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Characterization of different courses of atopic dermatitis in adolescent and adult patients

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Abstract

Background: Atopic dermatitis (AD) starts most often during the first years of life and goes into remission in a high proportion of cases during childhood. However, in severe cases, AD persists until adulthood or starts and relapses later in life. So far, studies investigating the natural course of AD during adolescence and adulthood are rare. The aim of our study was to classify different courses of AD and to correlate these with specific risk factors for severe variants of AD.

Methods: A detailed clinical examination and retrospective evaluation of the history of the disease were performed in a collective of 725 adolescent and adult patients with AD. Laboratory data including total and specific IgE were evaluated.

Results: Six hundred and seven patients of 725 patients could be classified into course types. Of these 607 patients 85.7% could be classified into five main different course types of all 31 course types recorded. The highest differences in the number of sensitizations, total immunoglobulin E serum levels and predilection of the skin lesions were observed between patients with an early type of onset of AD and a chronic persisting course until adulthood and patients with a late type of onset of AD, that is, after the 20th year of life.

Conclusion: Our data show that the natural course of AD can be divided into subgroups that display different clinical features. The data support the assumption of a broad heterogeneity of AD in adolescence and adulthood and emphasize the future need for careful stratification of patients with AD.

Atopic dermatitis (AD) is one of the most common skin disorders (1, 2). The disease starts commonly during the first year of life, this form being classified as the 'early type of onset' of AD (3–5). The disease clears up during infancy or childhood in a majority of these patients (6). However, in severe cases, AD can persist with a chronic recurrent course until adulthood and this subtype is often very recalcitrant to any treatment strategy (7). Early onset of AD can also be the start of an 'allergic career' or atopic march, which often leads to the manifestation of other atopic diseases such as allergic asthma and rhinoconjunctivitis (8, 9). In some patients, AD

is not present during childhood but starts or relapses later in life (i.e. after 20 years of age) (10).

Genetic predisposition to an impaired skin barrier, for example, caused by loss-of-function mutations in the filaggrin gene, which are present in about one-third of Caucasian patients with AD, was identified recently as another potential risk factor for severe courses of AD (11–15).

One of the most important tasks in the treatment of this chronic skin disease is effective prevention strategies, which should be aimed to achieve early intervention or by designing disease-modifying strategies (16) before serious pathologic changes such as the increase in sensitizations or the development of immunoglobulin E (IgE) autoreactivity (17) occur. It is obvious that the prerequisite for any interventional approach is the identification, ideally by relevant and validated biomarkers, of patients at risk for a chronic course (18) or to identify patients for a more personalized therapeutic

Abbreviations

AD, atopic dermatitis; IgE, immunoglobulin E; *S. aureus*, *Staphylococcus aureus*; HSV, *herpes simplex virus*; SCORAD, SCORing Atopic Dermatitis.

Table 1 Classification of the different subgroups and course types of AD are summarized. Frequencies of the different course types within the cohort of patients with AD are shown

Courses type of AD	infantile phase 0-2 years	childhood phase 2-6 years	juvenile phase 6-14 years	adolescent phase 14-20 years	adult phase >20 years	Number of patients (n)	Percentage of patients
Subgroup I: Start of AD between birth and 2nd year of life							
1						0	0%
2						2	0.33%
3						2	0.33%
4						1	0.16%
5						189	31.14%
6						1	0.16%
7						0	0%
8						4	0.66%
9						0	0%
10						7	1.15%
11						8	1.32%
12						0	0%
13						0	0%
14						15	2.47%
15						6	0.99%
16						13	2.14%
Subgroup II: Start of AD between 2nd and 6th year of life							
17						1	0.16%
18						0	0%
19						0	0%
20						84	13.84%
21						0	0%
22						7	1.15%
23						6	0.99%
24						3	0.49%
Subgroup III: Start of AD between birth and 6th and the 14th year of life							
25						0	0%
26						0	0%
27						58	9.56%
28						9	1.48%
Subgroup IV: Start of AD between 14th and the 20th year of life							
29						2	0.33%
30						77	12.69%
Subgroup V: Start of AD after the 20th year of life							
31						112	18.45%

approach (19). However, follow-up studies investigating the manifestation of AD after early childhood and in particular the course of AD during lifetime are rare. Moreover, only a few studies have been conducted to investigate patients with an onset of AD after the 20th year of life or later during adulthood.

