Atopic and atopiform dermatitis

Brenninkmeyer, E.E.A.

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Introduction and outline

Atopic dermatitis (AD) is a chronic skin disease, characterised by inflammation and pruritus.[1;2] With an increasing prevalence, AD is one of the most common skin disorders. AD accounts for 10%–20% of all referrals to dermatologists and about 30% of dermatologic consultations in general practice.[2-5]

Because AD lacks an objective diagnostic test and shows variable clinical features, it is difficult to define. The history of the clinical entity starts with Wise and Sulzberger who first distinguished AD from other chronic eczemas in 1933.[6] The uncertainty in the understanding of this disease is reflected in the more than 15 synonyms that have been proposed (Table 1). Till date, there is no consensus about its definition, diagnosis, diagnostic criteria, pathophysiology and therapy.

DEFINTION

Coca and Cooke introduced the term atopy in 1923.[7] Atopy is derived from the Greek words a (no) topos (place). Initially atopy was meant to describe the inherited tendency to develop immediate-type hypersensitivity reactions to common antigens. Atopy was found to be associated with an increased ability to form IgE antibodies.[8;9] Since then there is a striking variety of different meanings and definitions associated with the term "atopy".

The following definition of AD seems to be in accordance with the most recent consensus; an itchy, chronic or chronically relapsing, inflammatory skin condition. The rash is characterized by itchy papules, which become excoriated and lichenified, and typically have a flexural distribution.[10] AD is associated with allergen-specific IgE and a personal or family history of other atopic conditions such as hay fever and asthma. Although termed 'atopic', it is known that there are patients with the clinical phenotype who do not have allergen-specific IgE,[11] which is an observation that led the World Allergy Organisation to propose a revised nomenclature. In this nomenclature AD is a genetically determined, IgE sensitized skin disease.[12]

To describe AD patients lacking allergen-specific IgE, several subgroups have been proposed. Similar to the extrinsic and intrinsic types of asthma, the term "intrinsic type of AD" and "extrinsic type of AD" have been suggested.[11;13;14] For the "intrinsic type of AD" other resembling terms such as "non-allergic AD", "non-atopic eczema" or "non-allergic atopic eczema/dermatitis syndrome", were introduced.[15;16] We coined the term "atopiform dermatitis" (AFD) to avoid the connection with true atopy.[17;18]

Table 1. Examples of the nomenclature of Atopic Dermatitis (based on Wolkerstorfer 2003)

Mycosis sive eczema flexurarum (von Hebra)
Lichen simplex chronicus disseminatus (Vidal)
Prurigo à formé eczemat lichenienne (Brocq)
Neurodermite diffuse (Brocq)
Dermatitis lichenoides pruriens (Neisser)
Asthma-eczema (Jadassohn, Low, Drake)
Prurigo simplex chronica (Darier)
Eczema pruriginosum (Unna)
Prurigo diathèsique (Besnier)
Prurigo Besnier (Rasch)
Le prurigo-asthme (Saubouraud)
Früh- und Spätexudatives eczematoid (Rost)
Atopic dermatitis (Coca, Sulzberger & Wise)
Asthma-eczema prurigo complex (Drake)
Konstitutionelles eksem (Koch)
Neurodermatitis constitutionales (Schnyder)
Neurodermatitis disseminata (Lomholt)

EPIDEMIOLOGY

There is hardly any doubt that there has been an increase of the prevalence of AD in wealthy countries. The reasons for this increase are still a matter of discussion. Prevalence of AD has doubled or tripled during the past three decades; 15-30% of children and 2-10% of adults are affected.[5] AD frequently start in early infancy (early-onset AD) but can also start in adults (late-onset AD). Large, unexplained variations in prevalence have been reported between countries suggesting a critical role for environmental factors in disease expression.[19] The "hygiene hypothesis" is generally accepted as the best explanation for the growth in prevalence.[20-22] The lower prevalence of AD in rural areas, compared to urban areas, supports the 'hygiene hypothesis', which postulates that the absence of childhood exposure to infectious agents increases susceptibility to allergic diseases. Although there are several data from prevalence studies an overall estimate of AD frequency is difficult. Studies differed greatly in methodology, measuring disease frequency over different time periods, in different age groups, using different techniques of data collection and different definitions and diagnostic criteria.

