

Neonatal erythroderma

Sylvie Fraitag^a and Christine Bodemer^b

^aDepartment of Pathology, Hôpital Necker-Enfants Malades and ^bDepartment of Dermatology, National Reference Centre for Genodermatosis (MAGEC), Hôpital Necker-Enfants Malades, APHP, Université René-Descartes, Paris, France

Correspondence to Dr Sylvie Fraitag, Service d'Anatomie Pathologique, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France
Tel: +33 1 44494992; fax: +33 1 44494999;
e-mail: sylvie.fraitag@nck.aphp.fr

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Purpose of review

Neonatal erythroderma is a potentially life-threatening condition in neonates less than 1 month old. During the first month of life, erythroderma is generally a presentation of genodermatosis, primary immune deficiency, or, more exceptionally, severe psoriasis, metabolic disease or infection. Atopic erythroderma is observed later in life, usually after the age of 1 month. Rapid determination of the underlying cause is crucial for better management. However, the diagnosis is often a challenge for the clinician and is frequently delayed due to the nonspecific nature of the clinical signs. We summarize the different causes of neonatal erythrodermas and list their clinical, biological, histological, and sometimes genetic characteristics.

Recent findings

Severe erythroderma, typified by early onset, skin induration, severe alopecia and failure to thrive, is immediately suggestive of immunodeficiency or Netherton syndrome. In such cases, an early skin biopsy may be particularly of use in allowing accurate differentiation between these two disorders.

Summary

This review outlines the clinical and histological features of these disorders and suggests an approach to their differential diagnosis and management.

Keywords

Erythroderma, ichthyoses, Netherton syndrome, Omenn syndrome, skin biopsy

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Introduction

The term erythroderma refers to persistent generalized skin erythema, affecting at least 90% of the body surface. Scaling is common, and when a prominent feature, the condition is referred to as 'desquamative erythroderma' [1,2].

We have shown that the time of onset of the skin lesions is conditioned by the underlying cause [3] (Table 1). While other causes – including atopic erythroderma and seborrhoeic dermatitis – are sometimes observed in older infants, these are actually extremely rare in neonates [3]. Neonatal erythroderma is rare, but its true incidence is unknown [4–6]. Optimal care depends on identifying the underlying disease. Exhaustive clinical analysis of the neonate is essential and should take into account both family history and the characteristics of the last weeks of pregnancy (unusual events, maternal infections, drug use, etc.). We have recently shown that an early skin biopsy can be extremely useful for the diagnosis [7••]. A section has been included at the end of this article showing the results of skin biopsies.

Causes of neonatal erythrodermas

Broadly speaking, 'bullous erythroderma' can be distinguished from nonbullous or 'scaling and exfoliative' erythroderma (Table 1).

Bullous erythroderma

Bullous erythroderma is mainly staphylococcal scalded skin syndrome (SSSS). Neonates are particularly prone to hospital-acquired *Staphylococcus aureus* infection. SSSS is a toxin-mediated disease caused by diffusion of staphylococcal exfoliative toxins (ET-A or ET-B) from an infected focus (for instance omphalitis, staphylococcal conjunctivitis, etc.). These toxins are able to break the superficial epidermis. The syndrome includes a spectrum from limited to extensive and diffuse manifestations when the toxin enters the blood stream. SSSS has been described in neonates, and a diffuse form with a sudden, painful erythroderma preceding skin detachment is possible. Although this is an exceptional occurrence, the prognosis is poor [5,8]. While recovery is usual, severe sepsis and severe electrolyte disturbances can be fatal, particularly in neonates. Early detection of an SSSS

Table 1 Main causes of erythroderma in neonates (<1 month of life) and infants (>1 month of life) depending on age of onset

Congenital	<1 month	>1 month
Ichthyosis, NS PIDS	Ichthyosis, NS PIDS Psoriasis Metabolic disease	PIDS Seborrhoeic dermatitis Psoriasis Atopic dermatitis Ichthyosis, NS

NS, Netherton syndrome; PIDS, primary immune deficiency syndrome.

epidemic in newborn nurseries is therefore essential. Best management of the child includes identification of family members or healthcare workers colonized with toxigenic *S. aureus*.