Bacterial or viral infections are frequent complications, which are most often induced by high colonization of the skin of these patients with *Staphylococcus aureus* (*S. aureus*) bacteria (20) or by the dissemination of *herpes simplex* virus (HSV) infections of the skin (21–23). Another potential complication is the development of sensitizations against aero- and food allergens, which together with high IgE serum levels, correlates with the severity of the skin lesions as reported in some studies (24, 25). In regard to the atopic march, it is hypothesized that children with a manifestation

of AD before the 2nd year of life develop more often allergic rhinitis and allergic asthma later in life (4, 7), which could be linked by the increased skin-derived thymic stromal lymphopoietin (TSLP) (26). Moreover, IgE autoreactivity was observed in a subgroup of patients with AD and might represent another risk factor for chronic persistent courses (17, 27). Early preventive interventions such as synbiotics (28), the treatment with antihistamines (29, 30) or immunotherapeutic strategies (31) were proven to be useful for the reduction in the concomitant manifestation of atopic diseases of the upper airways.

The purpose of this study was to investigate the different courses of AD, to understand the natural history of AD in adolescent and adult patients to identify potential correlates with regard (i) to clinical aspects such as severity or predilection of the skin lesions and (ii) to biological markers

such as total and specific IgE. We analysed these features within the different course types of AD to identify patients at high risk for a chronic course with early onset of AD and chronic course until adulthood as well as to outline characteristics of the subgroup of patients with onset of AD in adulthood.

Material and methods

Patient collective and clinical data

A total of 725 patients with AD (293 male and 432 female patients; 12–89 years old; mean age of 32.6 ± 14.0 years) were recruited at the Department of Dermatology and Allergy in Bonn, Germany, and included into the study. Some of them were related to each other (affected parents and affected siblings). Because of study conditions, patients younger than 20 years were only included into the analyses of gender differences, so that a total number of 607 patients were classified into the different course types. All patients have been assessed by a combination of detailed clinical

examination and questionnaires [criteria of Hanifin and Rajka (32), the Diepgen score (33) and SCORAD (34)] and blood withdrawal by trained physicians. Affected body surface area (SCORAD A) and intensity of skin lesions (SCORAD B) were measured separately. Diagnostic and stratification of patients with AD were based on these data. In addition, the family history for atopic diseases and the predilection of AD lesions were documented. If available, medical records were used to complete missing data.

Laboratory data

Serum samples from all patients were analysed for total immunoglobulin E (IgE) level and level of allergen-specific IgE against mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), birch pollen, grass pollen, cat dander, hazelnut, peanut, cow's milk, hen's egg, green apple, codfish, moulds and yeasts (*Aspergillus fumigatus*, *Candida albicans* and *Pityrosporum ovale*) with the Immulite 2000 system (Siemens Healthcare Diagnostics, Eschborn, Germany). The protocol was approved by the local ethical committee, and

Table 2 Distribution of the criteria of Diepgen within the most frequent course types in comparison with course type 5 is depicted. Parameters higher in course type 5 are indicated as (++), and parameters lower in course type 5 are indicated as (‡)

