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Guidance for assessment of erythroderma in neonates and infants for the pediatric immunologist

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Abstract

Neonatal and infantile erythroderma (NIE) represent the common clinical phenotype of heterogeneous diseases ranging from benign and transient skin conditions to fatal multiorgan disorders. NIE regularly demands a comprehensive diagnostic workup in a multiprofessional setting, especially if newborns and young infants with the disease develop a failure to thrive and concomitant infectious, neurological or metabolic complications. By obtaining a detailed medical history and performing a thorough clinical examination, targeted diagnostic steps can be scheduled for most affected children. If NIE occurs in the early neonatal period, lesional skin biopsy and histology are often mandatory. Likewise, if monogenetic skin or immunological diseases are suspected, genetic testing with customized panels of potentially underlying genes is mandatory. Of note, if acute symptoms such as severe infections, metabolic acidosis or seizures occur, rapid microbiological and metabolic investigations are warranted to rule out immunodeficiency and inborn errors of metabolism.

Key words: neonate, infant, erythroderma, congenital ichthyosis, immunodeficiency

Abbreviations:

AD	atopic dermatitis
ARCI	autosomal-recessive congenital ichthyoses
CCC	congenital cutaneous candidiasis
CDS	Chanarin-Dorfman syndrome
CM	collodion membrane
DGS	DiGeorge syndrome
DSG1	desmoglein 1
DSP	desmoplakin
EI	epidermolytic ichthyosis
ET	exfoliative toxins
GVHD	graft-versus-host-disease
HSD	holocarboxylase synthetase deficiency
IgE	immunoglobulin E
IPEX	immune dysregulation, polyendocrinopathy, enteropathy, X-linked
KRT1	keratin 1
KRT10	keratin 10
LEKTI	lymphoepithelial Kazal-type 5 related protease inhibitor
MMA	methylmalonic acidemias
NIE	neonatal and infantile erythroderma
OS	Omenn syndrome
PID	primary immunodeficiency
PRR	pityriasis rubra pilaris
PSS-B	peeling skin syndrome type B
SAM	severe atopy with metabolic wasting
SCID	severe combined immunodeficiency
sIgE	specific IgE
SLS	Sjögren-Larsson syndrome
WAS	Wiskott-Aldrich syndrome

INTRODUCTION

Erythroderma is defined as a generalized reddening of the skin covering more than 90% of the body surface area. Especially in newborns and young children it is regularly associated with dry, scaling skin often referred to as ichthyosiform erythroderma. Widely believed to be a rare phenomenon, neonatal and infantile erythroderma (NIE) can be caused by a broad spectrum of underlying illnesses and may be the presenting sign of both benign skin diseases and fatal systemic disorders ¹⁻⁶. Accordingly, its mortality rate has been estimated at up to 25% depending on associated conditions and, perhaps even more importantly, the degree of epidermal disruption. As the result of an impaired skin barrier, affected neonates and infants are threatened by transcutaneous fluid and energy loss, hypothermia, hypernatremic dehydration and viral, bacterial or fungal infections ⁷.

Due to NIE's supposed phenotype of "severe eczema", paediatricians and particularly paediatric allergists are often the first specialized health care providers to be consulted by primary care physicians or caregivers of "red scaly babies". Therefore, paediatric allergists need to be familiar with benign, non-syndromic forms as well as potentially severe, syndromic NIE subtypes to avoid a critical delay in diagnosis and treatment.

This review focuses on clinical clues and additional diagnostic steps that are valuable in the differentiation of conditions regularly associated with NIE. For practical reasons, these disorders can be broadly classified into monogenetic skin diseases (genodermatoses), infections, transient erythematous squamous dermatoses, immunologic disorders and inborn errors of metabolism (**TABLE 1**).

1. DIFFERENTIAL DIAGNOSES OF THE RED SCALY BABY

Monogenetic skin diseases

Whenever erythroderma has its onset immediately after birth or in the early neonatal period, mendelian single-gene disorders of the skin, also designated as genodermatoses, should be suspected. As a next step, based on a detailed medical history (e. g. consanguinity, positive family history for genodermatoses), a thorough clinical examination will yield valuable additional clues such as failure to thrive, anomalies of the skin appendages or extracutaneous pathologies. In many patients, lesional skin biopsy and molecular genetic testing become necessary to determine the causing mutation.

