Severe atopic dermatitis in early infancy: characteristics, challenges and new perspectives in clinical practice

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MINIREVIEW

Severe atopic dermatitis in early infancy: characteristics, challenges and new perspectives in clinical practice

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Summary
Atopic dermatitis (AD) is the most common skin disease in infants and children with a prevalence of 10% in the first two years of life. In this age group up to 15% are severely affected. "Children are not little adults" - this applies in particular to infants with severe atopic dermatitis. Age-specific clinical aspects (psychosocial, neurocognitive, morphological) of the disease require an adjusted disease management. Considering recent approval of systemic treatment options, early identification of infants and children with severe and early persistent disease is of particular importance also in view of possible prevention of atopic comorbidity. As several inborn errors of immunity (IEI) share features of the atopic phenotype, it is essential for clinicians to distinguish signs of immunodeficiency from severe AD. Here, we describe a practical approach on the basis of clinical history and key dermatological and laboratory findings. Furthermore, this paper is aimed at providing an update on general management of severe AD in early infancy, including recommendations for systemic treatment.

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic skin disease in children. The condition is characterized by a genetic dysfunction of the skin barrier with increased transdermal water loss, immune dysregulation, and decreased diversity of the skin microbiome (dysbiosis). External factors such as irritants, allergens, or microorganisms may have an additional impact on the pathological immune response of the skin which is mainly effected by Th2 cells and their key mediators IL-4, IL-5, and IL-13.[1]

In 85% of cases, atopic dermatitis appears within the first five years of life, frequently as early as two to three months of age.[2] In Germany, about 10% of infants are affected, 15% of these severely.[3]

The individual course of the disease cannot be predicted with certainty at this early phase, but some predictive factors for persistent disease are known. These include a positive family history, filaggrin mutation, first appearance within the first two years of life, and severe disease. Other factors associated with an unfavorable prognosis are concomitant type-1 sensitization, increased total IgE, and wheezing (a sign of bronchial obstruction) in early childhood.[4–7]

Identifying infants and toddlers with a high risk for severe and chronic disease is important in view of new therapeutic options, both for management of the disease and for possible prevention of comorbidities.[8]

HOW ATOPIC DERMATITIS IMPACTS QUALITY OF LIFE, SLEEP, AND NEUROCOGNITIVE DEVELOPMENT IN YOUNG CHILDREN

Atopic dermatitis is a severe burden for patients at any age. Young children (infants and toddlers) are, however, affected during a particularly sensitive phase of their development.[9] Pruritus and a burning sensation on the skin are the main causes of suffering in AD patients. They lead to decreased

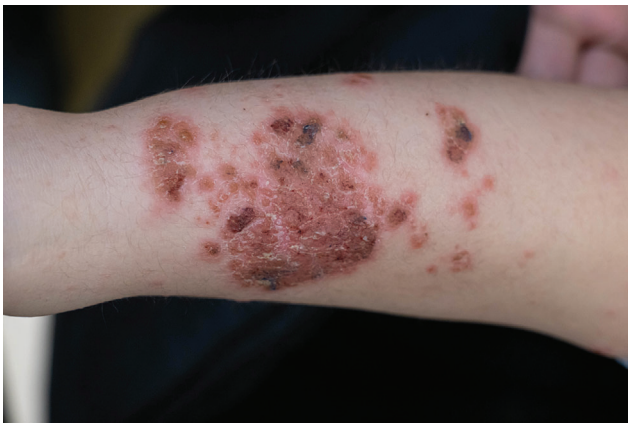

FIGURE 1 Atopic dermatitis, nummular type: infiltrated erythematous and weepy patches.

sleep duration and sleep quality and also affect concentration, memory, and stress response.[9]

More than 60% of young children affected by AD have relevant sleep impairment caused by eczema.[10–14] Due to impaired sleep architecture and decreased sleep efficiency, children and adolescents with atopic dermatitis suffer from a measurable impairment of their mental state during the day.[15,16]

In addition, functional impairment (for example when the hands are affected) or paresthesia may have a negative impact on psychomotor development in infants and toddlers with uncontrolled atopic dermatitis. This is particularly relevant for young children with pronounced affection of the limbs including the hands and feet (Figure 1).