Bullous ichthyosis can resemble SSSS in newborns with widespread areas of denuded skin. Diffuse erythroderma is unusual, sometimes accompanied by extensive blistering. A skin biopsy confirms the diagnosis.

Diffuse *cutaneous mastocytosis* can be observed at birth or during the neonatal period. Typically, the skin is diffusely thickened and may appear doughy. Diffuse erythroderma is unusual, extensive blistering more frequent. It can therefore mimic SSSS [9]. Darier's sign – a wheal and flare reaction on rubbing the skin – is usually positive. Skin biopsy is characteristic. Accompanying symptoms include diarrhoea, vomiting, abdominal cramps, wheezing, raised temperature, pruritus and flushing. Careful monitoring is necessary to avoid shock with hypotension in the rare but severe forms of diffuse involvement.

Scaling and exfoliative erythrodermas

These have extremely heterogeneous causes, including keratinization disorders, immune deficiencies and metabolic diseases.

Some clinical features may be helpful but no single feature is pathognomonic of a cause. Complete absence of hair, eyelashes and eyebrows with infiltrated skin, diarrhoea and failure to thrive are suggestive of *primary immune deficiency syndrome* PIDS [Omenn syndrome and severe combined immunodeficiency (SCID)] [3]. Mild to severe erythroderma with failure to thrive, sepsis and hypernatraemic dehydration is suggestive of Netherton syndrome (NS). A metabolic source should be sought in the event of desquamative erythroderma with severe neurologic manifestations such as coma. In all cases, rigorous analysis of familial history and detection of consanguinity are essential. Neonatal scaling and exfoliative erythroderma are most frequently caused by the group of primary ichthyoses, which include Netherton syndrome.

Ichthyoses

Hereditary ichthyoses are a large and varied set of inherited disorders whose common symptom is rough, dry,

scaly skin. They are part of a large group of Mendelian disorders of cornification (MEDOC). Neonatal erythroderma can be seen in several subtypes of autosomal recessive congenital ichthyoses. A consensus for the nomenclature and classification of inherited ichthyoses has been recently defined by an international network of expert clinicians, skin pathologists and geneticists (meeting in Sorèze in France, 2009), and is in press [10^{••}].

Nonsyndromic ichthyoses are characterized by an isolated skin involvement. The acronym ARCI (autosomal recessive congenital ichthyoses) has been used for nonsyndromic hereditary ichthyoses including *lamellar ichthyosis/congenital ichthyosiform erythroderma* (CIE) and *harlequin ichthyosis*. Babies with *harlequin ichthyosis* who survive the perinatal period go on to present severe and massively scaling erythroderma. At the present time, six genes are involved in nonharlequin ichthyosis ARCI, including *TGM1*, encoding transglutaminase-1 (TGase-1), *ABCA12*, *NIPAL4* (or *ICHTHYIN*), *CYP4F22*, and the lipoxygenase genes *ALOX12B* and *ALOXE3* [11–13]. At least 22% of the cases did not exhibit mutations in any of these ARCI genes. Lamellar ichthyosis is characterized by coarse and brown/dark scaling, frequently in a collodion membrane baby and after pronounced ectropion. CIE is characterized by fine, white scaling with varying degrees of erythroderma. Individuals with lamellar ichthyosis or CIE may have collodion baby syndrome at birth. Harlequin ichthyosis is related to *ABCA12* mutations.

In newborns, *bullous ichthyoses*, now called 'epidermolytic ichthyoses' [10^{••}], can present as widespread areas of denuded skin resembling epidermolysis bullosa or SSSS. However, a subtle hyperkeratotic component is usually present. Over time, the blistering diminishes and the underlying ichthyosiform erythroderma becomes more obvious. The erythroderma persists in some patients, but not in most. Epidermolytic ichthyosis is considered to be a dominantly inherited disorder caused by K1 or K10 mutations. However, a small number of keratin knockout families showing recessive inheritance have been reported to have keratin 10 gene mutations [13]. Histological findings are characteristic.

