CURRENT TOPIC

Neonatal erythroderma: differential diagnosis and management of the "red baby"

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It is essential for paediatricians to recognise erythroderma and distinguish it from eczema. The aim should then be to search for underlying disorders, some of which have a specific treatment. However, for others, much remains to be done until curative treatment will be established for diseases such as Netherton's syndrome and the ichthyoses.

Erythroderma is defined as an inflammatory skin disorder affecting more than 90% of the body surface.[1] It is a reaction pattern of the skin that can complicate many underlying skin conditions at any age. In adults erythroderma may be either drug induced or secondary to pre-existing diseases,[2] while in the neonatal period it can be the primary manifestation of several conditions. Table 1 shows the diseases causing congenital or early onset erythroderma. This review outlines the clinical features of these disorders and suggests an approach to differential diagnosis and management.

Infections

Many perinatal or early neonatal infectious diseases are associated with a skin eruption; however, only very few manifest as erythroderma.

Staphylococcal scalded skin syndrome (Ritter's disease, pemphigus neonatorum) is caused by the circulation of exfoliative toxins (ETA, ETB) produced by staphylococci in focal infections such as conjunctivitis, omphalitis, or rhinitis. These exotoxins act as "superantigens" by stimulating large numbers of T cells to release lymphokines (interleukin 2, tumour necrosis factor). Staphylococcal scalded skin syndrome usually manifests in infants and children up to the age of 5 years, but congenital and neonatal cases (following chorioamnionitis) have been described.[3 4] The children are irritable and febrile. Within one to two days they develop a generalised macular and subsequently erythrodermic rash, which is accompanied by increased skin tenderness. It precedes the formation of subcorneal blisters, exudation, crusting, and finally generalised exfoliation.

Toxic shock syndrome, similar to staphylococcal scalded skin syndrome, is caused by *Staphylococcus aureus* exotoxins (TSST-1, TSST-2). Toxic shock syndrome can present at or shortly after birth with fever, hypotension, and shock, following transmission of toxigenic *S aureus* from an intrauterine infection or at the time of delivery. The extensive skin rash initially resembles scarlet fever and can develop into erythroderma.[5] A similar syndrome can be caused by streptoccocal exotoxins.[6]

Congenital cutaneous candidiasis is caused by ascending infection involving the amnion. Vaginal candidiasis occurs in 20–25% of all pregnant women. Congenital cutaneous candidiasis is characterised by widely scattered macules, papules, and pustules. Individual skin lesions may become confluent before evolving into exfoliative erythroderma. Associated features can include paronychia and nail dystrophy.[7] Unlike neonatal candidiasis, which is acquired during passage through the birth canal, the oral cavity and nappy area are usually spared.[8] The course is usually benign, but systemic infections (pneumonia and septicaemia) have been described, especially in premature infants; urine, blood and cerebrospinal fluid cultures are therefore recommended. The very preterm infant is particularly susceptible to developing acquired disseminated cutaneous candidiasis.

Immunodeficiency syndromes

Because of the protective effect of maternal immunity, congenital immunodeficiency syndromes are rarely symptomatic at birth. Graft

Table 1 Causes of neonatal erythroderma

Infections
Staphylococcal scalded skin syndrome
Toxic shock syndrome
Candidiasis
Immunodeficiency
Omenn's syndrome
Graft versus host reaction
Ichthyoses
Non-bullous ichthyosiform erythroderma
Conradi-Hünermann syndrome
Bullous ichthyosiform erythroderma
Netherton's syndrome
Metabolic disorders
Disorders of biotin metabolism
Essential fatty acid deficiency
Drugs
Ceftriaxone
Vancomycin
Others
Infantile seborrhoeic dermatitis
Atopic dermatitis
Psoriasis
Pityriasis rubra pilaris
Generalised mastocytosis

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versus host reaction from maternal engraftment can however occur even during intrauterine development.