Congenital Ichthyoses

This heterogenous group of mendelian disorders of skin cornification comprises non-syndromic ichthyoses with exclusively cutaneous symptoms and syndromic ichthyoses linked to metabolic, neurologic, ophthalmologic or other abnormalities of varying severity. Comprehensive national and European guidelines of care for patients with congenital ichthyoses have only very recently been published ^{8,9}.

Non-syndromic ichthyoses

Non-bullous ichthyosiform erythroderma

Non-bullous congenital ichthyosiform erythroderma is a common phenotype of autosomal-recessive congenital ichthyoses (ARCI) which are currently known to rely on mutations in at least 10 different genes (TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4, SDR9C7, CERS3, PNPLA1, SLC27A4) ¹⁰. It should be expected whenever neonates are enveloped by a tight, thickened skin layer directly after birth, the so-called collodion membrane (CM). CM precedes non-bullous congenital ichthyosiform erythroderma in about 90% of cases and is usually shed within the following 2-3 weeks of life.

Afterwards, affected children show erythroderma (**FIGURE 1A**) and, in the further course, ubiquitous scaling of various degree, but without blistering or skin fragility (**FIGURE 1B**). Typical cutaneous complications of neonates and infants with the collodion baby phenotype and ensuing ichthyosiform erythroderma consist of ectropion, eclabium or obstruction of the external auditory canals by skin debris ¹¹.

Epidermolytic ichthyosis

Epidermolytic ichthyosis (EI) is caused by mutations in genes encoding the keratins 1 and 10 (KRT1, KRT10) and is usually inherited in an autosomal-dominant fashion. In rare instances, autosomal-recessive inheritance has been described relying on a limited set of mutations mostly located in the central region of KRT10 ¹². As the main clinical presentation, children with EI show fragile skin and exfoliation directly postnatally revealing underlying erythroderma (**FIGURE 1C**) accompanied by ichthyosiform erythroderma of varying severity in the following months of life. As a clue to the underlying mutation, thickened skin of the palms and soles (palmoplantar hyperkeratosis) is mainly observed in children with KRT1 and only very rarely with KRT10 mutations. Due to widespread erosions, other skin disorders of neonatal onset and enhanced skin fragility, especially hereditary epidermolysis bullosa and staphylococcal scalded skin syndrome (see below) need to be ruled out by skin biopsy ¹³.

Peeling Skin Syndrome Type B

Peeling skin syndrome type B (PSS-B), also designated as the inflammatory type of PSS, is caused by loss-of-function-mutations in or complete deletions of the corneodesmosin gene (CDSN). These lead to intercellular splitting at the upper epidermal granular layers and, clinically, to very superficial exfoliation of the epidermis (**FIGURE 1D**) ¹⁴. As a result, neonates suffer from pronounced ichthyosiform erythroderma, various degrees of skin fragility and often debilitating pruritus. As in other disorders of altered epidermal homeostasis, such as Netherton syndrome or SAM syndrome

(see below), children with PSS-B undergo transcutaneous allergen-specific sensitization. Besides marked eosinophilia, this is associated with elevated total and allergen-specific IgE serum levels and, consequently, a highly elevated risk of food anaphylaxis¹⁵.

Syndromic congenital ichthyoses

Sjögren-Larsson syndrome

One of the most severe syndromic ichthyoses, the autosomal recessive Sjögren-Larsson syndrome (SLS), is caused by mutations in the ALDH3A2 gene which interfere with the expression of fatty aldehyde dehydrogenase. This leads to an impaired lipid metabolism resulting in incurable neurocutaneous disease with the pathognomonic clinical picture of ichthyosiform erythroderma, psychomotor retardation, spastic di- or tetraplegia and ophthalmic complications (e. g. photophobia, impairment of visual acuity). Eventually, yellowish lichenification and hyperkeratosis develops which is most pronounced in flexural regions and the neck area (**FIGURE 1E**). Infants with SLS also suffer from refractory pruritus partially due to an elevation of proinflammatory leukotriene B4 that can be detected in urine samples of SLS patients^{16,17}. A definitive diagnosis of SLS is established by targeted sequencing of the ALDH3A2 gene.