Syndromic ichthyoses combine both skin and other organ involvement. A detailed report of all the syndromic ichthyoses displaying erythroderma in the neonatal period is beyond the scope of this article. Scaling erythroderma is a frequent presentation of syndromic ichthyoses, sometimes in collodion babies. In most cases, the syndromic ichthyoses are autosomal recessive. Confirming the syndromic involvement in the first weeks of life is not always easy. Physicians must be aware of this possibility and a rigorous clinical workup, which should include systematic analysis of the neonatal hair shaft

under polarizing microscopy, must be carried out. During this analysis, the dark and light bands are typical of trichothiodystrophy syndromes and trichorrhexis invaginata suggests the diagnosis of Netherton syndrome. Testing for lipids in peripheral blood smear granulocytes and monocytes is very useful for the diagnosis of neutral lipid storage disease with ichthyosis (Dorfman-Chanarin syndrome). Clinically, this resembles ARCI [14]. It is usually associated with, occasionally subtle, systemic manifestations, including mild myopathy, deafness, cataracts, slight developmental delay and growth retardation. Lipid vacuoles are present in numerous organs, including the skin and blood. However, it is important to stress that these highly characteristic features can be absent or difficult to detect in neonates. These tests should be repeated during follow-up if the aetiological diagnosis remains unclear. Family history must be taken into account. More specialized tests will be prescribed depending on the clinical course. Details concerning the more recent genotype classification of these rare diseases can be obtained from the article of Oji *et al.* [10**].

Netherton syndrome is a rare, autosomal recessive ichthyosiform dermatosis with variable clinical features. Classically it consists of ichthyosiform dermatosis, trichorrhexis invaginata (bamboo hair) and atopy. Neonates with Netherton syndrome often present with desquamative and/or scaling erythroderma. However, this aspect is not always present and the erythroderma has no specific features. Although bamboo hair is characteristic, the typical trichorrhexis invaginata feature often emerges after the age of 10 months [3] and not all patients with Netherton syndrome have the shaft defect in their hair, eyebrows and eyelashes. Thus, a negative result does not rule out the diagnosis. Neonatal desquamative erythroderma is frequently associated with failure to thrive, hypernatraemia, hypothermia, recurrent infections and sepsis. Hypernatraemia is suggestive of Netherton syndrome, but is not pathognomonic, and can also be observed in other forms of desquamative erythroderma. Typical findings include abnormal immunoglobulins, elevated IgE and quantitative lymphocyte defects, but there are no consistent immunological anomalies in Netherton syndrome [15]. Netherton syndrome has been related to *SPINK5* gene mutations. *SPINK5* encodes an antiserine protease (LEKTI) [16]. A skin biopsy with evaluation of LEKTI expression permits diagnosis of the condition. This possibility represents considerable progress for the early confirmation of suspected Netherton syndrome in a neonate with erythroderma [7**,17].

Moreover, a correlation has recently been found between cutaneous phenotype (severity of the skin lesion), serine protease activities in skin, residual LEKTI expression and degradation of desmoglein 1/desmocollin 1 in Netherton syndrome-afflicted skin [16,18]. Correlations

between *SPINK5* gene mutations and clinical manifestations have also been demonstrated [19].

Psoriasis

Psoriasis in the neonatal period is exceptional [3]. Only a few cases of congenital erythrodermic psoriasis have been reported [3,20,21]. Clinically, it can resemble ARCI; the distinguishing features between these entities are positive family history, areas of unaffected skin in psoriasis, and ectropion in ichthyoses [20]. Moreover, some patients with congenital psoriasis are positive for the HLA-B17 antigen. Histology can also be helpful. Most cases go on to develop classic erythematous lesions [5].

Immunodeficiency syndromes

Erythroderma may be the first clinical manifestation of a PIDS. Severe extracutaneous manifestations are systematic and usually occur in the first months of life: diarrhoea, failure to thrive, adenopathies and severe infections. In combination, these signs clearly point to PIDS and the neonate should be transferred to a highly specialized unit for subsequent management.