Criteria of diepgen	Course type 20	Course type 27	Course type 30	Course type 31
Family history				
First relatives affected by eczema	n.s.	n.s.	n.s.	n.s.
First relatives affected by rhinitis, conjunctivitis or asthma	n.s.	n.s.	n.s.	n.s.
Personal history				
Flexural eczema	n.s.	n.s.	0.0003 (++)	<0.0001 (++)
Allergic rhinitis/conjunctivitis	0.0047 (++)	0.0291 (++)	n.s.	<0.0001 (++)
Crusta lactea	0.0007 (++)	0.0058 (++)	0.0021 (++)	<0.0001 (++)
Intolerance to wool	n.s.	n.s.	n.s.	0.0072 (++)
Photophobia	n.s.	n.s.	n.s.	n.s.
Pityriasis alba	n.s.	n.s.	n.s.	0.0070 (++)
Perlèche	n.s.	n.s.	n.s.	0.0073 (++)
Cheilitis sicca	n.s.	n.s.	n.s.	0.0259 (++)
Pulpitis sicca	n.s.	n.s.	n.s.	0.0349 (++)
Hertoghe sign	n.s.	n.s.	n.s.	0.0091 (++)
Dennie–Morgan infraorbital fold	n.s.	n.s.	n.s.	0.0010 (++)
Elevated serum total IgE level	n.s.	0.0104 (++)	0.0062 (++)	0.0002 (++)
'Dirty Neck'	n.s.	n.s.	n.s.	0.0202 (++)
Acrocyanosis	n.s.	n.s.	n.s.	n.s.
Asthma allergicum	n.s.	0.0282 (++)	n.s.	<0.0001 (++)
Pruritus after sweating	n.s.	n.s.	n.s.	n.s.
Intolerance to metal	n.s.	n.s.	n.s.	0.0137 (‡)
Xerosis	n.s.	0.0444 (++)	n.s.	0.0482 (++)
Ear eczema	n.s.	n.s.	n.s.	0.0022 (++)
Dyshidrosis	n.s.	n.s.	n.s.	n.s.
Nipple eczema	n.s.	n.s.	n.s.	0.0011 (++)
Food intolerance	0.0089 (++)	0.0420 (++)	0.0362 (++)	<0.0001 (++)
Palmar hyperlinearity	n.s.	n.s.	n.s.	n.s.
Keratosis pilaris	n.s.	n.s.	n.s.	n.s.
White dermographism	n.s.	n.s.	n.s.	0.0031 (++)
Orbital darkening	n.s.	n.s.	n.s.	0.0007 (++)
Fur cap-like hairline	n.s.	n.s.	n.s.	n.s.

informed consent was signed by all patients participating in this study.

Definition of different subgroups and course types of AD

In a first step, the recruited patients with AD were classified into five subgroups according to the age of onset (Table 1), based on the classification of Wuthrich (10). Subgroup I had an onset of AD between birth and the second year of life; subgroup II had an onset of AD between the 2nd and 6th year of life; subgroup III had an onset of AD between the 6th and 14th year of life; subgroup IV had an onset of AD between the 14th and 20th year of life; and subgroup V had an onset of AD after the 20th year of life.

In a second step, depending on the affection during five different lifetime periods, they were further subdivided into 31 different course types. Patients younger than 20 years of age were not classified into the course types.

Statistical analysis

To assess differences between course types, logistic or linear regression was used depending on the type of the dependent variable. Generalized estimation equations were used to account for the correlation within families. A logarithmic transformation was used for total serum IgE before analysis. All statistical tests were performed using SAS 9 (SAS Institute, Cary, NC, USA).

Results

A chronic persisting course since early childhood lasting until adulthood is detectable in about one-third of all patients with AD

As a first step, patients included in this collective were stratified into the five different subgroups depending on the age

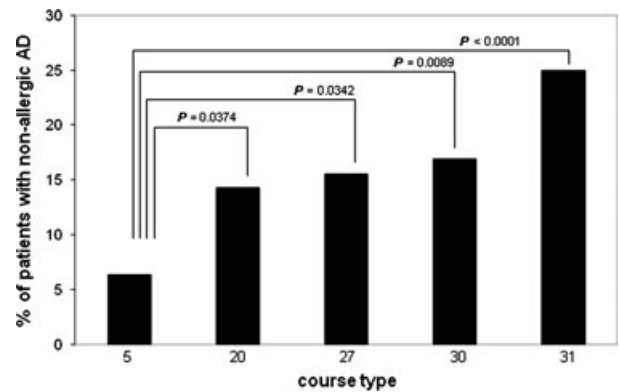


Figure 1 Percentage of patients per course type with nonallergic atopic dermatitis in the five most frequent course types (x-axis) is depicted (percentage on y-axis).

of onset and then in the course types of AD as defined above (see Material and Methods). The most frequent course type of AD in our collective was type 5 (31.1% of all classified patients) (Table 1), which is characterized by an early onset of AD before the 2nd year of life and a chronic persisting course until adulthood (Table 1). Besides type 5, the other frequent course types were type 31 (18.5%), type 20 (13.8%), type 30 (12.7%) and type 27 (9.6%) (Table 1).

