

ORIGINAL ARTICLE

Cutaneous findings in sporadic and familial autosomal dominant hyper-IgE syndrome: A retrospective, single-center study of 21 patients diagnosed using molecular analysis

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Background: Recent identification of STAT3 mutations in autosomal dominant (AD) hyper-IgE syndrome (HIES) has improved the clinical, genetic, and molecular classification of the HIES.

Objective: We sought to characterize the cutaneous signs observed in molecularly diagnosed AD-HIES.

Methods: We conducted a retrospective study of 21 patients with AD-HIES and confirmed STAT3 mutations, treated at Necker-Enfants Malades Hospital, Paris, France.

Results: A papulopustular rash on the face and scalp before the age of 2 months was observed in 67% of patients. This “early rash” was distinguished from other neonatal pustular eruptions by crusted papules and pustules, rash intensity, and a continuum with chronic dermatitis. An eczematous dermatitis was almost always present before the age of 18 months (95% of patients) and was mainly confined to the face, scalp, chest, and buttocks. All patients presented with infected dermatitis (*Staphylococcus aureus*) and 59% had chronic candidiasis of the oral mucosa and nails. Cutaneous herpes virus infections were not unusually severe. Coarse facial skin at puberty, and sometimes at a younger age, with prominent follicular ostia resembling atrophoderma vermiculatum was not related to severe acne or facial abscesses.

Limitations: This was a retrospective study with a small number of patients.

Conclusion: When associated with serum IgE levels 10 times the age-appropriate level, a neonatal papulopustular rash progressing to a chronic impetiginized eczematous dermatitis that differs from classic atopic dermatitis is highly suggestive of AD-HIES. Early recognition is important for initiation of prophylactic antistaphylococcal and antifungal treatment. (J Am Acad Dermatol 10.1016/j.jaad.2010.09.714.)

Key words: autosomal dominant; Buckley syndrome; cutaneous findings; cutaneous signs; hyper-IgE syndrome; Job syndrome; STAT3.

Autosomal dominant (AD) hyper-IgE syndrome (HIES), also known as Job syndrome or Buckley syndrome, is a rare primary immunodeficiency disorder characterized by

extremely elevated serum IgE levels (>2000 IU/L), eosinophilia, eczema, recurrent “cold” staphylococcal abscesses, pneumonia complicated by bronchiectasis and pneumatoceles, retained primary teeth,

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joint hyperextensibility, osteopenia, pathologic bone fractures, scoliosis, and characteristic facial features.¹⁻⁴ Infections are mainly caused by extracellular bacteria (*Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*) and fungal organisms.⁵ Mucocutaneous infections with *Candida* species are common. Fatal fungal infections (*Aspergillus* species, *Candida* species, *Cryptococcus neoformans*, *Pneumocystis jirovecii*) are also reported.⁵⁻⁷ Coronary artery aneurysms,⁸ brain lesions, Chiari malformations,⁹ and lymphomas^{10,11} have recently been described.

A multicomponent scoring system incorporating the clinical findings of AD-HIES has been proposed.¹² The first signs of the disease are often cutaneous. An early diagnosis can be difficult for dermatologists to make because the clinical features are nonspecific and age sensitive. Furthermore, patients with severe atopic dermatitis often have high serum IgE levels whereas AD-HIES may be accompanied by moderate or normal serum IgE levels early in the course of the disease.

AD-HIES may be familial or sporadic.^{5,13} Heterozygous mutations in STAT3 (transcription 3 gene activator and signal transducer) have been described in both sporadic and familial cases.¹⁴ The aim of this study was to analyze the dermatologic manifestations in a cohort of patients with molecularly confirmed AD-HIES treated at the French national center for study of primary immune deficiencies.

METHODS

Patients

Twenty-one patients with HIES were identified. The diagnosis of AD-HIES was confirmed by genetic analysis with identification of heterozygous dominant STAT3 mutations. Ten patients had a dominant negative mutation in the STAT3 DNA-binding domain, as described previously.¹⁵ The others had reduced STAT3 phosphorylation or DNA-binding ability.

