

Dermatitis and the Newborn Rash of Hyper-IgE Syndrome

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Objective: To characterize the dermatitis, the newborn rash, and cutaneous findings in hyper-IgE syndrome, also known as *Job's syndrome*.

Design: Prospective and retrospective evaluation and treatment of cutaneous manifestations in patients with a clinical diagnosis of hyper-IgE syndrome (HIES). Analysis of the newborn rash encountered in this population.

Setting: Dermatology clinic at the National Institutes of Health, Bethesda, Md.

Patients: Forty-three patients seen in our clinic between January 1998 and August 2003 who had a clinical diagnosis of HIES.

Interventions: The UK Working Party's Diagnostic Criteria for Atopic Dermatitis were used to assess for atopic dermatitis in this population. To assess the newborn rash, we performed a retrospective chart review and an in-

person or telephone interview of the parent or caregiver of each patient.

Results: Twenty-eight (65%) of 43 patients fulfilled the criteria for atopic dermatitis. Thirty-five (81%) of 43 patients reported a newborn rash. Eight (19%) of 43 were born with the rash; 23 (53%) of 43 had acquired the rash within 7 days; 32 (74%) of 43 within 14 days; 34 (79%) of 43 within 30 days; and 35 (81%) of 43 had the rash within 35 days of birth.

Conclusions: The dermatitis in HIES resembles classic atopic dermatitis but may have distinctive features. A newborn rash is almost always a presenting sign of HIES. After the newborn period, skin findings include retroauricular fissures, external otitis, infected dermatitis of the axillae and groin, folliculitis of the upper back and shoulders, cutaneous abscesses, mucocutaneous candidiasis, and in some patients pitted scarring of the face.

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IN 1966, DAVIS ET AL¹ COINED THE term *Job's syndrome* to describe the condition of 2 girls with severe dermatitis, recurrent staphylococcal infections with "cold" abscess formation, and an abnormal inflammatory response.¹ In 1972, Buckley et al² further defined this syndrome (Buckley syndrome) in 2 boys with similar problems: severe dermatitis, recurrent cutaneous, pulmonary, and joint abscesses, growth retardation, coarse facies, and exaggerated immediate hypersensitivity associated with markedly elevated serum IgE levels and eosinophilia. Today, this syndrome is known as hyper-IgE syndrome (HIES).³ Recent reports delineate additional associations, including retention of primary teeth owing to failure of root resorption, scoliosis, joint hyperextensibility, frequent bone fractures, and distinctive facial features that were found to be universal by age 16 years.⁴ Genetic analy-

sis has identified a dominant inheritance pattern in some instances, with at least 1 disease locus for HIES on chromosome 4, although a gene has not been identified.⁵

Patients with HIES are susceptible to superficial and systemic bacterial and fungal infections. *Staphylococcus aureus* frequently causes abscesses of the skin and lungs; *Candida albicans* leads to mucocutaneous candidiasis; and *Aspergillus* species commonly superinfect pneumatoceles and contribute to lung disease.^{4,6}

The dermatitis in HIES has been described in many ways. Davis et al¹ referred to it as "infected eczematoid skin lesions."¹ Buckley et al² reported a generalized dermatitis that was similar to, but atypical for, atopic dermatitis. Donabedian and Gallin³ documented that all of their patients had "eczematoid rashes." Erlewyn-Lajeunesse⁷ noted that the distribution of the rash in HIES was atypical for true atopic dermatitis. Because the treat-

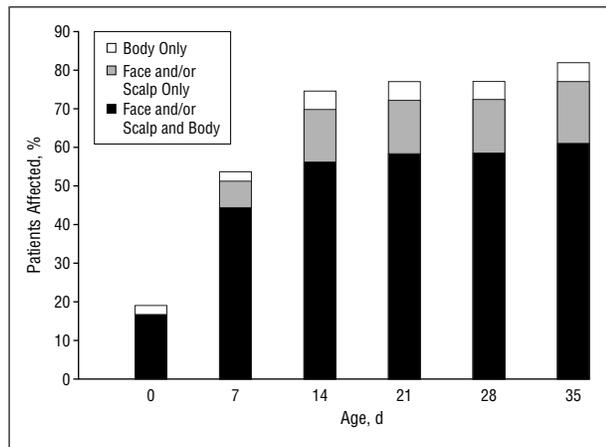


Figure 1. Study patients affected with newborn rash of hyper-IgE syndrome by age 35 days.

