Symposium - Pediatric Dermatoses

Erythroderma in children

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ABSTRACT

Although erythroderma is a well-recognized entity in the adult age groups and has been studied by various authors, there is a paucity of studies on erythroderma in the pediatric age group. It poses a greater challenge to the dermatologist and pediatrician because of its potential life threatening nature. In a study conducted by us in a large Indian hospital to delineate the causes of neonatal and infantile erythroderma, the causes identified were infections (40%), ichthyosiform erythroderma (25%), atopic dermatitis (15%), infantile seborrheic dermatitis (10%) and unidentified (10%). In another study of childhood erythroderma, etiologically, drugs (29%) showed the highest incidence, followed equally (18%) by genodermatoses, psoriasis and staphylococcal scalded skin syndrome (SSSS). The management of childhood erythroderma is mainly supportive with correction of the hematologic, biochemical and metabolic imbalance if required. In this review, the causes of childhood erythroderma, the clinical features useful to the diagnosis and management are discussed.

Key words: Children, erythroderma, etiology

INTRODUCTION

Erythroderma or exfoliative dermatitis is an inflammatory skin disorder in which there is an involvement of total, or near total, body surface with erythema and scaling [Figure 1]. It can be both acute (few days duration) or chronic. It is a non-specific disease pattern induced by different diseases or medications. Although erythroderma is a well-recognized entity in the adult age groups and has been studied by various authors,[1-5] there is a paucity of studies on erythroderma in the pediatric age group.[6-8] Childhood erythroderma, though similar in clinical characteristics to its adult counterpart, poses a greater challenge to the dermatologist and pediatrician because of its potential life threatening nature. Moreover, it is essential for pediatricians and dermatologists to recognize erythroderma and distinguish it from eczemas and other benign erythemas of childhood, and to prevent it from being misdiagnosed and mismanaged.

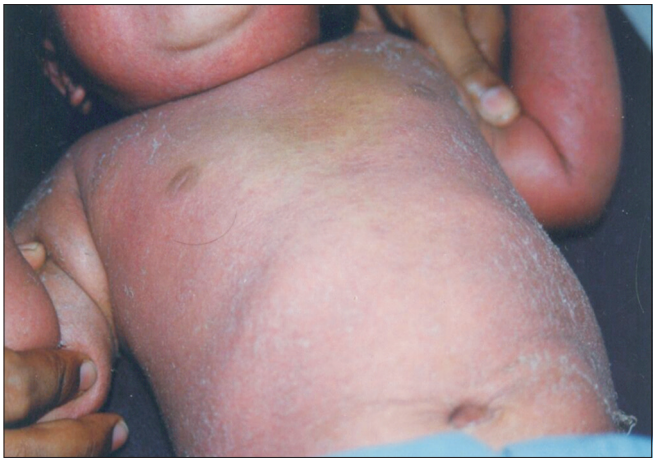

Figure 1: Psoriatic erythroderma with widesread erythema and minute easily removable scales

INCIDENCE

Erythroderma is an uncommon clinical entity in the pediatric age group. We had conducted a retrospective study of children having erythroderma, in the department of dermatology in Lady Harding Medical College and Kalawati Saran Children's Hospital, New Delhi where we found that of the 16,000 patients seen in the pediatric dermatology clinic over five years, 17 had erythroderma, revealing an incidence of 0.11%. There were eight males and nine females, the male: female ratio being 0.89:1.[6] The mean age of onset was 3.3 years. Eight (47%) of the patients were infants while nine (53%) belonged to the age group

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between 1 and 12 years. In one of the largest studies of erythroderma in patients of all age groups, conducted in India, out of 80 patients with erythroderma, only seven were children, of which only three belonged to 0-3 years. This study observed an incidence of 8.5% of children. The male to female ratio was approximately equal, though the age-at-onset varied according to its etiology.[4]