Procedures

We reviewed the medical records and collected data on clinical findings, laboratory and

microbiology test results (including the highest serum IgE level and concomitant blood eosinophil count for each patient), and histopathologic features. The time taken to reach a final diagnosis of HIES was noted. An “early rash” was defined as onset of skin lesions in the first 2 months of life. Eczematous dermatitis was evaluated for time of onset, associated

pruritus, dry skin, a personal or family (first-degree) history of atopic disease (asthma, atopic dermatitis, allergic rhinitis), initial and subsequent localization of the skin eruption, characteristic morphology (papular, papulopustular, or eczematous), lichenification, impetiginization, erythroderma, and use of topical corticosteroids. Nail dystrophy, alopecia, facial skin texture, mucocutaneous fungal infections, and cutaneous viral infections (varicella-zoster virus, herpes simplex virus, molluscum contagiosum) were also recorded. The time of onset of cold skin abscesses, defined as ab-

scesses without fever or local inflammation, was noted. The interval between the onset of cutaneous manifestations and development of classic systemic infections was recorded.

RESULTS

Of the 21 patients, 10 were female and 11 male; the age range was 2 to 37 years (mean age: 19 years). Two families each had 3 affected members. The other cases represented sporadic mutations. The cutaneous findings are reported in Table 1.

Fourteen (67%) patients had a papulopustular rash before the age of 2 months. Ten (71%) of these 14 patients were born with a rash or developed one within the first 2 weeks of life. No perinatal infections were reported. The rash was characterized by crusted pustules, first affecting the face (Fig 1) and particularly the scalp (Fig 2) and subsequently spreading to the upper aspect of the trunk, shoulders, and buttocks. Microbiologic cultures of pustules from 5 patients were positive for *S aureus* in two cases, and negative for fungal infection. Two patients underwent a skin biopsy: histopathologic examination showed nonspecific features in one case, and eosinophilic spongiotic dermatitis and eosinophilic folliculitis in the other (Fig 3). All

CAPSULE SUMMARY

- A neonatal papulopustular rash followed by an impetiginized eczematous dermatitis that differs from classic atopic dermatitis is a distinctive early presentation of autosomal dominant hyper-IgE syndrome.
- When associated with severe otitis media and a high serum IgE level, these skin findings are evocative of autosomal dominant hyper-IgE syndrome.
- Atrophoderma vermiculatum–like skin lesions on the cheeks with prominent follicular ostia and reticular atrophy are observed at puberty and could be considered a secondary clinical diagnostic criterion.

Table 1. Cutaneous findings in autosomal dominant hyper-IgE syndrome

	Present	Time of onset			
		Mean	Median	Minimum	Maximum
Early rash	67%				
Papulopustular rash before age 2 mo, arising on face and scalp; specific features are subsequent papulopustular crusting, intensity, and differences with neonatal acne					
Eczematous dermatitis	95%				
Papular or papulopustular rash before age of 18 mo, on face, neck, shoulders, axillae, upper aspect of trunk, and buttocks; recurs chronically and differs from classic atopic dermatitis					
Skin abscesses	90%	49 mo	36 mo	1 mo	166 mo
On neck and trunk, without signs of local or general inflammation caused by staphylococcal infection					
“Characteristic” facial findings	47%	Pronounced in adolescents and adults, but also observed in children			
Coarse texture of facial skin, broad nasal bridge, bulky nasal tip					
Chronic candidiasis	59%				
Oral candidiasis, chronic paronychia of fingers					
First-degree atopy	23%				
Age at diagnosis		104 mo	72 mo	1 mo	348 mo

patients received treatment, including topical corticosteroids, topical antifungal creams, or oral antibiotics, to variable effect. The lesions spontaneously regressed within several days, but recurred repeatedly throughout the first year of life.

Twenty (95%) patients developed an eczematous dermatitis before the age of 18 months. Moderate pruritus and dry skin were present in 18 (86%) patients. Substantial lichenification was observed in one patient only. Sixteen (77%) patients had no personal history of hay fever or asthma, or a first-degree relative with atopic dermatitis. The eczematous dermatitis was papular (prurigo-like) or papulopustular (folliculitis-like) in all patients (Fig 4). Starting on the face and scalp, it spread to include the shoulders, arms, axillae, upper aspect of trunk, and buttocks in 12 (57%) patients. Erythroderma was never recorded. Secondary *S aureus* infection was observed in all patients with eczematous lesions. Histopathologic examination revealed a lymphoid infiltrate with eosinophils in the papillary dermis. Chronic use of topical steroids was required in two (9.5%) patients. In the remainder, intermittent application of topical steroids improved the lesions and pruritus. Prophylactic antistaphylococcal antibiotic treatment with sulfamethoxazole-trimethoprim or penicillin dramatically improved the eczematous dermatitis in all cases.