Omenn's syndrome is characterised by exfoliative erythroderma with an onset at birth or in the early neonatal period. It is associated with diffuse alopecia, lymphadenopathy, hepatosplenomegaly, recurrent infections, and failure to thrive.[9] Omenn's syndrome is an autosomal recessive form of severe combined immunodeficiency with particular features: leucocytosis with prominent eosinophilia, the presence of increased numbers of (clonal) T cells and decreased numbers of B cells, hypogammaglobulinaemia, and raised IgE.[10] In some patients, maternal or clonal T cells can induce a graft versus host reaction.

Graft versus host reaction is seen mainly in children with a T cell immunodeficiency, but can occur in immunocompetent newborns, as a result of transplacental passage of maternal lymphocytes during intrauterine[11] or postnatal (exchange) transfusions.[12] The clinical manifestations of a graft versus host reaction include fever, a morbilliform rash, which in severe reactions may evolve into an erythroderma, eosinophilia, lymphocytosis, hepatosplenomegaly, and lymphadenopathy. The clinical presentation may resemble Omenn's syndrome, but the skin eruption is usually less eczematous in graft versus host reaction. In children with congenital immunodeficiency, graft versus host reaction occurs within the first two to three weeks of life, but may be present at birth as erythroderma, after intrauterine maternofetal transfusion.[13] In contrast, in the immunocompetent newborn with small numbers of transferred cells, clinical symptomatology is minimal and may involve only a transient macular rash.

Ichthyoses

The hereditary ichthyoses are a large and heterogeneous group of disorders, which have in common rough dry scaly skin. They range from the barely noticeable scaling of mild ichthyosis vulgaris to the large plate-like scales seen in lamellar ichthyosis. Of the different types of ichthyosis, non-bullous ichthyosiform erythroderma and bullous ichthyosiform erythroderma manifest at birth with variable degrees of erythroderma.

There are two syndromes associated with ichthyosis that can also feature erythroderma: Netherton's syndrome and Conradi-Hünermann syndrome.

Non-bullous ichthyosiform erythroderma is characterised by fine white-greyish scales and erythroderma. Many patients suffer from deep skin fissures, and some develop flexion contractures. About 90% of patients with non-bullous ichthyosiform erythroderma present as "collodion babies"[14] with a glistening membrane resembling sausage skin that envelops the neonate and can produce ectropion, lip eversion, and nasal obstruction.

Bullous ichthyosiform erythroderma also referred to as epidermolytic hyperkeratosis, presents with generalised erythema and superficial blisters that are frequently mistaken for staphylococcal scalded skin syndrome or epidermolysis bullosa. These children later develop typical ichthyosiform hyperkeratosis. Interestingly, some of the parents of children with bullous ichthyosiform erythroderma have had limited disease expression in the form of linear epidermal naevi with similar histology to epidermolytic hyperkeratosis.[15] The occurrence of epidermal naevi in a patient with bullous ichthyosiform erythroderma has been reported.[16]

Netherton's syndrome is characterised by a triad of generalised exfoliative dermatitis, sparse hair with trichorrhexis invaginata ("bamboo hair"), and atopic features. It usually presents at birth as erythroderma (fig 1). Because of the early paucity of hair, it can take some time before the diagnosis of Netherton's syndrome is confirmed, although examination of eyebrows or eyelashes is often rewarding.[17] During their first year of life, patients with Netherton's syndrome undergo a period of life threatening infections, hypernatraemic dehydration, diarrhoea, and failure to thrive, with a mortality of 30–40% during this period. Later in life, the exfoliative dermatitis tends to persist and vary in severity, with exacerbations triggered by intercurrent illness. Patients are atopic and often suffer from recurrent angio-oedema and urticaria associated with eating certain foods. Apart from raised total IgE and multiple positive specific IgE reactions, there are no consistent immunological abnormalities in Netherton's syndrome.[14]

Conradi-Hünermann syndrome can present at birth with erythroderma often in a swirled pattern and is associated with skeletal (chondrodysplasia punctata with epiphyseal stippling) and eye anomalies (cataracts).[14]