ment and prognosis of HIES is quite different from that of atopic dermatitis, it is important to differentiate the two.⁸ In an effort to assess whether patients with HIES have atopic dermatitis, we applied the UK Working Party's Diagnostic Criteria for Atopic Dermatitis⁹⁻¹¹ to our cohort of patients.

There have also been many reports of newborn rashes in HIES.¹²⁻¹⁶ Most recently, Chamlin et al¹² described the newborn rash as a papulopustular eruption predominantly affecting the face and scalp in the first year of life, with the eruption beginning within the first month of life in 6 of their 8 patients. In the present study, a retrospective review of the medical records and interviews with the parents or caregivers of each patient allowed us to determine the frequency, timing, and characteristics of the newborn rash of HIES. We also noted several other common skin manifestations of HIES and devised effective therapeutic strategies for the management of the recalcitrant cutaneous manifestations in this patient population.

METHODS

PATIENTS

Between January 1998 and August 2003, the dermatology service at the National Institutes of Health in Bethesda, Md, evaluated 43 patients from various ethnic backgrounds who had a clinical diagnosis of HIES, 27 female and 16 male (aged 3-50 years; mean age, 23 years). Patients were studied under approved protocols at the Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda. Informed consent was obtained from all subjects or their parents. Of the 43 patients included in this study, 18 were described in 1999.⁴

The diagnosis of HIES must be made clinically because there are no genetic or other confirmatory tests available. Inclusion in this study was based on an assessment by clinicians familiar with the syndrome and assisted by the scoring method for familial HIES (HIES score) developed by Grimbacher et al.⁵ Variables used to assign points for the HIES score include highest IgE level, skin abscesses, pneumonias, pneumatoceles, other serious infections, highest eosinophil count per microliter, newborn rash, eczema, upper respiratory tract infections, candidiasis, retained primary teeth, scoliosis, fractures with minimal trauma, joint hyperextensibility, characteristic facies, increased width across the bottom of the nose (interalar distance), high

palate, congenital anomaly, and lymphoma. An age correction is applied to subjects younger than 5 years. Five of 43 patients had a HIES score between 26 and 39, and the remainder scored 40 or higher. The average HIES score for all 43 patients was 61.2.

PROCEDURE

The UK Working Party's Diagnostic Criteria for Atopic Dermatitis were applied to all 43 patients. Compliance with these criteria was determined by a brief examination and evaluations of patient responses to a survey. To meet the criteria, patients must have had an itchy skin condition in the past year plus 3 or more of the following symptoms: (1) history of involvement of the skin creases such as folds of elbows (antecubital), behind the knees (popliteal), fronts of ankles, or around the neck (including cheeks in children younger than 10 years); (2) a personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children younger than 4 years); (3) generally dry skin in the past year; (4) flexural dermatitis at the time of examination; and (5) onset before age 2 years (criteria not used in children younger than 4 years).⁹⁻¹¹

A retrospective chart review was done to obtain any history regarding a newborn rash. A patient was considered to have had a newborn rash if the onset was within the first 35 days of life, was persistent, and was papulopustular in nature. Patients, and in most cases patients' mothers, were questioned regarding whether the patient "had a rash at birth or shortly thereafter." If the respondent answered in the negative, no further questions were asked. If the respondent answered in the affirmative, the distribution, appearance, and course of this rash were also elicited. Effort was made to ask open-ended, non-leading questions.

RESULTS

Of the 43 patients, 28 (65%) fulfilled the UK Working Party's Diagnostic Criteria for Atopic Dermatitis. Thirty-five (81%) of 43 patients reported having an itchy skin condition in the past 12 months. Thirty-two (74%) of 43 reported that this itchy condition began before age 2 years. Thirty-one (72%) of 43 gave a history of flexural involvement of dermatitis at some point in their life, but only 12 (28%) of 43 had flexural involvement at the time of evaluation. Twenty-two (51%) of 43 gave a history of asthma and 14 (33%) of 43 gave a history of hay fever. Twenty-eight (67%) of 42 reported dry skin in the past year.