Chanarin-Dorfman syndrome

Chanarin–Dorfman syndrome (CDS) represents an autosomal recessive neutral lipid storage disease with ichthyosis. Because of mutations in the CGI85 (ABDH5) gene, neutral lipids are accumulated in multiple organs. As a valuable screening sign, lipid-containing vacuoles are also present in granulocytes or monocytes and can be visualized in a peripheral blood smear upon Pappenheim staining (Jordan’s anomaly). Clinically, unspecific ichthyosiform erythroderma is preceded by a collodion membrane in a minority of neonates with CDS. As the most relevant extracutaneous feature, liver disease occurs in as much as 70% of patients who, therefore, require regular

hepatologic evaluations. This is highlighted by a recent case series of adolescent and adult CDS patients where one third of individuals deceased due to hepatic lipid infiltration and ensuing organ failure^{18,19}.

Netherton syndrome

Autosomal-recessive Netherton syndrome is observed in newborns harboring mutations in the SPINK 5 gene which lead to an inactivation of the lymphoepithelial Kazal-type 5 related protease inhibitor (LEKTI). LEKTI-deficiency entails severe disturbances in epidermal homeostasis with marked neonatal erythroderma, debilitating pruritus, recurrent skin infections and persistent skin inflammation (**FIGURE 1F**). Interestingly, besides high total serum IgE levels, these immunologic processes are characterized by systemic T-cell activation, Th-17-/Th-22-polarization in peripheral blood samples and upregulation of Th-17-pathway genes in skin specimens of patients with Netherton syndrome^{20,21}.

Consequently, affected neonates regularly develop a failure to thrive and additional systemic sequelae of critical skin barrier impairment. Especially hypothermia, hypernatremic dehydration and septicemia lead to a mortality rate of up to 20% during the first year of life which, therefore, is often referred to as the “stormy weather period” of children with Netherton syndrome. Similarly, most infants with this disease are at high risk of immediate type allergy against nutritive allergens and full-blown food anaphylaxis²². Thus, a thorough paediatric allergological workup including component-resolved IgE testing and, potentially, oral food challenges is warranted in every affected child.

As a valuable clue to clinical diagnosis, scalp hair remains short (“spiky hair”) and characteristic hair shaft anomalies (trichorrhexis invaginata, “bamboo hair”) can be demonstrated in 50% to 70% of scalp, eyebrow or eyelash hairs upon dermoscopy ¹⁵. In contrast, characteristic polycyclic, serpiginous plaques with erythematous borders and double-edged scaling (ichthyosis linearis circumflexa) are usually not encountered in early childhood. Finally, skin biopsy with immunohistochemical staining demonstrates absent LEKTI expression whereas molecular genetic analysis reveals the disease-defining SPINK 5 mutation.

Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome

Although currently not classified as an ichthyosis, SAM syndrome represents an important differential diagnosis of both Netherton syndrome and PSS-B. SAM syndrome is caused by impaired cell adhesion and aberrant epidermal differentiation due to homozygous mutations in the desmoglein 1-encoding (DSG1) gene and, in even rarer cases, the desmoplakin-encoding gene (DSP) ^{23,24}. As in Netherton syndrome and PSS-B, nearly all children suffer from ichthyosiform erythroderma, multiple food allergies and a severe failure to thrive ¹⁵. However, SAM syndrome can be differentiated clinically by palmoplantar keratoderma and genetically by DSG1- and DSP-sequencing. Recently, SAM syndrome has revealed extensive inter- and intra-familial phenotypic heterogeneity with some patients lacking erythroderma, allergic sensitization or failure to thrive ²⁵.

Infectious diseases

Staphylococcal scalded skin syndrome (SSSS)

SSSS is also designated as exfoliative dermatitis or Ritter’s disease and results from infection with phage group 2 Staphylococcus aureus. These bacteria synthesize exfoliative toxins (ET) A and B causing superficial cleavage of the epidermis by proteolysis of the desmosomal adhesion protein desmoglein I. Often following minor staphylococcal skin infection, SSSS manifests as wide-spread

erythema of the face and large skin folds which may coalesce into erythroderma. Subsequently, erythematous skin lesions become very tender and, finally, flaccid and rapidly eroding blisters appear (**FIGURE 1G**) while the mucous membranes are spared.