In another retrospective study conducted by us to delineate the various causes of erythroderma in the neonatal and infantile period over a period of six years, in one of the largest children's hospital in Asia, having its own dermatology unit, only 20(0.11%) neonates and infants had erythroderma out of 19,999 pediatric patients.[7] The causes indentified were infections (40%), ichthyosiform erythroderma (25%), atopic dermatitis (15%), infantile seborrheic dermatitis (10%) and unidentified (10%). The results of this Indian study were different from the results of a study conducted by Pruszkowski *et al* in France, which was another important study on neonatal and infantile erythroderma in literature.[8] In this retrospective study, 51 infants and neonates with erythroderma were studied in order to determine the frequency of the various underlying causes. The study does not mention the incidence of erythroderma in this age group. However, the causes identified in this study were immunodeficiency (30%), ichthyosis (21%), Netherton's syndrome (18%), eczematous or papulosquamous dermatoses (20%) and unknown origin (5%).

ETIOLOGY

As in adults, the cause of erythroderma in children is difficult to establish and delayed due to poor specificity of clinical and histological features. It is an uncommon, yet striking entity in the pediatric age group.[9] The clinical picture may appear uniformly similar, but the underlying etiology is variable.

In a study conducted by us at Lady Harding Medical College and associated Kalawati Saran Children's Hospital, New Delhi, India, seventeen children of both sexes, between 1993 and 1998, were inducted into the study to delineate the causes of erythroderma in this age group. Etiologically, drugs (29%) showed the highest incidence, followed equally (18%) by ichthyosis, psoriasis and staphylococcal scalded skin syndrome (SSSS). In two patients, erythroderma was due to atopic dermatitis, while one was due to infantile seborrheic dermatitis co-existing with dermatophytosis.[6] The drugs which were responsible for the erythroderma were antiepileptics (phenytoin in 2 and phenobarbitone in 1), amoxycillin and indigenous medicines in one each. Tables 1 and 2 enumerates some of the important causes of erythroderma in children.[6,9,10]

GENERAL CLINICAL FEATURES

The main presenting features were itching in 41% and burning in 18% of patients.[6] In this study, we observed an equal ratio of males to females, though a male preponderance is usually observed in earlier studies in adult age group.[2,4,5,11,12] Face was the initial site of involvement in majority (52.9%) of the patients and scalp involvement was observed in 53%, which could be due to rapid generalization of the disease process.[6] Scalp involvement with or without alopecia also occurred in 10 (30%) of the 20 patients with neonatal and infantile erythrodermas in the Indian

Table 1: Important causes of erythroderma in neonates and infants

Causes	Diseases
Ichthyosis	• Non-bullous ichthyosiform erythroderma • Bullous ichthyosiform erythroderma • Netherton's syndrome • Conradi-Hunermann syndrome • Sjogren Larssen syndrome • Lamellar ichthyosis • Trichothiodystrophy
Infections	• Staphylococcal Scalded Skin Syndrome • Scarlet fever • Neonatal candidiasis • Toxic shock syndrome
Infestations	• Norwegian scabies
Immunodeficiency	• Omenn's syndrome • Graft vs. host disease
Drug induced	• Boric acid toxicity • Ceftriaxone, vancomycin • Antiepileptics • Sulfonamides • Antitubercular drugs • Homeopathic • Indigeneous
Metabolic/Nutritional	• Disorders of biotin metabolism • Essential fatty acid deficiency • Kwashiorkor • Acrodermatitis entropathica • Cystic Fibrosis • Leiner's disease
Other disorders	• Infantile seborrheic dermatitis • Atopic dermatitis • Psoriasis • Pityriasis rubra pilaris • Diffuse cutaneous mastocytosis