SCID and Graft-Versus-Host Disease (GVHD) from maternal engraftment can occur even during intrauterine development. GVHD is seen mainly in children with a T cell immunodeficiency (SCID) caused by transplacental passage of maternal lymphocytes during intrauterine or postnatal (exchange) transfusions [22,23]. The classic clinical manifestations of materno-foetal GVHD include fever, a morbilliform rash which, in severe reactions, can evolve into erythroderma, eosinophilia and hepatosplenomegaly and lymphadenopathies. In such cases, GVHD occurs within the first 2–3 weeks of life, but may also be present at birth [24]. Alopecia or sparse hairs are frequent, but not specific for PIDS, since they may also be observed in other conditions presenting as neonatal erythroderma [3].

Erythroderma is always observed in patients with Omenn syndrome. Omenn syndrome is a rare autosomal recessive disease, characterized by SCID symptoms and always associated with erythroderma, eosinophilia, hepatosplenomegaly, lymphadenopathies and elevated serum IgE levels [25–28]. While not completely typical, the alopecia universalis experienced by patients with Omenn syndrome is remarkable, and the presence of an extensive inflammatory infiltrate leading to a pachydermal appearance is highly evocative of the diagnosis. The inflammation observed in these patients is believed to be triggered by clonally expanded T cells, which are predominantly of the T(H)2 type. In the absence of proper regulation by other components of the immune system, these abnormal T cells secrete a host of cytokines promoting autoimmune as well as allergic inflammation. These T-cell clones arise in patients with hypomorphic mutations in recombination activating gene (*RAG*) 1 or 2.

Careful analysis of Omenn syndrome mutations therefore suggests that, while SCID can be related to 'null' *RAG* alleles, Omenn syndrome is caused by hypomorphic *RAG* alleles, which permit partial V (D)J recombination activity. Omenn syndrome appears to be a 'leaky' SCID.

Recently, Omenn syndrome was also included in the growing list of other leaky SCIDs with mutations in the RNA component of mitochondrial RNA processing endoribonuclease, adenosine deaminase, IL-2 receptor-gamma, IL-7 receptor alpha, ARTEMIS, and DNA ligase 4. This new information revealed Omenn syndrome to be a distinct inflammatory process that can be associated with genetically diverse leaky SCIDs [29]. An Omenn-like syndrome with early and severe erythroderma has been described related to mutations in *CHD7* in patients with CHARGE syndrome (coloboma, heart defect, atresia chonae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) [30].

Metabolic disorders

Very rarely, neonatal erythroderma can be related to a metabolic disorder. In later infancy, squamous erythematous lesions – often first observed in periorificial areas – and even erythroderma has been observed in cases of severe protein malnutrition (kwashiorkor) or zinc deficiencies, for example.

A metabolic cause must be suspected if the neonate's skin lesions are associated with neurological symptoms (coma). This mainly applies to multiple carboxylase deficiencies [15] or urea cycle disorders (arginosuccinic aciduria, citrullinaemia). Exfoliative erythroderma and alopecia are frequent, but not specific. Chromatography of blood and urinary amino acids and organic acids is of assistance in reaching the diagnosis. As the neurological symptoms related to a serious metabolic disorder (ketoacidosis) can be extremely severe, these babies must be transferred to a highly specialized centre for care.

Congenital cutaneous candidiasis

Congenital cutaneous candidiasis is a very rare cause of neonatal erythroderma. It is caused by ascending infection involving the amnion. Congenital candidiasis is characterized by widely scattered macules, papules and pustules. Individual skin lesions may become confluent before evolving into exfoliative erythroderma. Unlike neonatal candidiasis, which is acquired during passage through the birth canal, the oral cavity and diaper area are usually spared [31]. The course is usually benign but systemic infections have been described, especially in premature infants.

Drugs-related erythroderma

Likewise, drugs-related erythroderma is extremely rare. Although antibiotics such as penicillin, ampicillin,

aminoglycosides and cephalosporins can cause an erythematous maculopapular rash, erythroderma has only been described in neonates with ceftriaxone [32] and vancomycin [33].

Diagnostic approach to neonatal erythroderma

Erythrodermic neonates are frequently misdiagnosed with eczema. A delay in reaching the correct diagnosis can be fatal [3,15]. The differential diagnosis of erythroderma is a multistep procedure involving clinical assessment, knowledge of any relevant family history and a battery of specialized laboratory tests.