Data from the GINIplus and LISAplus studies show an increased incidence of emotional and behavioral problems in ten-year-old children who were affected by atopic dermatitis within the first two years of life, even if the disease had resolved in the meantime.[17,18] Epidemiological studies world-wide show an association between atopic dermatitis and attention deficit hyperactivity disorder (ADHS) in school-age children. Odds ratios increase with the degree of sleep disturbance.[19,20] Severely affected children also have higher rates of absence from kindergarten.[21]

HOW EARLY-CHILDHOOD ATOPIC DERMATITIS IMPACTS FAMILY ENVIRONMENT

Atopic dermatitis affects patients' sleep and general well-being, but also their nutrition, clothing, and social participation. It demands temporal, financial, and emotional resources and thus always impacts family life.[21–25]

The earlier the disease appears, the more intense are also the effects on the patient's direct environment (parents, siblings). This concept has been termed as "The Greater Patient" and incorporated into clinical research, e.g. in form of adapted quesionnaires.[26,27]

It is known that not only children with this skin disease but also a majority of parents and siblings regularly suffer from impaired sleep.[28]

Interviews with parents (of children with an average age of five years) showed an association between parental burden of disease and children's severity of eczema.[29] More than 50% of parents stated that they wake up more than two times a night to care for their child with atopic dermatitis. One-third of parents said that the disease influences their further family planning.[29] A majority of parents also reported an impact on their jobs due to absences, reduced work times, or delayed return to work.[29]

AGE-SPECIFIC ASPECTS OF MANIFESTATION AND PROVOCATION FACTORS

Typically, atopic dermatitis commonly affects the head and neck region and extensor surfaces of the limbs in babies, while in older children flexural involvement predominantes.

The nummular type is characterized by a more pronounced infiltration of the eczematous plaques (Figure 1) while sebostasis may be absent. These nummular lesions are frequently exsudative. Response to topical anti-inflammatory treatment is typically less effective, a fact which may lead to a misdiagnosis of dermatophyte infection. Pronounced exudation ("weeping eczema") is usually associated with *staphylococcus aureus* colonization. This requires targeted antiseptic treatment in addition to anti-inflammatory therapy.

Typical irritant provocation factors in young children include inappropriate clothing (wool-silk rompers, synthetic tights), heat/occlusion (sleeping in baby carriage, or longer rides in a baby car seat), or baby swimming in highly chlorinated water.

About one-third of severely affected infants have food allergies associated with their atopic dermatitis. The most commonly found sensitizations are those against egg protein, cows' milk, peanuts, soy, or tree nuts. Expert consensus as well as the current guidelines recommend that allergological diagnostics should only be performed if severe eczema cannot be controlled with intensified topical anti-inflammatory treatment, or if indicated due to personal history (such as, for example, sustained deterioration of symptoms after a switch from breast milk to infant formula).[30] Testing should be targeted and should always consider clinical relevance (elimination diet and provocation over a limited period).[31] Polyvalent sensitizations are not uncommon in children with atopic dermatitis but they do not justify overall allergen avoidance. Avoidance of basic foods constitutes a significant limitation and should always be based on evidence, not only on suspicion. It is important to protect the child from unwarranted dietary restrictions. Early introduction of a variety of solid foods is explicitly recommended for primary prevention.[8]

Among the various types of AD, the early persistent type (appearance within the first year of life, persistent

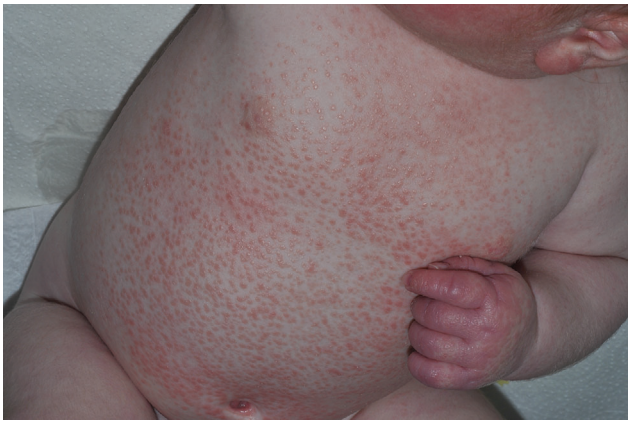

FIGURE 2 Omenn syndrome with granulomatous dermatitis.