DIAGNOSIS

In clinical studies very often no definition of AD is given. AD is a difficult disease to define, as the clinical features are highly variable with regard to morphology, body site, duration and course of disease. Because there is no definitive diagnostic test for AD, the diagnosis of AD is still a clinical one.[23]

For diagnosing AD, the presence of pruritus is a generally accepted essential but subjective feature. In general the clinical diagnosis is based on clinical features of pruritic and chronic or relapsing eczematous lesions with typical morphology and distribution combined with the disease history. The morphology and distribution varies according to the patient´s age and disease activity. During infancy AD is generally more acute and affects the scalp, face and extensor surfaces of the extremities. For older children and in adults more chronic lichenified lesions on the flexural folds of the extremities are present.[24;25]

Due to the wide spectrum of dermatological manifestations of AD, it is of importance to consider that there is a differential diagnosis of AD:

DIFFERENTIAL DIAGNOSIS

The most important differential diagnoses are other forms of eczema. Besides, combination of different forms of eczema are prevalent with components of atopic, contact, and irritative dermatitis. AD of the hands and feet must be differentiated from contact dermatitis or psoriasis in the palms and soles and from tinea. Scabies infection must always be considered. The differential diagnosis of acute AD with intense erythema of the skin, together with exudation or blistering, for example, differs from differential diagnoses of the chronic lichenified forms. Other, rarer diseases should be suspected in children e.g. genodermatoses such as Netherton syndrome. An overview of the differential diagnosis of atopic dermatitis phenotype has been summarized in Table 2.

DIAGNOSTIC CRITERIA

During the last decades several diagnostic sets of criteria have been proposed to bring some uniformity in the diagnostic process.[26-33]

A major development in describing the clinical features of AD were the Hanifin and Rajka's diagnostic criteria published in 1980.[29] Until now, these criteria are commonly used in clinical trials, at least to provide some confidence that researchers have been selecting similar patients when using these criteria. It should be noticed

Table 2. Differential diagnosis in patients with AD clinical phenotype (based on Leung 2004)

(1) chronic dermatoses	**(4) immunologic disorders**
atopiform dermatitis	juvenile lupus erythematodes
prurigo	dermatitis herpetiformis
seborrhoeic eczema	graft-vs-host disease
allergic contact dermatitis	dermatomyositis
irritant contact eczema	
nummular eczema	
rosacea	
couperose	**(5) immunodeficiencies**
essential teleangiectasia	Wiskott-Aldrich syndrome
ulerythema ophryogenes	severe combined immunodeficiency disease
keratosis pilaris	hyper-IgE syndrome
juvenile acne	DiGeorge syndrome
psoriasis	
ichthyosis	
(2) infections and infestations	**(6) metabolic disorders**
scabies	zinc, pyridoxine, or niacin deficiency
human immunodeficiency virus	phenylketonuria
dermatophytosis	
erythema infectiosum	
other viral exanthema	
(3) malignancies	
cutaneous T-cell lymphoma	
Letterer-Siwe disease	

that this large list of 28 features, has been developed during a consensus meeting and has only been validated once. In order to refine this set of criteria into an applicable set for epidemiological studies, the UK diagnostic criteria were introduced in 1994.[33] These criteria have been widely validated since then. [34]

More recently, the Millennium Criteria (JD Bos et al) were developed to underline the importance of allergen specific IgE as a mandatory criterion.[27] This up to date set is in line with the most recent nomenclature, but validity and repeatability should be investigated. Hanifin & Rajka, UK, and the Millennium criteria are summarized in Table 3.

PATHOFYSIOLOGY

The cause of AD remains uncertain. AD is probably a complex disease relying on the interplay of several factors. Interaction between susceptibility genes, the host's

Table 3. Integrated list of diagnostic criteria

	Hanifin & Rajka Criteria 3/4++, 3/25 +	Millennium Criteria 1+++, 2/3++	U.K. Criteria 1+++, 3/5+
pruritus	++	++	+++
typical morphology and distribution	++	++	
chronic or relapsing course	++	++	+
personal or family history of atopy	++		+
xerosis	+	+	+
ichthyosis	+	+	
immediate (type I) reaction	+		
elevated serum IgE	+		
early age of onset	+		
cut. infections, impaired cell-mediated immunity	+		
tendency to non-specific hand or foot eczema	+	+	
nipple eczema	+	+	
cheilitis	+	+	
recurrent conjunctivitis	+		
Dennie-Morgan infraorbital fold	+	+	
keratoconus	+		
anterior subcapsular cataracts	+	+	
orbital darkening	+	+	
facial pallor/erythema	+	+	
pityriasis alba	+	+	
anterior neck folds	+	+	
itch when sweating	+	+	
food intolerance	+		
influenced by environmental, emotional factors	+		
intolerance to wool and lipid solvents	+	+	
perifollicular accentuation	+	+	
white dermographism, delayed blanch	+		
presence of allergen specific IgE		+++	
cradle cap		+	
palmar hyperlinearity	+	+	
keratosis pilaris	+	+	
perleche		+	
auricular rhagades		+	
hertoghe sign		+	
photophobia		+	
history of flexural involvement			+
rash under age of 2 years			+
visible flexural dermatitis			+