Clinical assessment

For collodion babies, the differential diagnosis is virtually restricted to the hereditary ichthyoses. Once the collodion membrane is shed, a skin biopsy must always be taken. Children with congenital ichthyosiform erythroderma should be monitored for hair shaft abnormalities and for associated skeletal, neurologic and ophthalmologic abnormalities.

Increased skin tenderness, irritability and fever should prompt a search for signs of congenital infections. Skin blistering is suggestive of epidermolytic hyperkeratosis, SSSS and mastocytosis. Darier's sign is positive in mastocytosis. The Nikolsky sign – when the application of pressure extends the blister under the skin – is positive in SSSS. Early and severe erythroderma associated with alopecia and hyper-IgE may be suggestive of both Netherton syndrome and immunodeficiency. Neonates with erythroderma, alopecia and coma should be tested for an inherited biotin metabolism disorder. PIDS must be suspected in cases of severe erythroderma, diarrhoea, severe failure to thrive, alopecia, infectious complications, no or only partial improvement under topical corticosteroids or suggestive histological findings [3]. Early and severe pruritic erythroderma with skin induration resulting in exaggerated skin folds; severe alopecia (head hair, eyelashes and eyebrows); widespread lymphadenopathies and deep systemic infection caused by *Candida* or rare or opportunistic microorganisms are highly suggestive of Omenn syndrome [3]. Skin biopsies are helpful when a PIDS is suspected [7••].

Histopathology

A skin biopsy is essential. It has recently been shown that an early skin biopsy is valuable in the aetiological diagnosis of early erythroderma. In particular, accurate distinction of the most severe diseases, immunodeficiency and Netherton syndrome, is possible using histological and immunohistochemical means (LEKTI) [7••]. The blistering disorders, epidermolytic hyperkeratosis and staphylococcal epidermolysis, are also easy to diagnose.

Immunodeficiencies, including GVHD and Omenn syndrome, usually include widespread epidermal and/or adnexal epithelial keratinocyte necrosis and a mild to severe lymphocytic dermal infiltrate with epidermal and adnexal exocytosis. No significant histological differences can be found between Omenn syndrome and GVHD associated with other PIDS, most often SCID. It has been said that dermal eosinophils and highly lymphocytic infiltration are suggestive of Omenn syndrome [34], but some Omenn syndrome cases do not present with any eosinophils while some GVHDs may include a misleading heavy lymphocytic reaction all over the dermis and occasionally eosinophils. In addition, some PIDS-related erythrodermas can present with an intense lymphocytic dermal infiltrate located only in the upper and mid-dermis, especially around the adnexae, with spongiosis rather than any necrotic changes. When a spongiotic reaction combined with a highly dermal lymphocytic inflammation at biopsy is observed, PIDS must be suspected even when no necrotic cells are detected [7**] (Fig. 1).