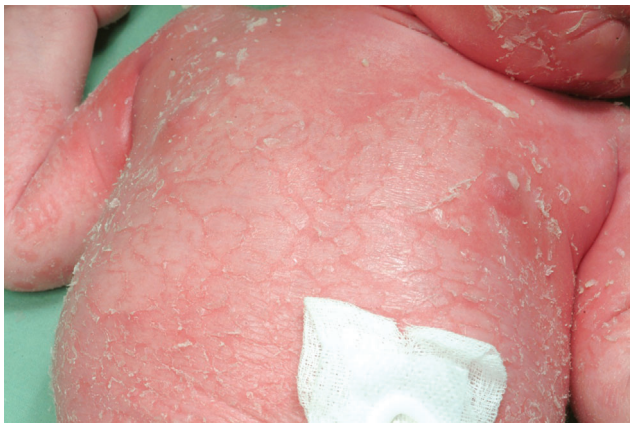

FIGURE 3 Ichthyosiform suberythroderma in Netherton-Syndrome with characteristic ichthyosis circumflexa.

symptoms) is most frequently associated with a high risk of developing concomitant allergic disease (food allergies, asthma, allergic rhinitis).[32–34]

DIFFERENTIAL DIAGNOSES OF ATOPIC DERMATITIS IN INFANTS

Atopic dermatitis can usually be diagnosed quite easily in clinical practice. However, since the "atopic phenotype" (especially eczema, peripheral eosinophilia, increased total IgE) shows some clinical overlaps with the spectrum of immunodeficiencies, correct classification of clinical skin findings in infants with severe and treatment-refractory eczema is of particular importance for further diagnostics and therapy.

Congenital immunodeficiencies with "atopic phenotype" include:

- *Hyper-IgE syndrome*: recurrent pneumonias, skin infections, "cold" abscesses
- *Omenn syndrome*: congenital ichthyosiform erythroderma, alopecia, hepatosplenomegaly, lymphadenopathy, failure to thrive (Figure 2)
- *Wiskott-Aldrich syndrome*: male infants/toddlers, eczema with petechial features, recurrent infections
- *Netherton syndrome*: congenital ichthyosiform erythroderma (Figure 3), serpiginous erythema with double-edged scaling (ichthyosis linearis circumflexa), rarefied hair on the scalp, trichorrhexis invaginata
- *IPEX*: male infants/toddlers, immune dysregulation, polyendocrinopathy, enteropathy, X-chromosomal inheritance
- *CBM-opathies*: immunodeficiencies due to mutations in the CARD11-BCL10-MALT1 complex

History, distinctive clinical features and basic laboratory diagnostics are important to differentiate severe atopic dermatitis from eczematous lesions caused by immunodeficiency:

- Unusually early manifestation (postpartum period or during the first weeks of life)
- Disseminated/Severe disease, such as neonatal erythroderma or congenital ichthyosis
- Treatment-refractory disease[35]

Immunodeficiency should be suspected when eczema collides with petechiae, granulomas, recurrent skin abscesses, and chronic fungal infection of the skin, mucous membranes and/or nails. The spectrum of primary immunodeficiencies is typically associated with failure to thrive and pathological susceptibility to infection.

The various aspects of chronic susceptibility to infection are summarized by the German acronym "ELVIS": *E*rregerspektrum, Infektfokus (*L*okalisation), *V*erlauf (prolongiert) bei allgemein gehäuftem Auftreten (*I*ntensität, *S*umme),[36] meaning "spectrum of infectious agents, focus/location of the infection, (prolonged) clinical course with increased incidence (intensity, number of infections)". More than twelve infections per year are considered pathological in young children – particularly if these are severe, prolonged, or recurrent, and leave residues.[37,38]

It is also important to look for signs of immune dysregulation, summarized by the German acronym GARFIELD (*G*ranulombildung, *A*utoimmunität, *R*ezidivierendes *Fi*eber, ungewöhnliche *E*kzeme, *L*ymphoproliferation und chronische *D*armentzündung) comprising granulomas, autoimmunity, recurrent fever, unusual eczema, lymphoproliferation, chronic intestinal inflammation.[36]

For severe eczema in early childhood, it is recommended to investigate a differential blood count as well as serum immunoglobulins (IgG, IgA, IgM, IgE) as a initial laboratory workup.

Hypogammaglobulinemia, for example, may indicate a B-cell defect. Red flags according to Castagnoli et al.:

- Serum IgE > 2000 kU/l in children during the first three weeks of life,
- Severe eosinophilia (> 1500/µl),