Thirty-five (81%) of the 43 patients in the study gave a history of having the typical newborn rash of HIES within the first 35 days of life (**Figure 1**): 8 (19%) of 43 were born with the rash; 23 (53%) of 43 developed the rash within the first 7 days of life; 32 (74%) of 43 within the first 14 days of life; and 34 (79%) of 43 within the first 30 days of life. The average age of onset was 7 days.

In 33 of the 35 patients with the newborn rash, the face (**Figure 2A**) or scalp was the first area to be involved. Of these 33 patients, 26 reported that the rash progressed to include other parts of the body. The rash started on the neck in 1 patient and on the buttocks in another. In aggregate, 29 (67%) of 43 patients had rash in areas other than the face and scalp. Areas that were frequently involved included the shoulders, arms, chest, and buttocks. In 9 (21%) of 43 patients, the entire body was involved (**Figure 2B**). One patient reported "raised, red, pinhead-sized, pink bumps with no fluid in them that covered the entire body including the palms and soles."



Figure 2. The newborn rash of hyper-IgE syndrome began on the face of this 5-day-old infant (A) and progressed to involve most of the body by age 2 weeks (B).

The newborn rash on the face or scalp characteristically began as pink papules that developed into pustules within a few days of onset. Typically, the rash “oozed” and spread to other parts of the body. Three parents reported that the exudate from the pustules had a distinctive odor. Six patients were diagnosed with neonatal acne. The rash involved the face and other parts of the body in 5 of those patients and the entire body in 1. In these 6 patients, the rash did not resolve until age 3 to 12 months. Three of these cases required treatment with oral antibiotics for impetigo, while 1 case improved with Burow solution baths.

Of the 8 patients from whom a history of a newborn rash was not obtained, 2 did not have an accessible historian. In 1 case, the historian did not remember. Of the remaining 5 who did not have the typical newborn rash, 1 had a “yeast infection” at age 90 days, 1 had boils at age 6 weeks, 1 had “severe eczema” of the anterior neck at age 90 days, and 2 did not have any rash in the first 3 months of life. In assessing the rate of skin abscesses in our cohort, we found that 36 (84%) of 43 patients had had skin abscesses in the past.

COMMENT

DERMATITIS

Using the validated UK Working Party’s Diagnostic Criteria for Atopic Dermatitis,¹⁷ we showed that most of our patients (65%) had features consistent with classic atopic dermatitis. While these patients fit the criteria for atopic



Figure 3. Dermatitis of the antecubital fossa pictured here is in a typical distribution for atopic dermatitis before treatment with antistaphylococcal therapy.

dermatitis, it was clear to us that something more was going on. The dermatitis in HIES invariably becomes infected or colonized with *S aureus*, thus providing the necessary conditions for an “autosensitization reaction” and a generalization of the dermatitis. This reaction is similar to that seen in infectious eczematoid dermatitis,¹⁸ which is considered to be a form of autosensitization.

In the case of HIES, frequent infections with *S aureus*, which may be methicillin resistant, can serve as the initial autosensitizing trigger that leads to dermatitis over an increasing surface area of the skin. In addition to the typical findings of atopic dermatitis such as lichenified plaques of the anterior neck, antecubital fossa (**Figure 3**), and popliteal fossa, our patients frequently had diffuse areas of infected dermatitic skin (**Figure 4**) that responded well to intensive and organism-specific antibiotic treatment. Although these acute episodes can be cleared up, recurrences are not infrequent if patients fail to take prophylactic antibiotics such as trimethoprim-sulfamethoxazole.