Metabolic disorders

Holocarboxylase synthetase deficiency presents with neonatal erythroderma and alopecia. The children are acutely ill with ketoacidosis, dehydration, and coma, and most of them die within the first week if untreated. In contrast, biotinidase deficiency presents later (mean age of onset 3 months) with hypotonia, lethargy, and seizures; the skin lesions resemble acrodermatitis enteropathica,[18 19] and the alopecia is usually patchy. Both types of enzyme deficiency have previously been described as "multiple carboxylase deficiency". Because of the lower concentration of biotin in human milk, breast fed babies with biotinidase deficiency may become symptomatic earlier than formula fed infants.[19] With early biotin substitution, all skin and neurological symptoms are completely reversible.

Essential fatty acid deficiency is known to cause an ichthyosiform erythroderma. This can occur as a result of malabsorption or maldigestion, as in severe gastroenteritis and malnutrition, and cystic fibrosis.[20]

Drugs

Although antibiotics, such as penicillin, ampicillin, aminoglycosides, and cephalosporins, can cause an erythematous macular papular rash, erythroderma has only been described in

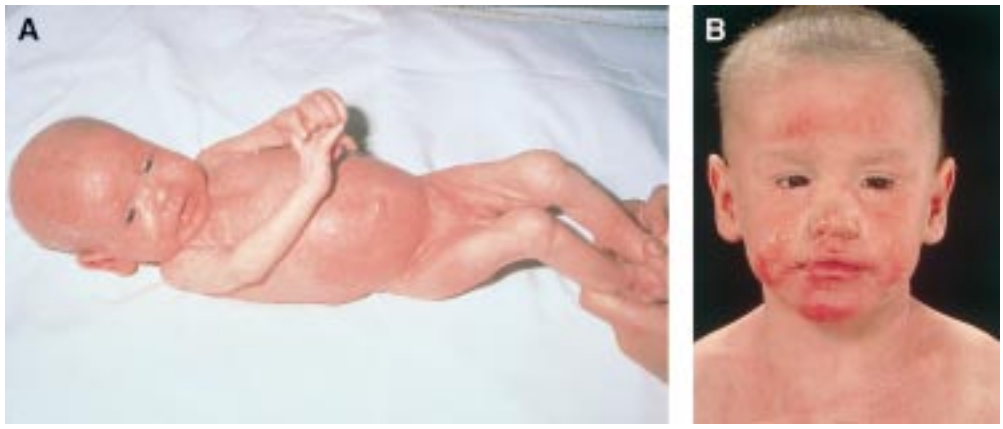

Figure 1 (A) Neonatal erythroderma as a presentation of Netherton's syndrome. (B) Same boy aged 5 years exhibiting the characteristic facial appearance and short hair of Netherton's syndrome. (Reproduced from reference 14 with permission of Butterworth Heinemann.)

neonates with ceftriaxone[21] and vancomycin.[22] Vancomycin causes a generalised erythema and hypotension owing to histamine release.

Others

Infantile seborrhoeic dermatitis typically presents during the first month of life. The characteristic feature of infantile seborrhoeic dermatitis is an inflammatory, yellowish, scaling on the scalp (cradle cap) often with involvement of the skin folds of the neck, axillae, and groin. Other forms of presentation are a psoriasiform appearance or rarely erythroderma.[23] In a 10 year follow up study, 15% of patients originally presenting with infantile seborrhoeic dermatitis developed atopic dermatitis; 28% of children who had psoriasiform infantile seborrhoeic dermatitis on first presentation and 50% with an erythrodermic presentation went on to develop psoriasis.[23]

Although about 18% of all children with atopic dermatitis develop skin symptoms within the first 4 weeks of life,[24] the rash is rarely erythrodermic at this age. In young infants, the primary lesion of atopic eczema is frequently vesicular and exudation is common. There is a considerable clinical overlap between manifestation of infantile seborrhoeic dermatitis and atopic dermatitis, and some authors believe that infantile seborrhoeic dermatitis is a variant of atopic dermatitis. Atopic dermatitis more often involves the face, especially the cheeks, flexural creases of the limbs, and usually spares the nappy area. In atopic dermatitis itching is usually not apparent until 2 to 3 months of age.