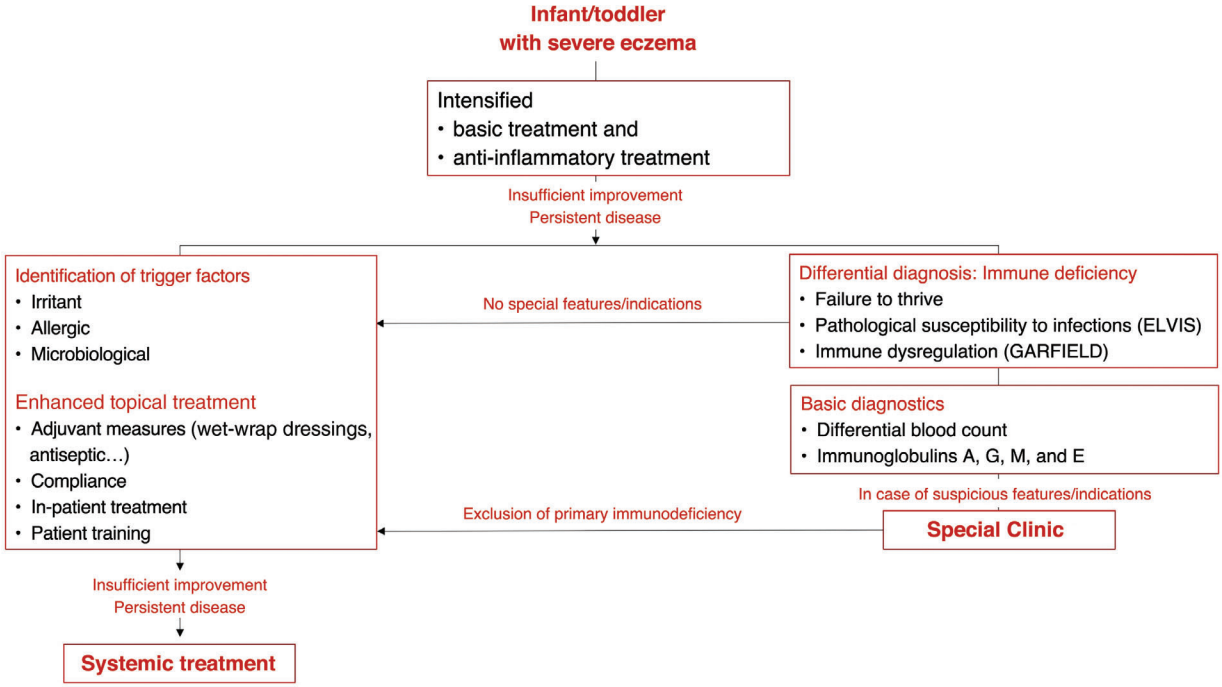

FIGURE 4 Recommendations for the management of severe atopic eczema in early childhood.

- Lymphocytopenia, neutropenia, thrombocytopenia, anemia.[35]

In case of abnormal findings or suspected primary immunodeficiency, it is essential to initiate additional diagnostics as soon as possible. This should be undertaken in a specialized pediatric clinic since the basic diagnostic measures described here do not cover the total spectrum of immunodeficiencies (Figure 4).

SYSTEMIC TREATMENT FOR ATOPIC DERMATITIS IN INFANTS AND TODDLERS: INDICATIONS AND CHALLENGES IN DAY-TO-DAY PRACTICE

If an underlying immunological condition has been excluded and the eczema still does not respond sufficiently to basic and anti-inflammatory treatment as recommended in the guideline (topical glucocorticoids, calcineurin inhibitors), in-patient/rehabilitative measures should be considered – not least to ensure adequate compliance.[30]

Significant improvement can frequently be achieved by intensified guidance and incorporation of parental education components (according to the *Arbeitsgemeinschaft Neurodermitisschulung e.V.* guidelines). Concerns about the use of topical glucocorticoids ("cortisone phobia") or topical calcineurin inhibitors, as well as uncertainties about the necessary dosage, are common obstacles that limit efficiacy of topical treatments. If, however, non of the graded therapeutic measures including adjuvant measures (avoidance of trigger factors, bandaging, antiseptic treatment) result in sustained improvement of the skin findings, systemic treatment is indicated.

Due to severe side effects, systemic glucocorticoids are not indicated for long-term treatment of severe atopic dermatitis. Intermittent treatment can in individual cases be utilized to curtail an acute episode in adult patients, but this should be avoided in children.[30]

Non-steroidal systemic treatment beyond licensed indications and age ("off label") has been common practice in pediatric atopic dermatitis for a long time. These treatments include long-established medications such as ciclosporine, (which is approved for AD in patients 16 and above) as well as other immunosuppressants: mainly methotrexate but also azathioprine and mycophenolate mofetil.[30,39] A study by the *Treatment of Atopic Eczema in Children Taskforce* (TREAT) showed that children developed frequently and often pronounced side effects under these treatments, including diabetes mellitus, hypertension, or hepato/nephrotoxicity.[40]

The first approved systemic treatment for severe atopic dermatitis in children aged six months and above is available since April 2023. Dupilumab is a monoclonal antibody targeting the alpha subunit of IL-4 and IL-13.