It is likely that superantigen-producing *S aureus* contributes to the development of dermatitis in this patient population. McFadden et al¹⁹ found no difference in the colonization rate of superantigen-producing *S aureus* in atopic patients vs controls. However, Bunikowski et al^{20,21} found that the severity of atopic dermatitis in children



Figure 4. The dermatitis pictured here, on the same patient as shown in Figure 3, is diffuse and affects atypical areas for atopic dermatitis, sparing the areas usually covered by the patient's socks.

was correlated not only with the level of IgE antibodies to staphylococcal enterotoxins A and B, but also with the density of colonization of *S aureus* strains on atopic skin and episodes of superficial *S aureus* skin infections. Although we did not document the carriage rate of enterotoxin-producing *S aureus* in our patient population, we believe that because patients with HIES have extremely high IgE titers as well as a great propensity to *S aureus*-infected dermatitis, a superantigen effect might underlie the relationship between their IgE elevations and the severity of their dermatitis.

The superantigen effect refers to the exaggerated activation of T cells by pathogens, including gram-positive and gram-negative bacteria, viruses, parasites, fungi, and yeasts.²² By binding to major histocompatibility complex (MHC) class II molecules on the surface of antigen-presenting cells in a nontraditional way, the superantigens are recognized by T-cell receptors in a non-MHC-restricted manner. The MHC II molecule is able to cross-link with a larger number of T-cell receptors than would a normal antigen, thus leading to exaggerated immune stimulation.^{23,24} The fact that patients with HIES are commonly infected with superantigenic organisms such as *S aureus* and *C albicans*²² may explain the frequent exacerbation of dermatitis that is seen in correla-

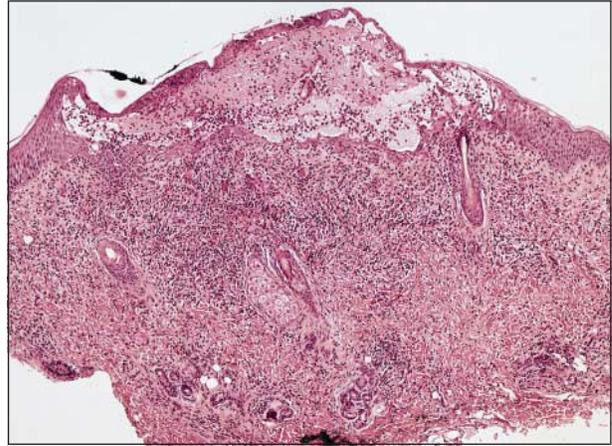


Figure 5. Punch biopsy specimen of newborn rash from the preauricle of a 3-week-old boy who was later proven to have hyper-IgE syndrome. There is an intraepidermal eosinophilic pustule showing superficial perivascular and perifollicular lymphoid infiltrate with eosinophils in the upper dermis (hematoxylin-eosin, original magnification $\times 5$).

tion with treatment or with the development of resistance to prophylactic antibiotics and antifungal agents.

NEWBORN RASH

Most of our patients had a history of a rash beginning in the first 2 weeks of life up to age 35 days. Several of our patients were initially diagnosed as having neonatal acne. The papules and pustules often began on the face or scalp, as neonatal acne does, but then unlike neonatal acne, they progressed to involve other areas of the body. In many cases, the rash had a protracted course that developed into "eczema," while in others, there was improvement or resolution following treatment with oral antibiotics or topical hydrocortisone cream.

The newborn rash of HIES usually begins on the face and/or scalp as pink to red papules that become pustules then break down, exude pus, and become crusted. Many of the patients' parents explained that the rash developed into eczema that persisted, sometimes for years. The rash almost always involves the face and scalp, but it may involve the entire body or just the upper chest and shoulders. **Figure 5** shows a punch biopsy specimen of newborn rash from the preauricle of a 3-week-old boy who was later proven to have HIES. This patient was born with 2 pink papules on his face. By age 2 weeks, he had draining pustules on his face, scalp, chest, shoulders, and upper arms that improved with oral antibiotics and topical mupirocin. The histologic findings in this patient were similar to those described by Chamlin et al,¹² who described an eosinophilic spongiotic dermatitis, eosinophilic folliculitis, superficial and deep perivascular dermatitis with abundant eosinophils, and abundant eosinophils extending into the subcutaneous fat. They also found Demodex folliculitis in 1 patient.