Fortunately, recent reports suggest that in-hospital mortality of childhood SSSS is clearly lower than previously reported (0.33% ²⁶). Still, affected neonates and infants usually need to be hospitalized to monitor for extracutaneous symptoms such as fever and a decline of their general condition ²⁷. To differentiate SSSS from other exfoliative skin diseases such as hereditary epidermolysis bullosa or epidermolytic ichthyosis, a skin biopsy is mandatory in clinically uncertain cases ²⁸. In addition, PCR-based screening of the ETA- and ETB-encoding genes in isolated *Staphylococcus aureus* strains can be helpful.

Congenital cutaneous candidiasis (CCC)

CCC manifests in the first days of life as a generalized maculopapular and sometimes also pustular rash often accompanied by paronychia, whereas intraoral involvement is not typically present. In severe cases, this rash may progress into exfoliative erythroderma. Whereas term infants usually present with a mild phenotype, very low birth weight infants (< 1000 g) develop invasive candida infection in 66% of cases with a fatal course in up to 40% ²⁹. Yet, if empiric antimycotic treatment with a systemic agent is initiated timely and continued for at least 14 days, the survival rate of infants with CCC can be increased dramatically ³⁰.

Benign erythematous squamous disorders

Infantile seborrheic dermatitis and atopic dermatitis

Infantile seborrheic dermatitis normally has an early onset before two months of life and is encountered in 70% of infants younger than 3 months of age ³¹. Typically, affected children reveal

transient inflammatory skin disease with sharply delineated erythematous macules and papules mainly on the head and in skin creases. These lesions frequently display yellowish, greasy crusts and may appear as an adhesive “cradle cap” in the scalp region while dryness of skin is not a main feature. In severe cases, seborrheic dermatitis may be refractory to topical anti-inflammatory and anti-fungal treatments. This may lead to erythroderma with involvement of the diaper area, which is in clear contrast to atopic dermatitis where the diaper area is usually spared.

Atopic dermatitis (AD) is a chronic inflammatory, highly pruritic skin disease that affects up to 30% of children in industrialized countries and usually has its onset after the second month of life. Yet, young infants may already suffer from widespread erythematous macules, papules and plaques with fine scaling evolving into erythroderma. In infants, the scalp and the facial region as well as the extensor surfaces of the extremities are affected whereas the anogenital region is usually spared. In contrast to more serious NIE causes, extracutaneous manifestations or a failure to thrive are rare in infants with AD. Moreover, persisting alopecia or adnexal anomalies are usually not encountered. Likewise, highly elevated total serum IgE levels are unspecific and may also be associated with more serious disorders such as Omenn syndrome or Wiskott-Aldrich syndrome (see below).

Psoriasis and pityriasis rubra pilaris

Congenital and neonatal psoriasis are very rare phenomena. Still, about one third of children suffering from plaque psoriasis and nearly half of children with pustular psoriasis develop symptoms during the first year of life ³². Infantile psoriasis often starts with a refractory, well demarcated diaper rash and may disseminate turning into generalized psoriasiform plaques (**FIGURE 1H**). As the non-pustular phenotype of psoriatic erythroderma is not easily distinguished from e. g. Netherton syndrome or severe AD, lesional skin biopsy may become necessary.

Pityriasis rubra pilaris (PRP) most probably corresponds to a polyetiologic group of erythemosquamous diseases and may occur in neonates and young infants, albeit very rarely. Of note, familial PRP should be suspected in neonatal-onset PRP which is associated with activating mutations in the gene encoding CARD14, a known activator of nuclear factor kappa B signaling³³. Typical clinical signs of PRP are follicular hyperkeratoses and wide-spread, coalescing, scaling erythema with islands of spared skin ("nappes claires") (**FIGURE 1I**). Characteristically, affected infants also show palmoplantar erythema and hyperkeratosis.