Psoriasis at birth or in the neonatal age is very rare. Only 15 cases of congenital erythrodermic psoriasis have been reported.[25 26] It can be similar to non-bullous ichthyosiform erythroderma; distinguishing features between these entities are positive family history and areas of unaffected skin in psoriasis, and ectropion in non-bullous ichthyosiform erythroderma.[26] More than half of congenital psoriasis patients are positive for the HLA antigen B17.[26] Most cases later develop classic erythematosquamous lesions.[3] Congenital and neonatal erythrodermic psoriasis are among the most serious and difficult forms of psoriasis to treat. Psoriasis can persist into adulthood and may be complicated by pustulosis and early onset arthropathy.[25]

Pityriasis rubra pilaris is characterised by erythematous scaly plaques similar to psoriasis and follicular hyperkeratosis. These can coalesce to larger plaques and become generalised as erythroderma. Palmoplantar keratoderma is frequently associated. Congenital erythrodermic pityriasis rubra pilaris has been described.[27] It is inherited as an autosomal dominant trait and, unlike the acquired forms of pityriasis rubra pilaris, tends to run a life long course.

Diffuse cutaneous mastocytosis can present at birth or in the neonatal period.[28 29] The skin is diffusely thickened and may appear doughy. There can be numerous orange papules or diffuse erythroderma. It can be accompanied by extensive blistering and mimic staphylococcal skin syndrome.[28] Children with congenital diffuse or erythrodermic mastocytosis may have extracutaneous mast cell infiltrates (gastrointestinal tract, bone, liver, spleen, lymph nodes). Accompanying symptoms include diarrhoea, vomiting, abdominal cramps, wheezing, raised temperature, pruritus, flushing, and hypotension. Darier's sign—a wheal and flare reaction on rubbing the skin—is positive. Careful monitoring for systemic involvement is mandatory in diffuse cutaneous mastocytosis. It should include full blood count, liver function tests, bone scan and, if appropriate, gastrointestinal studies.

Diagnostic approach to neonatal erythroderma

Neonatal erythroderma is a diagnostic and therapeutic challenge. Erythrodermic neonates and infants are frequently misdiagnosed with eczema and inappropriate topical steroid treatment can lead to Cushing's syndrome.[30] Delay in the establishment of the correct diagnosis can be fatal. The differential diagnosis of erythroderma is a multistep procedure that involves clinical assessment, knowledge of any relevant family history, and certain laboratory investigations (table 2).