The differential diagnosis of the newborn rash seen in HIES includes eosinophilic pustular folliculitis of infancy (EPF), erythema toxicum neonatorum (ETN), and neonatal cephalic pustulosis (NCP). The distribution, appearance, and histologic characteristics of the newborn rash of HIES are similar to those of EPF. The age of on-



Figure 6. Retroauricular fissures are very common in hyper-IgE syndrome, as is weeping crusted external otitis.



Figure 7. A virulent *Staphylococcus aureus* folliculitis is common in the axillae in hyper-IgE syndrome.

set is older in EPF, with most cases occurring between ages 5 and 10 months rather than in the first month.²⁵ Lucky et al²⁶ described EPF in 5 patients younger than 1 year who had recurrent crops of pruritic papulopustules on the scalp. Intermittent outbreaks on the trunk and extremities occurred in 3 children. Cultures of the pustules were sterile, and biopsy specimens of scalp and skin tissues showed eosinophilic folliculitis. Some patients had peripheral blood eosinophilia during outbreaks of pustules, and 1 case of EPF was reported to be present at birth.²⁶

Eosinophilic pustular folliculitis of infancy does not tend to improve with antibiotic treatment and will sometimes improve with topical steroid treatment.^{25,26} In our cohort, the newborn rash of HIES often required antibiotic treatment. In fact, 9 parents gave a history of successful treatment of their child's newborn rash with oral antibiotics (6 patients), Burow soaks, and gentian violet baths. One reported that the rash worsened with steroid cream, and 2 reported improvement after using steroid cream in combination with oral antibiotics.

Erythema toxicum neonatorum can also simulate the newborn rash of HIES in appearance, age of onset, distribution, and histologic characteristics. It usually presents on the first or second day of life and resolves in 1 to 5 days. Milder recurrences may occur within 5 to 11 days after the original eruption.²⁷ Similar to HIES, ETN has been documented at birth.²⁸ However, the newborn rash of HIES is more severe and has a prolonged course.

Neonatal cephalic pustulosis is considered to be synonymous with neonatal acne. Many of our patients were initially diagnosed as having neonatal acne, though the distribution of the lesions in our patients tended to be more extensive than that seen in NCP. Our patients' rash often required treatment with antibiotics and was more chronic than NCP.²⁹

It is possible that the newborn rash of HIES represents EPF, ETN, or NCP that has become infected, leading to a progressive course that requires antibiotics. It is also possible that the newborn rash of HIES is an aberrant response to *S aureus* with eosinophils rather than neutrophils because of an underlying immune defect.

CUTANEOUS FINDINGS AND TREATMENT

In addition to the newborn rash and the dermatitis that are encountered in HIES, many interesting cutaneous manifestations are common. These skin findings include retroauricular fissures (**Figure 6**), severe folliculitis of the axillae (**Figure 7**) and groin, cutaneous abscesses, and a distinctive monomorphic folliculitis, most likely *Pityrosporum* folliculitis, of the upper back, shoulders, and face. Because of the underlying immune defect in HIES, we often see chronic candidiasis of the nails and mucous membranes that is effectively controlled by oral antifungal agents such as fluconazole or itraconazole (**Figure 8**). This treatment, in conjunction with topi-



Figure 8. *Candida* paronychia and onychodystrophy as a manifestation of mucocutaneous candidiasis in hyper-IgE syndrome before (A) and after (B) long-term therapy with fluconazole.

cal antifungal shampoo and cream such as ketoconazole, also tends to help control the folliculitis encountered on the face, shoulders, and back.

Older subjects with HIES, despite having no history of severe acne, show distinctive thick and doughy texture of the facial skin, and their follicular ostia are quite prominent (**Figure 9**).⁴ In a retrospective chart review of our cohort, we found that at least 1 aspect of these features was documented in 34 of 43 patients' charts. Additional facial features of HIES are also very helpful in making a diagnosis. These findings include facial asymmetry, a prominent forehead, deep-set eyes, a broad nasal bridge, a wide, fleshy nasal tip, and mild prognathism. Chamlin et al¹² noted the onset of some of these facial features by childhood in 2 of their 8 patients with HIES. We have noted prominent varioliform scarring of the face in some of our patients. Three of these patients attributed this scarring to severe chicken pox.