Table 2: Important causes of erythroderma in preschool and school going children

Causes	Diseases
Ichthyosis	• Simple and complex ichthyosis
Atopic dermatitis	
Infestations	• Norwegian scabies
Papulosquamous disorders	• Psoriasis • Pityriasis Rubra ilaris
Drug induced	• Antiepileptics • Sulfonamides • Antitubercular drugs • Homeopathic • Indigeneous
Metabolic/Nutritional	• Kwashiorkor • Acrodermatitis entropathica • Cystic Fibrosis
Cutaneous T-cell lymphoma	
Miscellaneous and rare disorders	• Kawasaki's Disease • Dermatomyositis • Sarcoidosis • Pemhigus foliaceus
Idiopathic	

study.[7] Pruszkowski *et al*. have correctly pointed out that immunodeficiency should be suspected when diagnosing the condition of such patients.[8] Nail involvement was seen in 18% and composed of changes such as shining nails, pitting, Beau's lines and paronychia, which has also been observed by other authors in adult patients.[4,5]

Systemic complaints in the form of fever (53%), tachyardia (53%) and pedal edema (12%) were observed in the patients in the pediatric age group.[6] In our study of childhood erythroderma, lymphadenopathy was observed in 18% and hepatomegaly in 12%. On the other hand, systemic features such as lymphadenopathy, hepatosplenomegaly and failure to thrive were absent in our study of patients of neonatal and infantile erythrodermas.[7] Although challenging, a systematic and combined approach by the dermatologist and pediatrician can lead to a clinical diagnosis.

IMPORTANT ETIOLOGIES OF CHILDHOOD ERYTHRODERMAS

INFECTIONS

In most of these infectious conditions, the erythroderma is of acute onset and is characterized by diffuse erythema and scaling in the subsiding phase. Some authors feel that such acute conditions should not be clubbed under erythrodermas, but Hoeger and Harper have very clearly included them in their list of etiologies of "the red baby".[9] In fact, widespread erythema with scaling due to any cause, specific or nonspecific could qualify as erythroderma.

Staphylococcal Scalded Skin Syndrome

Systemic features such as fever, irritability and increased skin tenderness would point toward the causes of infections. The Nikolsky's sign will be positive. Unlike the large French study conducted by Pruszkowski *et al*,[8] which did not include neonatal and infantile erythodarma with blister formation, we had included such conditions in our study.[7] It is well known that bullous diseases can have an initial generalized erythrodermic phase that may subsequently evolve into a definite clinical entity;[13,14] hence, we strictly included only erythrodermic cases of SSSS in our study of neonatal and infantile erythrodermas. The erythema generalizes rapidly and progresses to sloughing and erosions. Histopathology would help to differentiate this condition from toxic epidermal necrolysis.[10] The condition is responsive to appropriate antistaphylococcal antibiotics.[15]

Scarlet fever: Scarlet fever is a toxin mediated illness caused by pyogenic exotoxin produced by group A beta-hemolytic streptococci usually harbored in an infection of the pharynx. This is a rare condition nowadays. This occurs in children below 10 years of age mostly and is marked by a constellation of features such as fever, associated constitutional symptoms, exanthem and enanthema. The rash starts 1-2 days after fever and pharyngitis starting from head and neck and following a caudal distribution involving trunk and extremities. Palms and soles are usually spared. This condition is an important differential diagnosis of conditions such as rubella, toxic shock syndrome, drug eruptions, and staphylococcal infections and can be differentiated by the constellation of clinical features. However, the erythroderma is transient and successfully resolves after treatment with antibiotics.