Table 2 Neonatal erythroderma: differential diagnosis and management

Disease	*Clinical features*	*Investigations*	*Treatment*
Infections			
Staphylococcal scalded skin syndrome	Preceding purulent infection; skin tenderness; superficial blisters; positive Nikolsky sign	Skin swab; assessment of toxin production by *S aureus*. Skin biopsy: superficial split (below granular layer), few or no inflammatory cells within bulla or dermis	Intravenous antibiotics (flucloxacillin, amoxycillin/clavulanic acid), contact tracing (carriers of toxigenic strains)
Toxic shock syndrome	Concomitant maternal infection; skin tenderness; hypotension/shock	Skin swab, assessment of toxin production by *S aureus* or *Streptococcus pyogenes*. Skin biopsy: superficial perivascular and interstitial neutrophilic infiltrates	As above; intravenous immunoglobulins
Congenital cutaneous candidiasis	Maternal vaginal candida infection; oral cavity spared; may have paronychia and nail dystrophy	Skin swab, KOH preparation; pseudohyphae; cultures: urine, blood, CSF. Skin biopsy: pseudohyphae and spores in the corneal layer (PAS stain)	Topical (nystatin, miconazole) and oral (nystatin, fluconazole) antimycotics; may need intravenous amphotericin; also eradication of maternal vaginal yeast infection
Immunodeficiency			
Omenn's syndrome	Lymphadenopathy; sparse hair; unexplained death of previous children; consanguinity	Eosinophilia; IgE raised; decreased B cells; increased activation markers on T cells (CD25, HLA-Dr, CD45RO); Skin biopsy: activated T cells; eosinophils and histiocytes	Supportive care; eventually will need a bone marrow transplant
Graft versus host reaction	Fever; diarrhoea; antecedent transfusion; immunodeficiency	Mixed lymphocyte populations Skin biopsy: basal cell vacuolation; exocytosis, satellite cell necrosis, HLA-Dr + basal keratinocytes	Use of irradiated blood products is mandatory; for those with SCID supportive care and bone marrow transplant
Ichthyoses			
Non-bullous ichthyosiform erythroderma	Collodion baby; when shed leaves disseminated ichthyosiform scaling	Skin biopsy: hyperkeratosis, acanthosis, minimal lymphocytic infiltrate	Emollients
Bullous ichthyosiform erythroderma	Superficial blistering and erosions; ichthyosiform erythroderma; family history; linear epidermal naevus parents or sibling	Skin biopsy: epidermolytic hyperkeratosis	Emollients
Netherton's syndrome	Diarrhoea; failure to thrive; atopy; sparse hair, trichorrhexis invaginata (bamboo hair)	Hair microscopy shows characteristic features. IgE raised, eosinophilia Skin biopsy: psoriasiform acanthosis, parakeratosis, perivascular lymphocytic infiltrate	Emollients, adequate hydration
Conradi-Hünermann syndrome	Linear and swirled patterning	Skin biopsy: hyperkeratosis, reduced granular layer. *x* Rays show stippling in infancy	Emollients
Metabolic			
Holocarboxylase synthetase deficiency	Lethargy, coma, apnoea	Ketoacidosis, organic aciduria; decreased enzyme activity in leukocytes and fibroblasts	Oral biotin (5–10 mg/day) (normal daily requirement > 0.1mg/kg/day)
Essential fatty acid deficiency	Ichthyosiform erythroderma; wasting	Blood fatty acid screen	Topical linoleic acid (sunflower seed oil)
Drugs			
Ceftriaxone	Infective illness for which this antibiotic has been prescribed	None	Substitute the antibiotic
Vancomycin	"The red man syndrome" sudden hypotension and erythema	None	Reversible on discontinuation
Others			
Infantile seborrhoeic dermatitis	Cradle cap, accentuation in the skin folds of the neck, axillae, and nappy area		Moisturising agents; miconazole-hydrocortisone ointment protective cream nappy area
Atopic dermatitis	Encrusted eczema on the scalp and face; generalised eczematous skin; family history for atopy	IgE raised; eosinophilia. Skin biopsy: spongiosis, lymphocytes, exocytosis	Weak topical steroid; systemic antibiotics if skin infected. Possible cows' milk allergy
Psoriasis	Erythematosquamous patches; can be pustular (sterile); may have positive family history	Skin biopsy: hyper and parakeratosis, microabscesses	Bland emollient creams, wet dressings helpful
Pityriasis rubra pilaris	Similar to psoriasis; follicular accentuation skin thickening of palms and soles; may have positive family history	Skin biopsy: like psoriasis, follicular hyperkeratosis	Along the same lines as psoriasis
Diffuse mastocytosis	Darier's sign often with blistering	Serum/urine histamine and metabolites. Skin biopsy: mast cell infiltrate	H_1 and H_2 antagonists; oral sodium cromoglycate; avoidance of substances with potential for mast cell degranulation (for example, codeine, opiates, aspirin, procaine, radiographic dyes, scopolamine, pancuronium)

CSF, cerebrospinal fluid; SCID, severe combined immunodeficiency.

CLINICAL ASSESSMENT

In the presence of a collodion baby, the differential diagnosis is virtually restricted to the hereditary ichthyoses. Once the collodion membrane is shed, skin biopsy will aid in the differential diagnosis. Children with congenital ichthysiform erythroderma should be monitored for associated skeletal, neurological and ophthalmological abnormalities.