+++= mandatory criteria; ++=major criteria; +=minor criteria

environment, infectious agents, defects in skin barrier function and immunological factors contribute to the pathogenesis of AD. Two hypotheses concerning the mechanism of AD have been proposed: the inside and the outside paradigm.[35] One focuses on the immunologic disturbance that results in IgE-mediated sensitization, with epithelial barrier dysfunction being of secondary importance. The other proposes a primary barrier dysfunction caused by an intrinsic defect in the epithelial cells, leading to enhanced penetration of allergens and secondary IgE sensitization.[4]

Most of the progress made in understanding the immunology of the disease is related to the IgE response.[22;36] It is clear that AD has an immunological basis. The inflammatory infiltrate is a mix of subsets of T lymphocytes, dendritic cells, macrophages, keratinocytes and eosiniphils.[22;36] There appears to be an activation of T lymphocytes, which leads to an abnormal response of cytokines.[23;37] In the central immune organs, Th2 cells secrete interleukins IL–4, IL-5, and IL-13, of which IL-4 and IL-13 serve to promote the synthesis of IgE by B lymphocytes / plasma cells and to activate the vascular endothelium. IL-5 enhances eosinophil-mediated responses. The exact role of T-cell subpopulations such as Th1, Th2, Treg and Th17 remains to be established. Recently, another cytokine has been found of importance: IL-31 is highly prutitogenic and has been found to have increased levels in AD. [38-40]

Besides this immunological approach the barrier theory suggests that due to defect in skin barrier, enhanced penetration of environmental allergens and irritants occurs, leading to chronic inflammation, and, secondarily, to central immune organ sensitization. The alterations in the epidermis have been highlighted by the importance of filaggrin mutations in AD.[41]

Several loss-of-function mutations of the gene have been identified. [42-47] In 50% of the European AD patients FLG mutations have been identified. AD is a complex genetic disease and probably emerges in the context of two groups of genes: genes encoding epidermal or other epithelial structural proteins, and genes encoding major elements of the immune system.[4]

TREATMENT

The management of AD presents a clinical challenge. Basic therapy of AD should compromise optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration, along with identification and avoidance of specific and nonspecific trigger factors. Besides regular medical supervision, education and psychological support of the patient contribute to the optimal disease management.

Topical treatment consists of emollients, topical corticosteroids and topical immunomodulators (TIM's). Since a key feature of AD is severe dryness, the use of emollients is the mainstay of the general management of AD.[48] Emollients should be applied continuously to optimize the skin condition. Topical corticosteroids are important. They reduce inflammation and pruritus and are useful for both the acute and chronic phases of the disease. Since the side effects of uncontrolled use of corticosteroids are well documented, they should be applied preferably in a pulse scheme. Application once daily is, from a pharmaco-dynamic point of view, enough.[49;50] In addition, recent data indicate that application twice-weekly both in adults and children might prevent further flare-ups. The TIMs tacrolimus and pimecrolimus are non-steroidal, anti-inflammatory therapies for AD. Both compounds have shown to be effective and safe for adults and children with AD.[51-54] Although topical corticosteroids are still the standard of care in AD, TIM's might be the first line treatment in several situations such as eye-lid dermatitis and in other facial regions. In March 2005 the Food and Drug Administration issued an alert concerning a potential link between TIM's and certain forms of cancer.[55] The use of TIM's should be as labelled, and when first-line treatment has failed or cannot be tolerated, their use is advised.[34] Finally, topical tar treatment can be effective, however due to carcinogenicity and mutagenicity its use has been limited in daily practice.

For severe AD treatment often relies on systemic immunosuppressive therapy.

Systemic corticosteroids are frequently used as short-term therapy for controlling AD. Although in most cases highly effective, there is insufficient evidence of efficacy from clinical studies.[56] Rebound flare-ups and diminishing effectiveness severely limits their use.[57] To date, ciclosporine is the only systemic treatment for which convincing evidence of efficacy exists in patients with severe AD.[56] Data on the use of mycophenolate mofetil (Cellcept®), azathioprine (Imuran®) and intravenous immunoglobulin are conflicting. There is no evidence to support the use of leukotriene inhibitors, methotrexate, desensitization injections, theophylline or oral pimecrolimus.[58]

The treatment of patients with chronic AD with UVB phototherapy is widely recognized as an effective treatment modality. Narrow-band ultraviolet B (NB-UVB) phototherapy is effective against moderate to severe AD, and is well tolerated by most patients.[59;60] Long wave UVA (UVA-1) is also effective in AD, but treatment is time consuming and thus not patient friendly.[61]