Supporting our theory that the dermatitis in HIES is superantigen mediated, this condition generally remains under good control when patients are treated with maintenance regimens of antibiotics such as trimethoprim-sulfamethoxazole and antifungals such as fluconazole. Our patients are also instructed to soak daily for 20 minutes in a full bathtub to which one-half to 1 cup of household chlorine bleach has been added. We have achieved a higher compliance rate by explaining to the patient that soaking in a tub with this much bleach is similar to swimming in a chlorinated swimming pool or hot tub. In fact,

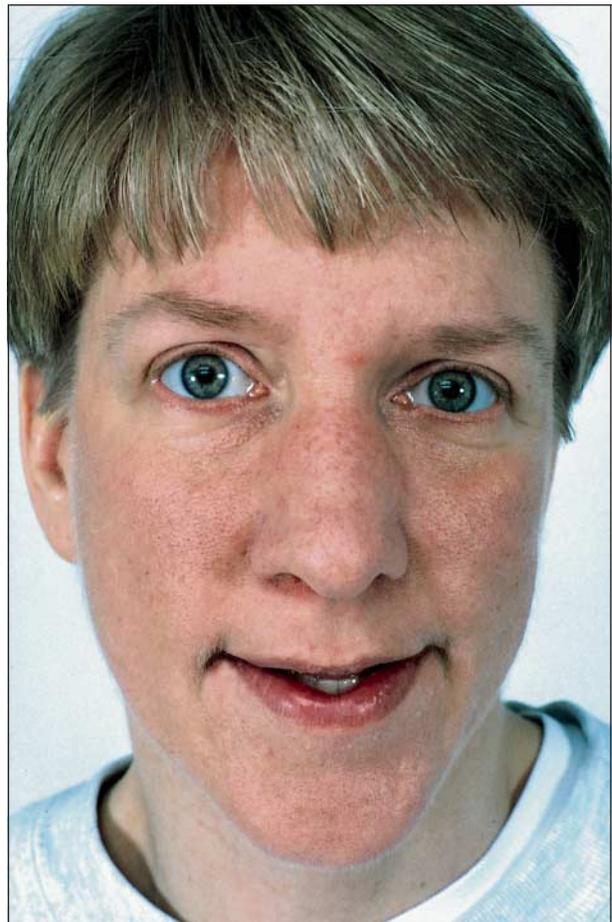


Figure 9. Older patients with hyper-IgE syndrome show thickened doughy texture of the skin, markedly dilated pores, and a broad-based nose. This patient also has angular cheilitis, a very common finding in hyper-IgE syndrome. Many patients also exhibit distinctive varioliform scarring on their faces.

the dermatitis also improves if the patient swims frequently in a chlorinated pool. We have found the antiseptic effect of chlorinated water to be a helpful adjunct in controlling the dermatitis and pruritus and have noted a marked reduction in the frequency and potency of topical steroid use, as well as a reduction in the use of antibiotics other than trimethoprim-sulfamethoxazole.

In the period during which we observed this cohort of patients, oral steroids were not needed to treat severe dermatitis. While 65% of our patients fulfilled the diagnostic criteria for atopic dermatitis, their underlying immune defect made them susceptible to bacterial and fungal infections that could incite an auto sensitization reaction.

Although cutaneous abscesses are part of the original defining triad of HIES (abscesses, pneumonia, and elevated serum IgE levels), we observed very few abscesses in our patients while they were under our care. Although 36 (84%) of the 43 patients had suffered from abscesses in the past, early administration of antibiotics for any sign of infection and prophylactic antistaphylococcal antibiotic use proved very effective at limiting the numbers and severity of abscesses once the diagnosis of HIES was established. In the patients who developed abscesses under

this treatment regimen, most of the abscesses developed during periods of decreased compliance.

This study points out that a papulopustular eruption that starts in the neonatal period and mainly involves the face, head, and neck is characteristic of HIES. Most of these patients eventually develop dermatitis with features of classic atopic dermatitis but differing from it by its propensity to generalize following superinfection with *S aureus*.

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