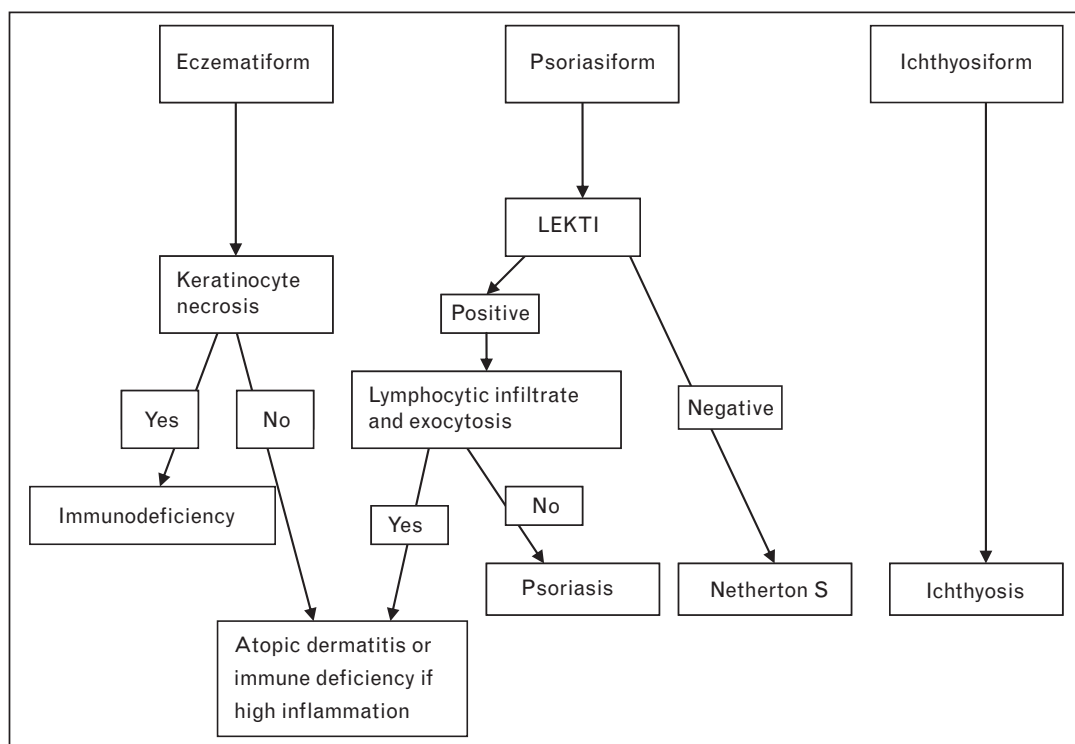
Netherton syndrome is diagnosed when the histological findings are psoriasiform epidermal hyperplasia with parakeratosis but no neutrophils, mild upper dermal inflammation and, in addition, no LEKTI immunostaining. Before the advent of LEKTI antibody (2000),

Netherton syndrome was often misdiagnosed as psoriasis or chronic atopic dermatitis [7**].

ARCI is diagnosed when the biopsy shows an ichthyosiform epidermal reaction pattern, that is thick and compact hyperkeratosis leading to ostial plugs, normal or thickened granulosus layer and absence of inflammation [7**]. Development of new tools for a rapid immunopathological diagnosis of ichthyoses is under evaluation. Epidermolytic ichthyosis is always histologically distinctive: epidermolytic hyperkeratosis with intracytoplasmic vacuolation and keratin inclusions within the spinous and granular layer. However, if an early biopsy is taken, hyperkeratosis may be absent and distinguishing it from SSSS may be difficult, particularly if only the roof of the blister is analysed. The entire skin sample, including both roof and floor of the blister, must therefore be analysed. Histological diagnosis of SSSS is usually easy: bullous lesions develop in the superficial layers of the epidermis and small foci of acantholysis are occasionally seen.

The histological features of psoriasis are often less specific when an early biopsy is taken even if, in some cases, biopsy can be helpful in ruling out other most severe causes. Likewise, metabolic disorders lack specificity on a histological level. With mastocytosis, a high

Figure 1 Decision-making tree for scaling and exfoliative nonbullous erythrodermas skin biopsy



Reproduced from [7**].

number of mast cells are commonly observed, mainly in the upper dermis.

Management of children with neonatal erythroderma

Erythroderma is a potentially life-threatening condition and children are at risk of hypernatraemic dehydration, hyperpyrexia, hypoalbuminaemia and sepsis. Topical application of emollients will hydrate the skin and prevent fissuring [15]. Cutaneous infections caused by *Staphylococcus* spp., or, more rarely, *Gram-negative bacilli* are common and may result in septicaemia infections. Repeated bacteriological testing and prophylactic topical antiseptic treatments are appropriate in such cases. Only immunodeficient patients have deep visceral or opportunistic infections and cutaneous fungal infections (*Candida*) [3]. The treatment of erythroderma is often limited to local care with careful topical steroid therapy or emollients, whose efficacy varies depending on the underlying cause. The aetiological treatment has to be managed in specialized units.

Conclusion

Neonatal erythroderma is a potentially life-threatening condition and its clinical care and prognosis are related to its underlying causes. It is usually difficult to reach an aetiological diagnosis on the basis of clinical information alone and additional measures, especially skin biopsy, may be very helpful.

References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 552).

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