Congenital cutaneous candidiasis: Congenital cutanous candidiasis is caused by ascending infection involving the amnion. It is clinically characterized by widely spread macules, papules and pustules. Lesions are especially present over the palms and soles. The lesions become confluent and generalize into an erythroderma. Unlike neonatal candidiasis, the oral cavity and napkin area are usually spared.[16] The diagnosis is established through demonstration of myecelia/conidia in 10% potassium hydroxide mount

or on Gram's stain followed by positive culture of candida species. In our study of neonatal and infantile erythaderma, 10% of the patients had erythroderma due to candidiaisis.[7]

DRUG-INDUCED ERYTHRODERMA

Drug-induced erythrodermas are common in children. In our study of childhood erythroderma, drugs were implicated in the majority (29%) of pre-school and school age children, which was attributed due to unavoidable prescriptions for epilepsy or upper respiratory tract infections in the pediatric age group by general physicians.[6] Drug-induced erythrodermas are commonly observed in children due to sulfonamides, antimalarials, penicillins, isoniazid, thioacetazone, streptomycin, nonsteroidal anti-inflammatory drugs (NSAIDS), topical tar, homeopathic and ayurvedic medicines, captopril, cimetidine and ampicillin.[3,4,17,18] In our series, antiepileptics, amoxycillin, indigenous or ayurvedic medicines were implicated in causation of erythroderma. In such cases, if the incriminating drugs are withdrawn and a timely symptomatic treatment is started, these cases have a good prognosis.

In neonatal erythroderma, ceftrioxane and vancomycin have been incriminated.[19,20]

ICHTHYOSIS

Simple and complex ichthyoses as well as several syndromes with ichthyosis as an important component may be responsible for erythroderma in infants and children.[21] A congenital onset of erythroderma would be indicative of ichthyosis or immunodeficiency. They range from the just observable scaling of mild ichthyosis vulgaris to the easily diagnosable thick and massive scales of lamellar ichthyosis. A collodion membrane is an important part of both congenital ichthyosiform erythroderma (CIE) and lamellar ichthyosis. CIE is later replaced by erythroderma, while it is replaced by generalized ichthyosis with plate-like scale in the case of lamellar ichthyosis.[10] Harlequin's icthyosis may prove to be a fatal condition due to respiratory and feeding problem. Epidermolytic hyperkeratosis presents with generalized erythema and superficial vesicles and bullae which is later replaced by icthyosiform erythroderma.[12]

There are two important syndromes associated with ichthyosis which can also feature erythroderma: Netherton's syndrome and Conradi-Hunermann's syndrome. Infants and children with Netherton's symdrome show a triad of generalized erythroderma, sparse hair with trichorrhexis invaginata (bamboo hair) and atopic features.

The disease may have to be differentiated from generalized atopic dermatitis.[22,23] As there is scarcity of hair in an infant, it can take some time before the diagnosis is confirmed, though light microscopy of the hair and examination of the eyebrows, and eyelashes may be rewarding.[9,24] Conradi- Hunermann syndrome can present at birth with erythroderma often in a swirled pattern and is associated with chondrodysplasia punctata with epiphyseal stippling and cataracts.[25]

In our series of childhood erythroderma, epidermolytic hyperkeratosis and nonbullous icthyosiform erythroderma was observed in one patient each,[6] while 25% of the cases of neonatal and infantile erythrodermas were due to ichthyosis.[7] In the study by Pruszkowski *et al*, ichthyosis was the cause of erythroderma in 24% neonates and infants whereas Netherton's syndrome attributed to 18% of the cases.

ATOPIC DERMATITIS

Some authors feel that there is a considerable clinical overlap between clinical feature of infantile seborrheic dermatitis and atopic dermatitis.[10] Although atopic dermatitis can present with skin symptoms in neonates, erythroderma is a rare manifestation of the disease in the neonatal period.[26] A positive family history of atopy and presence of dermatitis on the cheeks, flexural creases of the limbs and itching which is apparent after three months of age would point to the diagnosis.[2] In young infants, the primary lesions of atopic dermatitis is frequently vesicular and exudation is common.

Sparing of the napkin area and axilla is also characteristic,[27,28] and 15% of children in our two series of erythroderma had atopic dermatitis. Despite being widespread, the children were apparently well and thriving.