Despite the fact that tremendous progress has been made concerning therapeutical strategies for AD, development of new, targeted therapeutic approaches is still

needed to control and, if possible, cure AD. Several biologics may be of interest for further development in AD, such as efalizumab (Raptiva®), which interferes with T cell migration and adhesion, and anti-IgE (omalizumab, Xolair®).[58;62-64]

IMPACT

Embryologically, skin and the central nervous system have the same origin and are functionally closely related. One can speak of the skin as 'reflecting the soul'. Skin diseases have a direct impact on health status and psychosocial wellbeing. Chronic skin diseases, like AD, can lead to severe psychosocial burdens that are quite frequently underestimated, since as a rule they are not life-threatening.[65] With this, it is of great importance to realise that AD can have a significant impact on morbidity and quality of life especially in case of severe AD.[66;67] Patients may be affected by itching and associated sleep disturbance.[68;69] Moreover, the social stigma of a visible skin abnormality is present, and in addition there is a need for frequent application of topical medications and physician visits. The chronic aspect of AD can be very worrying for patients as well for their family and therefore the psychological impact of AD has to be well considered. When onset of AD is in infancy, self-esteem is likely to be diminished. During their life patients may withdraw socially, becoming isolated and function suboptimally in all areas of their lives.[70;71]

The last decade serious attention has been paid to the quality of life (QoL) in patients with AD.[67;72-74] The QoL is a very important aspect of the care for patients with dermatological diseases which has implications not only for patients but also for the family and community. Measurements like the Dermatology Quality of Life Index, the Children Quality of life Index and the Skindex-29 have been developed to give insights into physical and psychological aspects of a chronic skin disease.[75-77]

More recently the Course of Life Questionnaire was developed to gain insight in the course of life in young adults suffering from chronic childhood diseases.[74;78;79] Knowledge about the impact of a chronic skin disease like AD is of great importance in clinical practice because it enables health care providers, and especially family doctors and dermatologists to aim for the most optimal medical care support, both during as well as after treatment. Attention should be paid not only to the physical aspects but also to the psychological and social aspects of AD. In clinical care a systematic evaluation of physical and psychosocial consequences in patients with AD seems to be required.

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OUTLINE OF THIS THESIS

Atopic dermatitis (AD) is a serious challenge in terms of research and management. For future research, there is an increasing need for how to define, diagnose and treat this disease. With this thesis a mirror has been posted to AD in order to face the criteria, definition, diagnosis, therapy and impact of AD.

Clinical studies require valid and manageable diagnostic criteria for reliable and reproducible results.

As a starting point of this thesis, a systematic review of diagnostic criteria of AD was conducted (Chapter 2). This was done in order to summarize the evidence concerning the validity of diagnostic criteria for AD. To access the methodological quality of the studies the Quality Assessment of Diagnostic Accuracy Tool (QUADAS) was used.

To make progress in AD research, manageable modern diagnostic criteria are essential to create a clear clinical phenotype of AD.

In order to validate the Millennium Criteria (MC), a case-control study was performed (Chapter 3). Besides the assessment of the validity of the MC, we intend to improve and refine the MC into a manageable and clinical applicable set of criteria. After logistic regression and tree analysis, revised Millennium Criteria were introduced.

A clear definition is necessary in order to diagnose AD and inform AD patients properly.

We consider Atopiform dermatitis (AFD), which is characterized by the absence of allergen-specific IgE, as a distinct entity from AD with different specific characteristics. In order to investigate AFD, a case control study was performed to compare the clinical and diagnostic features of AD and AFD (Chapter 4).

Since most patients with a prurigo form of AD are therapy resistant, there is a need for development of a new treatment modality.

Recent findings establish the 308 xenon chloride (XeCl) ecximer laser to be a new treatment option in the area of UVB phototherapy. In order to investigate the efficacy of the XeCl excimer laser, a prospective randomised within-patient controlled study was conducted (Chapter 5). In patients with a prurigo form of AD, the effect of the excimer laser was compared with clobethasol propionate, by a side-to-side comparison. By 6 months follow-up, the duration of remission, achieved with the excimer laser, was investigated.

The impairment of quality of life of patients with AD has been well documented, but so far no knowledge exists about the impact of AD on the course of life.
By introducing the Course of Life Questionnaire within dermatological research, the course of Life in patients with childhood AD was investigated (Chapter 6). Within this study, the influence of the severity of AD on the course of life, the disease related consequences and quality of life was assessed by questionnaires.

All studies were performed at the outpatient clinic of the Department of Dermatology in cooperation with the Department of Clinical Epidemiology and Biostatistics, both at the Academic Medical Center of the University of Amsterdam in Amsterdam, the Netherlands.