This medication has been approved for the same indication in adults since 2017, and approval was extended to adolescents in 2018 and children aged six years or above in 2020.

The approval for young children was based on a Phase III study in 162 children aged six months to five years, with uncontrolled moderate to severe atopic dermatitis. After 16 weeks of treatment (in combination with topical corticosteroids), 28% of patients showed extensive to complete

improvement (as compared with 4% in the placebo group). In the majority of cases (53%) the *Eczema Area and Severity Index* was improved by ≥ 75% (EASI-75). This degree of improvement was only seen in 11% of the patients in the placebo arm. Pruritus intensity was reduced by a similar degree (–48%), measured via a numeric self-assessment scale. Bacterial or viral infections were less frequently observed in the dupilumab group, except herpes simplex infection, hand-foot-mouth disease, and viral papilloma. These were seen more frequently in the treatment group.[41]

Dosage was adapted to body weight (5–15 kg: 200 mg; ab 15 kg: 300 mg); the drug was administered every four weeks via subcutaneous injection. Unlike in older children and adults, dosage is not increased at initiation of treatment.

Safety profiles were similar to those seen in older children and adolescents. Injection site reactions were a common side effect. This can be partly explained by the relatively large volume which must be administered subcutaneously, frequently resulting in transient complaints such as pressure or burning. Dupilumab-induced conjunctivitis may also occur in children younger than six years. However, in the studies this was observed less frequently than in adults and adolescents.

One advantage of dupilumab is its low potential for interaction as compared with conventional immunosuppressants: All common medications can be administered during dupilumab therapy, such as antiinfectives, antiphlogistics, antipyretics, or antiallergics. Another advantage is that laboratory monitoring is not required under treatment. This supports parents' trust in the medication and minimizes stressful blood sampling in children.

Due to the immunomodulatory effect of dupilumab, however, it is important that patients have reveal an age-appropriate/complete vaccination status before initiation of treatment. Inactivated vaccines can be administered during dupilumab treatment, but recommendations for live vaccines are still under discussion.

In the relevant age group of infants and toddlers, this mainly concerns the vaccines against measles-mumps-rubella, and chickenpox. According to the German Standing Committee on Vaccination (STIKO, Ständige Impfkommission), these vaccines should be administered between 11 and 15 months of age. Vaccination for rotavirus is usually completed at the age of four months (STIKO recommendation: Two doses at six weeks and three months of age).

The current recommendation is that dupilumab should be initiated four weeks after a live vaccine at the earliest. If a live vaccine is scheduled during ongoing treatment with a biologic, treatment should be interrupted 12 weeks before administration of the vaccine (manufacturer's recommendation).

Vaccination against varicella is particularly important for children with atopic dermatitis, because of potential disease complications such as bacterial superinfection or scarring.

For a variety of reasons, however, the vaccination status is frequently incomplete in young children with atopic dermatitis: Exacerbation of eczema in a temporal connection with vaccinations is misinterpreted as causal by parents; scheduled vaccinations are postponed due to eczematous skin; combined vaccines are split into single components in the hope of reducing side effects. Last but not least, there is still concern in regard to the safety of out-patient vaccination against measles-mumps-rubella in children with sensitization against egg protein. Actually, the vaccines currently used for vaccination do not contain any allergologically relevant amounts of antigen, so they can be safely used even in children with manifest allergy against egg protein.[42]

There is currently no data on the effect and potential side effects of live vaccines in infants and toddlers treated with dupilumab. Individual case reports in adult patients receiving influenza and yellow fever vaccinations while treated with dupilumab did not find any negative impact of dupilumab on either complication rates or the protective effect of the vaccines.[43]

It will require real life data analysis to decide if dupilumab treatment can be modified (for example by extending administration intervals), interrupted, or even discontinued after achieving sustained remission. Due to the clinical heterogeneity of atopic dermatitis, individualized decisions will be required until such data become available.

As there is growing evidence that the time of manifestation and the severity of atopic dermatitis impacts the risk of additional atopic diseases, it will be interesting to see if early and effective treatment can influence the course of this disease.[34–46]

Authors' note: after submission of this manuscript baricitinib has been licensed for treatment of severe atopic dermatitis (aged > 2 years) in October 2023.

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CONFLICT OF INTEREST STATEMENT

ABW has received lecture honoria from Sanofi-Regeneron and Lilly. SK has received consultant and lecture honoria from Sanofi-Regeneron. CS has served as a paid consultant for and received lecture honoria from Sanofi-Regeneron and Lilly.

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