INFANTILE SEBORRHEIC DERMATITIS

Infantile seborrheic dermatitis typically presents during the first months of life and is in the form of inflammatory, yellowish, scaling on the scalp with

involvement of the skin folds of the neck, axillae and groins. It is amenable to various treatments.[16]

Psoriasis: Congenital erythrodermic psoriasis is a rare condition.[29] It can be similar in appearance to NBIE, they are differentiated by positive family history and areas of unaffected skin in psoriasis, versus ectropion in non-bullous ichthyosiform erythroderma.[29] Later on they developed the typical psoriasiform lesions. The prognosis of the condition is poor in infants and young children,[8] In our study, 18% of the children with erythroderma had psoriasis. The higher figure could be due to ours being a referral hospital where patients had come to avail better services.

IMMUNODEFICIENCY SYNDROMES

Erythroderma, failure to thrive, lymphadenopathy and recurrent infections are the salient clinical features of Omenn's syndrome. Omenn's syndrome is an autosomal recessive form of severe combined immunodeficiency with leucocytosis with prominent eosinophilia, the presence of increased numbers of clonal T cells and decreased numbers of B cells, hypogammaglobalinemia and raised lgE.[30] Graft versus host reaction is seen mainly in infants with T-cell immunodeficiency, but can occur in immunocompetent newborns, who are transfused with non-irradiated blood or have received small amounts of maternal blood via placenta in utero. The clinical features include a nonspecific morbilliform rash which gradually progresses to erythroderma with epidermal sloughing.[31,32]

Immunodeficiency was the leading cause (30%) of erythroderma in Pruszkowski's study of neonatal and infantile erythroderma.[8] The authors have attributed the high frequency of immunodeficiency due to the recruitment of this patient population to the specialized pediatric department of their hospital. They also suspected immunodeficiency in five cases, but no firm diagnosis had been made because these cases of erythroderma were severe, were only moderately improved by topical corticosteroids and were associated with skin infiltration, failure to thrive, serious infections and histological features, suggestive of immunodeficiency. In literature, such cases have been formally classified as Leiner disease,[33] which is no longer appropriate and is used as an "umbrella" term to refer to a heterogeneous group of disorders with erythroderma when other causes have been ruled out. In our Indian study of neonatal and infantile erythroderma, we suspected immunodefiency in one unclassified case and two cases of erythroderma due to candidiasis.[7] Like Pruszkowski *et al*, we too observed alopecia in all three cases, but systemic features such as lymphadenopathy, hepatosplenomegaly and failure to thrive were absent in these patients. However, owing to lack of laboratory facilities, they were referred to higher center and were subsequently lost to follow up.

METABOLIC AND NUTRITIONAL DISORDERS

Multiple carboxylase deficiency

Holocarboxylase synthetase deficiency and biotinidase deficiency are autosomal recessive deficiencies. The clinical manifestations include lactic acidosis in the neonatal period, progressive erythroderma with alopecia, severe bacterial and viral infections, neurological abnormalities and other associations. In biotinidase deficiency, the clinical features are less severe and appear later than holocarboxylase synthetase deficiency.

Essential fatty acid deficiency

Essential fatty acids are not synthesized in the body and deficiency occurs due to long-term parenteral nutrition and disorders of fat malabsorption. The clinical features are growth retardation, alopecia, erythroderma with intertriginous erosions and systemic manifestations such as anemia, thrombocytopenia, fatty liver and increased susceptibility to infection.

Protein malnutrition

Amino acid deficiencies are associated with dermatological manifestations. Acrodermatitis enteropathica such as erythroderma may occur in leucine and isoleucine deficiency and also other amino acid deficiencies.

