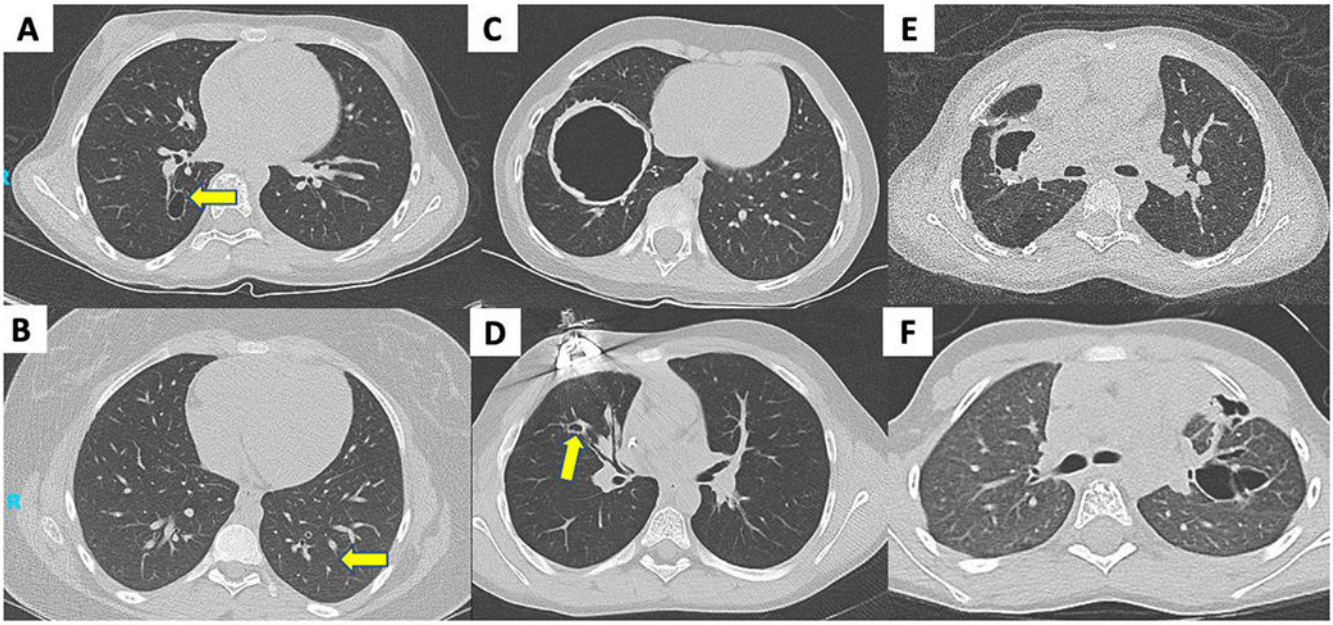

Figure 1.

Parenchymal lung findings on CT. (A) small pneumatocele in 12-year-old with family history; (B) subtle bronchiectasis in 13-year-old with family history (C) large pneumatocele in 7-year-old proband; (D) bronchiectasis and small pneumatocele in 10-year-old proband with prior lobectomy; (E) pneumatocele in 9-year-old with prior lobectomy; (F) cystic bronchiectasis in 6-year-old with prior pneumothorax and bronchopleural fistula.

Table 1:

Clinical characteristics of STAT3DN pediatric patients

Total n = 18	Family History (n= 8, 44%)	Proband (n= 10, 56%)	P-value
Female	6 (75%)	5 (50%)	0.28
Current age (years, median)	9	13	0.32
Age at diagnosis (years, median)	0.2	2	0.001*
STAT3 mutation domain			
DNA	5 (63%)	5 (50%)	0.60
SH2	3 (38%)	4 (40%)	0.91
TA	0 (0%)	1 (10%)	0.36
CLINICAL FEATURES	**Family History**	**Proband**	**P-value**
	6,865	13,317	0.31
Abs eosinophil count (cells/μL, mean)	1,023	1,182	0.73
HIES score (median)	32	60.5	0.001*
Skin abscesses (>4)	1 (13%)	9 (90%)	0.001*
Parenchymal lung abnormalities	1 (13%)	5 (50%)	0.09
Bronchiectasis	1 (13%)	5 (50%)	0.09
Pneumatoceles	1 (13%)	3 (30%)	0.37
Eczema			
None	1 (13%)	0 (0%)	0.25
Mild	3 (38%)	0 (0%)	0.03*
Moderate	3 (38%)	4 (40%)	0.91
Severe	1 (13%)	6 (60%)	0.04*
Recurrent pneumonia	1 (13%)	9 (90%)	0.001*
Chronic lung infection	0 (0%)	3 (30%)	0.04*
Pulmonary *Aspergillus*	0 (0%)	2 (20%)	0.07
Lifetime Hospitalizations (mean)	0.875	6.3	0.02*
Severe Infections**	0 (0%)	4 (40%)	0.04*
Mucocutaneous candidiasis	6 (75%)	9 (90%)	0.40
Oral	4 (50%)	8 (80%)	0.18
Nail	0 (0%)	3 (30%)	0.09
Groin/vaginal	4 (50%)	4 (40%)	0.67
Sinus infections	3 (38%)	7 (70%)	0.17
Fractures	2 (25%)	6 (60%)	0.14
Ear infections/tympanostomy tubes	0 (0%)	6 (60%)	0.01*
Newborn rash	6 (75%)	10 (100%)	0.09
Allergies			
Drug allergy	1 (13%)	2 (20%)	0.67

Total n = 18	Family History (n= 8, 44%)	Proband (n= 10, 56%)	P-value
Food allergy	2 (25%)	4 (40%)	0.50
TREATMENTS			
Antiseptic washes			
Chlorhexidine usage	6 (75%)	3 (30%)	0.06
Bleach bath usage	4 (50%)	10 (100%)	0.01*
Age initiated chlorhexidine washes (years, mean)	0.2	4.7	0.001*
Age initiated bleach baths (years, mean)	2	4.4	0.28
Immunoglobin Replacement Therapy (igRT)	1 (13%)	6 (60%)	0.04*
Lung surgery (VATS)	0 (0%)	4 (40%)	0.04*
Hematopoietic stem cell transplant (HSCT)	0 (0%)	1 (10%)	0.36
Prophylactic antifungal medications	2 (25%)	6 (60%)	0.14
Prophylactic antibiotics	8 (100%)	10 (100%)	
Dupilumab	2 (25%)	3 (30%)	0.81

* denotes statistically significant features

** excludes severe bacterial pneumonias