Increased skin tenderness, irritability, and fever should prompt a search for signs of congenital infections. Blistering of the skin is suspicious of bullous ichthyosiform erythroderma, staphylococcal scalded skin syndrome, and mastocytosis. Darier's sign is positive in mastocytosis. The Nikolsky sign—the blister can be propagated within the skin—is evident in staphylococcal scalded skin syndrome. Alopecia, either total or partial, is obvious in Netherton's syndrome, Omenn's syndrome, and disorders of biotin metabolism. Lymph node enlargement is a characteristic feature of Omenn's syndrome, but can also be seen in graft versus host reaction and atopic dermatitis.

LABORATORY INVESTIGATIONS

Differential diagnosis of erythroderma can be facilitated by a few laboratory tests. Serum IgE

levels are profoundly increased in Netherton's and Omenn's syndromes and mildly increased in early atopic eczema. Swabs from the skin or other potential sites of infection (eyes, nose, umbilicus, or high vaginal swab from the mother) may show growth of *S aureus* in staphylococcal scalded skin syndrome and toxic shock syndrome, and of yeasts in congenital cutaneous candidiasis. Serum electrolyte and albumin concentrations should be measured because children with erythroderma are at risk of hypernatraemic dehydration and loss of albumin from enteral and transcutaneous protein losses. A full blood count should be supplemented by more detailed immunological studies if Omenn's syndrome or graft versus host reaction are suspected.

HISTOPATHOLOGY

A skin biopsy is essential. As it is very important to establish the diagnosis rapidly, it is advisable to take two or three simultaneous biopsies from different sites.[31] Samples for routine histopathology can be formalin fixed, but it is valuable to have a sample frozen in liquid nitrogen for immunohistochemical studies. Histology and immunohistochemistry can differentiate Omenn's from Netherton's syndrome and the other ichthyoses.[32] Non-bullous and bullous ichthyosiform erythroderma are distinguishable on histology. In the graft versus host reaction, histopathology is valuable in severe cases, but in milder cases only some of the findings may be present, and the diagnosis could easily be missed if the histopathologist is not specifically alerted. In blistering diseases, it is helpful to take the biopsy from the border of the blister, including its roof, to facilitate assessment of the level of cleavage.

Management of children with neonatal erythroderma

Irrespective of its cause, neonatal erythroderma is a potentially life threatening condition. Erythrodermic neonates and infants are at risk of hypernatraemic dehydration and hyperpyrexia. Maintaining adequate oral or parenteral fluid intake and monitoring serum electrolytes is therefore mandatory. Topical applications of emollients (such as white soft paraffin) hydrate the skin and prevent fissuring. Blisters and erosions, as seen in bullous ichthyosiform erythroderma, staphylococcal scalded skin syndrome, and mastocytosis, should be treated with a topical astringent, such as 0.01% potassium permanganate soaks, and systemic antibiotics given if appropriate. As transcutaneous absorption is profoundly increased,[3] additives such as salicylic acid or lactic acid should be strictly avoided in the young infant, and topical steroids used cautiously and only after the establishment of a diagnosis warranting its use. Table 2 lists specific treatment options.

The term "Leiner's disease", which is sometimes used synonymously for infants with erythroderma, is confusing and often misunderstood. In 1908 Carl Leiner, a paediatrician from Vienna, described a series of young infants with desquamative erythroderma, sparse hair, diarrhoea, and failure to thrive.[33] He was the first to separate this syndrome from seborrhoeic and exfoliative dermatitis, respectively. However, it has become clear over the past decade that Leiner's disease is an umbrella phenotype rather than a specific entity, and often applied to babies in whom the known causes of erythroderma have been excluded. It is our opinion that most, if not all, of these patients have Netherton's syndrome, which can be difficult to confirm in the early months of life. In a study by Glover and colleagues[34] of five patients with "erythroderma, failure to thrive and diarrhoea: a manifestation of immunodeficiency", one patient went on to develop the typical features of Netherton's syndrome; of the other four, three had features consistent with Netherton's syndrome (one died and the other two were lost to follow up) and the fourth had severe combined immunodeficiency.

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