Diffuse cutaneous mastocytosis

This is a rare variant of mastocytosis. There is diffuse infiltration of the skin by mast cells, it is thickened and yellowish in appearance. Mild trauma to the skin can lead to release of mast cells with formation of urticaria which further progresses to bullae formation

APPROACH TO THE DIAGNOSIS OF CHILDHOOD ERYTHRODERMA

In patients with characteristic features, diagnosis is simple. But most of the times, diagnosis can be

challenging. In the history, points such as age of onset, family history, consanguinity, failure to thrive, recurrent infections, associated systemic complaints especially neurological complaints, fever, drug intake, history of transfusion can be useful. In the examination, features such as type of scales (ichthyosiform or fine scales), spared areas, discrete lesions (such as keratotic follicular papules or psoriasiform plaques, eroded areas or intact blisters, Nikolsky's sign, skin tenderness), distribution (predominantly flexural or extensor involvement), state of nails, hairs and mucosae can point to the diagnosis.

LABORATORY INVESTIGATIONS

Although laboratory investigations contribute minimally to the diagnosis, they may be done to ascertain the diagnosis in certain cases which would also help to alleviate the anxiety of the parents. Some laboratory tests, which can be done after causes such as atopic or seborrheic dermatitis, ichthyosis, nutritional causes and drugs have been ruled out, are potassium hydroxide preparations, swabs from skin, eyes, nose, umbilicus or high vaginal swabs from mother to show growth of *Staphylococcus aureus* or yeasts, blood culture, Gram's stain, complete blood counts, hair mount, total 1gE levels and quantitative immunoglobulin, eosinophil count, sweat chloride levels in relevant cases to rule out cystic fibrosis, zinc and alkaline phosphatase levels for acrodermatitis enteropathica, biotinidase and holocarboxylase assays and essential fatty acid levels to rule out metabolic disorders.[10] Genetic analysis such as SPINK 5, if available, should be done for Netherton's syndrome. These laboratory investigations have to be done where relevant for the clinical diagnosis.

Skin biopsy is important and it is advisable to take two or three simultaneous biopsies from different sites.[34] Histopathology reveals only dermatitis or psoriasiform changes, most of the time as observed in the three main studies of childhood erythrodermas where the histopathology contributed to the diagnosis only in 50%,[6] 45%[7] and 35%[8] respectively. However in cases of erythroderma due to immunodeficiency, it may reveal changes of significant lymphocytic infiltration and keratinocyte necrosis with satellite lymphocytes in cases of GVHD or Omenn's syndrome.

PROGNOSIS AND TREATMENT

Childhood erythroderma could be a potentially life threatening condition, especially in the neonatal and infantile period. The severe complications that can occur are septicemic infections, hypoalbunimea, hyperpyrexia and hypernatremic dehydration which if not managed timely could lead to increased mortality.

The management of childhood erythroderma is mainly supportive with correction of the hematologic, biochemical and metabolic imbalance. This would include monitoring of vital signs and electrolyte levels, adequate oral or parenteral fluid intake, prevention and treatment of infection, correction of caloric and protein intake, topical applications of emollients and antifungals, wet dressing or topical steroids in localized area. The pediatrician has to work in liaison with the dermatologist in these scenarios. A recognition and proper diagnosis by a dermatologist is necessary to allay anxiety of the parents and to prevent mismanagement of the patient.

The prognosis would largely depend on the primary cause of erythroderma. Erythrodermas due to drugs, infantile seborrheic dermatitis, nutritional deficiencies and Staphylococcal scalded skin syndrome respond well to treatment. Atopic dermatitis and drug-induced erythroderma may need a short course of systemic steroids initially in some cases. Psoriatic erythroderma would need systemic methotrexate or acitretin, if required. Ichthyotic erythroderma would be most difficult to manage as retinoids may have to be continued for a long time.[35] In the French study, the mortality was quite high (16%) and attributed to primary dermatosis or the complications.[8]

CONCLUSION

Erythroderma in children is a well-established entity but has only occasionally received attention. It could be a potentially life-threatening condition. However, diagnosing this condition remains a challenge due to poor specificity of clinical and histological signs. Careful monitoring of the patient and correction of the hematologic, biochemical and metabolic imbalance when required would improve the final outcome in these patients.

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