**Fig 1.** Early papulopustular rash on face.

Twelve (59%) patients presented with chronic candidiasis of mucosal sites and nails: oral candidiasis was present from birth in 4 patients (Fig 5); chronic paronychia of one or several fingers was found in 8 (38%) patients. This was effectively managed with a combination of prophylactic oral itraconazole and topical antifungal treatment.

Uncomplicated varicella-zoster virus ($n = 9/21$) and localized herpes simplex virus ($n = 3/21$) infections were not particularly intense and did not recur. Only one patient had extensive herpes simplex virus infection, without major organ involvement, a few days after birth. The outcome was favorable with intravenous acyclovir therapy. One (4.8%) patient had extensive molluscum contagiosum.

Recurrent otitis media developed during the same time period as the eczematous lesions (mean age of onset: 6 months; range: 1 week–36 months). In contrast, the first cold skin abscesses, observed in



Fig 2. Crusted pustules on scalp in neonate.

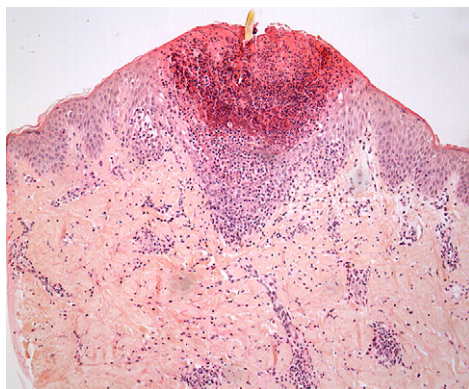


Fig 3. Eosinophilic folliculitis in autosomal dominant hyper-IgE syndrome: histopathology shows spongiosis and exocytosis involving infundibular region of hair follicle with superficial follicular pustulosis and some superficial follicular necrosis. (Original magnification: $\times 100$.)

all but one patient (mean age of onset: 49 months; range: 1-166 months), and the first episode of pulmonary infection (mean age of onset: 53 months; range: 1 week-329 months), occurred later. Staphylococcal abscesses were most common on the neck and the trunk. They tended to be pustular with no signs of local or general inflammation. Surgical drainage was performed to prevent rapid recurrence of these abscesses.

Characteristic AD-HIES facial findings with coarse facial skin and a broad nasal bridge were noted in 47% of cases, all adolescents. In teenagers, and sometimes in younger children, the skin was described as having an unusually rough and thickened texture with prominent follicular ostia (Fig 6).

Serum IgE levels (normal range: 0-150 IU/L) and eosinophil counts fluctuated markedly over time. The median highest serum IgE level was 7000 IU/L (mean: 13,500 IU/L; range: 1000-32,000 IU/L). Circulating T-cell counts and T-lymphocyte proliferation were normal in all patients.

Three patients developed lymphoma in adulthood, including one case of pilotropic cutaneous T-cell lymphoma in a 33-year-old woman.



Fig 4. Papular and prurigo-like lesions, occurring on shoulders and back.



Fig 5. Chronic candidiasis of nails.

Diagnosis

The average age at AD-HIES clinical diagnosis was 8.5 years. Diagnosis was based on a combination of elevated serum IgE levels, recurrent staphylococcal cutaneous abscesses, pneumonia, and otitis media. The use of molecular analysis to confirm the diagnosis was a recent development.

DISCUSSION

Chamlin et al¹⁶ and Eberting et al¹⁷ suggested that a papulopustular neonatal rash involving the face, head, and neck could be highly evocative of HIES. Our findings in 21 patients with molecularly confirmed AD-HIES confirm this hypothesis. An early papulopustular rash on the face and scalp, occurring before the age of 2 months, was observed in 67% of cases. Unusual features were crusting and secondary involvement of other areas of the body. Histopathologic examination showed a nonspecific eosinophilic spongiotic dermatitis and eosinophilic folliculitis, as reported elsewhere.^{16,17} Most of our cases were initially diagnosed as eosinophilic pustular folliculitis, a rare benign transient disorder,¹⁸ or as neonatal acne. Eosinophilic pustular folliculitis involves the scalp and, although cases have been described in neonates, it is more common after 5



Fig 6. Cheeks of teenager with autosomal dominant hyper-IgE syndrome. Skin is rough in texture with prominent pores and reticular atrophy.

months of age. Pustules are sterile and histopathology shows a dense eosinophilic infiltrate. It resolves spontaneously. Because the origin of eosinophilic pustular folliculitis has not yet been elucidated, we recommend careful monitoring of babies with this condition. Neonatal acne presents as papulopustules located on the cheeks, chin, and forehead. A relationship with *Malassezia* skin colonization is controversial.^{18,19} It generally resolves within a few weeks and may be treated with topical antifungal creams.