Primary immunodeficiencies (PID)

Omenn syndrome

Omenn syndrome (OS) is an autosomal recessive severe combined immunodeficiency (SCID) often due to mutations in the recombination activating genes 1 and 2 (RAG-1/RAG-2), the Interleukin-7R α chain or the non-homologous end-joining factor Artemis. Besides severe NIE, alopecia and debilitating pruritus, affected neonates reveal progressing lymphadenopathy and hepatosplenomegaly as well as severe infections and profuse diarrhea entailing a life-threatening failure to thrive³⁴. In addition to extremely elevated serum IgE levels and eosinophilia, laboratory investigations demonstrate oligoclonal expansion of autoreactive T-cells and a lack of circulating B-cells. If OS is suspected, patients depend upon rapid referral to paediatric immunology, because bone marrow- or umbilical cord blood-derived hematopoietic stem cell transplantation are the only viable therapeutic options³⁵. Intriguingly, recent lentivirus-based gene therapy investigations in a murine model of OS have yielded promising results raising hopes for future causal treatments³⁶.

Graft-versus-host disease

In a significant number of children with T-cell deficient SCID, maternal T cells may be found in peripheral blood inducing graft-versus-host-disease (GVHD) in more than half of these cases ³⁷.

Clinically, neonatal and infantile GVHD can manifest with alopecia of both scalp and eyebrow hairs, pruritus and erythroderma often affecting the palms and soles, too. If suspicion arises, a comprehensive immunological workup including differential blood counts, lymphocyte phenotyping and chimerism analysis should be performed. Upon analysis of the affected baby's peripheral blood, the identification of accessory HLA haplotypes, high numbers of maternal lymphocytes or an XX genotype in a male neonate are highly suggestive of GVHD.

Other primary immunodeficiencies

Further PIDs are occasionally associated with NIE. For example, patients with hemizygous deletion of chromosome 22q11.2 and associated *DiGeorge syndrome* (DGS) are known to also show eczematous lesions closely resembling those of AD. Yet, generalized eczematous eruptions or even erythroderma have only very rarely been observed in newborns or infants with DGS ^{38,39}.

Wiskott-Aldrich-syndrome (WAS) represents an X-linked immunodeficiency with thrombocytopenia, recurrent infections and secondary autoimmune disorders. It also goes along with persisting eczematous dermatitis in nearly 90% of affected patients. However, as in DGS, only very few WAS cases have been reported to present with neonatal erythroderma. Inflammatory skin lesions and recurrent cutaneous infections, petechiae and ecchymosis in a male neonate or infant should therefore prompt further diagnostic tests, especially full blood count, peripheral blood smear and sequencing of the underlying WAS gene ⁴⁰.

The Immune dysregulation, polyendocrinopathy, enteropathy, X-linked or *IPEX syndrome* is caused by mutations in the FOXP3 gene encoding an essential transcription factor required for maintenance of thymus-derived regulatory T cells ⁴¹. At disease-onset, failure to thrive and the classical clinical triad of diabetes, enteropathy and eczema is most frequently encountered. Additionally, IPEX syndrome has been linked to food allergy⁴². Therapeutic options consist of immunosuppressive therapy, especially rapamycin, and hematopoietic stem cell transplantation ⁴³.

Inborn errors of metabolism

Holocarboxylase synthetase deficiency (HSD) is a very rare autosomal recessive disease arising from a defect in biotin metabolism. HSD's main clinical symptoms include lethargy, seizures and severe metabolic acidosis. Infants with the disease present with perioral, periorbital and perineal lesions and may also have eczematous erythroderma and alopecia. If clinically suspected in neonates and corroborated by urine organic acid analysis, HSD should lead to neonatal intensive care and biotin substitution ⁴⁴.

Methylmalonic acidemias (MMA) represent various disorders of methylmalonate and cobalamin metabolism. Like HSD, the infantile, non-Vitamin B12-responsive subtype of MMA is accompanied by severe neurologic symptoms, respiratory distress and metabolic acidosis. Likewise, MMA-associated skin lesions are initially accentuated in the periorificial regions and may turn into exfoliative erythroderma in untreated patients ^{45,46}.

2. DIAGNOSTIC WORK-UP OF NEONATAL AND INFANTILE ERYTHRODERMA

In the quest for diseases causing ichthyosiform erythroderma in very young children, a structured diagnostic approach (**FIGURE 10**) and the following five key questions are frequently helpful in daily clinical practice:

- Has wide-spread erythema with dry skin been present from birth?
- Has the affected neonate or infant developed failure to thrive?
- Does the child reveal extracutaneous complications, e. g. neuropathy, enteropathy or hepatopathy?
- Have severe and/or atypical infections of the skin or other organs been observed?
- Have bullous skin changes or pathologies of the skin appendages occurred?

Irrespective of its suspected cause, NIE should prompt a full paediatric and dermatologic clinical examination. Additional capillary blood gas analyses and serum electrolytes in combination with a limited number of other screening tests such as differential blood count and total serum IgE levels are advisable in many patients. In exfoliative erythrodermas or blistering disease, a skin biopsy is mandatory to locate the cleavage level and to differentiate SSSS from epidermolytic ichthyosis, hereditary epidermolysis bullosa or PSS-B.

However, if physical examination and medical history are consistent with psoriasis, atopic dermatitis or seborrheic dermatitis, benign erythemasquamous disorders can be suspected and treated without further laboratory or histological analyses. Still, if there is insufficient response to conventional therapy, clinical clues to alternative diagnoses should be actively sought, i. e. pustules in congenital candidiasis or periorificial accentuation of skin lesions in metabolic disorders.

Neonatal erythroderma that is preceded by a collodion membrane often hints at non-syndromal congenital ichthyoses. In these cases, definitive diagnosis is best established by skin biopsy and tailored gene panels that are readily available in specialized genetic centres.

Red flags indicating an urgent need for rapid diagnostic and therapeutic interventions are a failure to thrive with or without atypical, severe infections and/or neurological symptoms. In this situation, a blood gas analysis proving metabolic acidosis with concomitant hypoglycemia and hyperammonemia represents a metabolic emergency. Affected patients depend upon a swift referral to specialized centres for substitution therapy or dietary counselling and further diagnostic testing (e. g. organic acids in urine, holocarboxylase-synthetase activity in cultured fibroblasts).

In neonates with the inflammatory phenotype of NIE accompanied by persistent and often refractory pruritus, Netherton syndrome is characterized by hair shaft dermoscopy (trichorrhexis invaginata) and immunohistochemistry of lesional skin biopsies (absent epidermal LEKTI expression). In contrast, PSS-B patients do not show typical hair shaft anomalies and histology reveals subcorneal cleavage while LEKTI staining is positive.

Especially if a clearly elevated serum IgE level is observed in very young children with erythroderma and failure to thrive, lymphocyte phenotyping and possibly further immunological assays are warranted. In patients with B lymphocytopenia, mutation analyses should be obtained to rule out Omenn syndrome while a chimerism analysis should be performed to detect engraftment of maternal T lymphocytes in children with T-cell deficient SCID.

3. CONCLUSION

Neonatal or infantile erythroderma represents a polyetiologic phenotype linked to potentially fatal disorders of various organ systems. Thus, the ensuing differential diagnostic workup should be multiprofessional including neonatologists, specialized nurses, geneticists, paediatric dermatologists or immunologists and other specialties as required by the clinical circumstances. Particularly newborns and young infants with a failure to thrive and concomitant infectious, neurological or

metabolic disease depend upon targeted diagnostic steps to allow for timely symptomatic or causal treatment. A thoughtful and stepwise diagnostic approach leads to a straightforward diagnosis in most cases.

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TABLES

Table 1 Differential diagnoses regularly associated with neonatal or infantile erythroderma