The skin findings of AD-HIES may be confused with atopic dermatitis. A continuum between the neonatal papulopustular rash and a chronic eczematous dermatitis was observed in 95% of our patients younger than 18 months. Eberting et al¹⁷ estimated that most (65%) patients with atopic dermatitis fulfilled the validated criteria of United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis. This was not evident in our series: there was no personal or familial history of atopy; dry skin and pruritus were very moderate or even absent; the periorificial facial skin and the scalp were particularly inflamed and crusted; and, although other parts of the body could be involved, the dermatitis elsewhere essentially involved the neck, shoulders, axillae, upper aspect of the trunk, and buttocks. Retroauricular fissures were sometimes observed but always in combination with extensive staphylococcal infection. The distinctive eczematous dermatitis was often described as papular (prurigo-like) or papulopustular. A sharp decrease in the recurrence of severe dermatitis was observed after the introduction of prophylactic antibiotics such as sulfamethoxazole-trimethoprim. It was difficult to establish the benefit of treatment with topical corticosteroids or other topical agents. It is possible that the susceptibility of patients with AD-HIES to *S aureus* infection and the colonization of the upper respiratory tract by this pathogen could result in a nonspecific eczematous reaction. This might explain the location of the rash around the mouth and on the scalp and its presence in the neonatal period.

The causative agents in AD-HIES cutaneous infections are mostly *S aureus* and/or *Candida albicans*. The characteristic cold skin abscesses were observed later (mean age of onset: 4 years). It should be noted that, although recurrent abscesses are highly suggestive of the diagnosis, they are not a ubiquitous feature, probably as a result of early prophylactic antibiotic therapy. Chronic candidiasis of mucosal sites and nails (57% in our series) can also arise in very early life (4 patients were born with persistent oral candidiasis). Prophylactic oral antifungal treatment with itraconazole improved chronic mucocutaneous candidiasis. None of our patients had recurrent viral infections, and severe recurrent or chronic cutaneous viral infections are exceptional in patients with AD-HIES. This is in contrast with the frequency and severity of viral infections observed in autosomal recessive HIES, related in one case to a null mutation in tyrosine kinase 2.²⁰ Patients with autosomal recessive HIES tend to have a higher incidence of intracellular bacterial infections (mycobacteria, salmonella), fewer pneumatoceles, and no connective tissue or skeletal abnormalities.²¹ In addition, AD-HIES differs from autosomal recessive combined immunodeficiency associated with mutations in the dedicator of cytokinesis 8.^{22,23} Patients with dedicator of cytokinesis 8 mutations also have high serum levels of IgE but viral cutaneous infections, and particularly pox virus infections (molluscum contagiosum), are widespread.

Atrophoderma vermiculatum-like skin lesions, particularly on the cheeks, with prominent pores and reticular atrophy (observed in 47% of cases in our series) were unrelated to severe acne or a history of facial abscesses, and persisted into adult life. It is possible that this characteristic facial finding is related to primary abnormalities of collagen tissue in AD-HIES, as scoliosis and joint hyperlaxity are frequently observed in patients with AD-HIES.

In conclusion, a neonatal papulopustular rash, immediately followed by an impetiginized eczematous dermatitis, without the typical features of atopic dermatitis, is suggestive of AD-HIES. When combined with severe otitis media and serum IgE levels 10 times the age-appropriate level, this rash may provide sufficient evidence for an early clinical diagnosis of AD-HIES. A secondary clinical diagnostic criterion could be the rough and pitted appearance of the facial skin observed mainly at puberty but also sometimes in younger children. Early diagnosis and prompt introduction of prophylactic antistaphylococcal and antifungal treatment improves both the chronic inflammatory skin disorder and the prognosis of AD-HIES.

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