Disease	Clinical clues	Confirming diagnostic steps
Non-syndromic congenital ichthyoses		
Non-bullous ichthyosiform erythroderma	- Collodion membrane - Ectropium, eclabium - Lamellar scaling	- Gene panel analysis (TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4, SDR9C7, CERS3, PNPLA1, SLC27A4)
Epidermolytic ichthyosis	- Skin blistering - Palmoplantar Hyperkeratosis	- Skin biopsy - Targeted sequencing KRT1, KRT10 gene
Peeling skin syndrome type B	- Generalized superficial skin peeling - Severe pruritus - Food allergy / anaphylaxis	- Skin biopsy - Targeted sequencing CDSN gene
Syndromic congenital ichthyoses		
Sjögren-Larsson syndrome	- Yellowish hyperkeratosis - Psychomotor retardation - Spastic di-/tetraplegia	- Comprehensive neuropsychiatric evaluation - Targeted sequencing ALDH3A2 gene
Chanarin-Dorfman syndrome	- Collodion membrane - Hepatopathy	- Granulocyte microscopy - Targeted sequencing CGI85 (ABDH5) gene
Netherton syndrome	- Severe inflammatory erythroderma - Debilitating pruritus - Hair shaft anomalies	- Hair shaft dermoscopy - Immunohistochemistry - Targeted sequencing SPINK5 gene
Infections		
Staphylococcal scalded skin syndrome	- Omphalitis, impetigo etc. - Erythema beginning in skin folds - Superficial skin exfoliation	- Skin biopsy - PCR screening of toxin genes in <i>S. aureus</i> strains
Congenital cutaneous candidiasis	- Postpartal pustular rash - Paronychia	- Microbiological swabs
Benign erythematous skin disorders		
Seborrheic dermatitis	- Early onset before 2 months of life - Involvement of flexural areas, "cradle cap"	- Clinical diagnosis - Skin biopsy in clinically atypical cases
Atopic dermatitis	- Onset > 3 months of life - Diaper area usually not involved	
Infantile psoriasis	- Sharply delineated plaques	

	- Diaper area typically involved	
Infantile pityriasis rubra pilaris	- Large, confluent plaques - Islands of spared skin (“nappes claires”)	
Primary immunodeficiencies (PID)		
Omenn syndrome	- Severe failure to thrive - Recurrent atypical / severe infections - Hepatosplenomegaly, lymphadenopathy	- Lymphocyte phenotyping - Gene panel analysis - Evaluation in PID referral center
Graft-versus-host disease	- Severe failure to thrive - Recurrent atypical / severe infections - Alopecia	- Lymphocyte phenotyping - Chimerism analysis - Evaluation in PID referral center
Wiskott-Aldrich syndrome	- Eczematous dermatitis - Petechiae, ecchymosis - Thrombocytopenia	- Peripheral blood count - Targeted sequencing of WAS gene - Evaluation in PID referral center
IPEX syndrome	- Failure to thrive - Diabetes, enteropathy	- Endocrinological and GIT work-up - Targeted sequencing of FOXP3 gene - Evaluation in PID referral center
Inborn errors of metabolism		
Holocarboxylase synthetase (HCS) deficiency	- Lethargy, seizures - Metabolic acidosis	- Newborn screening, blood gas analysis - Urine organic and amino acid analysis - HCS activity in leukocytes, genetic testing
Methylmalonic acidemia	- Neurologic symptoms, respiratory distress - Metabolic acidosis	- Newborn screening, blood gas analysis - Urine organic / amino acid analysis, genetic testing

FIGURE LEGENDS

Figure 1A: Non-syndromal autosomal recessive ichthyosis, neonatal stage: non-bullous erythroderma with a partially shed collodion membrane

Figure 1B: Non-syndromal autosomal recessive ichthyosis, infantile stage: non-bullous erythroderma with ubiquitous lamellar scaling

Figure 1C: Epidermolytic ichthyosis: extensive skin exfoliation with underlying erythema. Note bacterial superinfection in both inguinal areas.

Figure 1D: Peeling skin syndrome type B: marked erythema, fragile skin and superficial cutaneous peeling

Figure 1E: Sjögren-Larsson syndrome: ichthyosiform erythroderma and grey-yellowish hyperkeratosis in the neck area

Figure 1F: Netherton syndrome: severe, generalized inflammatory skin disease with erythroderma and debilitating pruritus

Figure 1G: Staphylococcal scalded skin syndrome: superficial blistering and erythroderma

Figure 1H: Infantile psoriasis: coalescing annular erythematous plaques on the trunk and diaper area

Figure 1I: Infantile pityriasis rubra pilaris: generalized confluent erythematous papules and plaques with islands of spared skin (“nappes claires”)

Written informed consent to the publication of these photos was obtained by the children’s caregivers.

Figure 10: Clinical diagnostic approach in neonates and infants with erythroderma (A) without or (B) with accompanying extracutaneous disorders (black arrows designate confirmatory diagnostic steps displayed in **TABLE 1**)