Male patients with AD have significantly higher total serum IgE levels and a higher objective SCORAD value than female patients with AD

A slight female predominance in the most frequent course types was observed, ranging from 57.1% in course types 5 and 31 to 65.5% in course type 27. Male patients with AD displayed a significantly higher serum IgE level than female

Table 3 Differences of the percentage of patients with allergen-specific IgE within the most frequent course types in comparison with course type 5 are summarized. Parameters higher in course type 5 are indicated as (++), and parameters lower in course type 5 are indicated as (‡)

Type of allergen	Course type 20	Course type 27	Course type 30	Course type 31
<i>Dermatophagoides pteronyssinus</i>	0.0072 (++)	n.s.	n.s.	<0.0001 (++)
<i>Dermatophagoides farinae</i>	0.0053 (++)	n.s.	n.s.	<0.0001 (++)
Cat dander	0.0082 (++)	0.0108 (++)	0.0002 (++)	<0.0001 (++)
Hen's egg	n.s.	n.s.	n.s.	0.0002 (++)
Cow's milk protein	n.s.	n.s.	n.s.	0.0216 (++)
Wheat	n.s.	n.s.	n.s.	0.0004 (++)
Codfish	n.s.	n.s.	n.s.	0.0058 (++)
Birch pollen	n.s.	0.0198 (++)	0.0348 (++)	<0.0001 (++)
Grass pollen	0.0254 (++)	0.0006 (++)	0.0025 (++)	<0.0001 (++)
Hazelnut	0.0021 (++)	0.0138 (++)	0.0028 (++)	<0.0001 (++)
Peanut	n.s.	0.0062 (++)	0.0268 (++)	<0.0001 (++)
<i>Aspergillus fumigatus</i>	n.s.	n.s.	0.0094 (++)	<0.0001 (++)
<i>Candida albicans</i>	n.s.	n.s.	0.0165 (++)	<0.0001 (++)
<i>Pityrosporum orbiculare</i>	n.s.	n.s.	0.007 (++)	<0.0001 (++)
Apple	0.0091 (++)	0.0098 (++)	0.0089 (++)	<0.0001 (++)

Table 4 Clinical features of the four most frequent course types compared to course type 5 are shown in this histogram. Parameters higher in course type 5 are indicated as (++), and parameters lower in course type 5 are indicated as (±)

Course types compared to course type 5	Significant differences		
	Stigmata	Numerical values	Allergen-specific IgE
20	Crusta lactea (++) Rhinitis (++) Food intolerance (++) Perifollicular accentuation (++)	Total IgE (++)	<i>Dermatophagoides pteronyssinus</i> (++) <i>Dermatophagoides farinae</i> (++) Cat dander (++) Hazelnut (++) Grass pollen (++) Apple (++)
27	Crusta lactea (++) Rhinitis (++) Asthma allergicum (++) Food intolerance (++) Immediate (type I) skin test reactivity (++) Xerosis (++)	Total IgE (++) Diepgen criteria (++)	Cat dander (++) Birch (++) Grass pollen (++) Hazelnut (++) Peanut (++) Apple (++)
30	Flexural lichenifications (++) Flexural eczema (++) Nonspecific hand or foot dermatitis (++) Crusta lactea (++) Course influenced by environmental/emotional factors (++) Food intolerance (++)	Diepgen criteria (++) Total IgE (++)	<i>Pityrosporum orbiculare</i> (++) <i>Candida albicans</i> (++) <i>Aspergillus fumigatus</i> (++) Cat dander (++) Birch (++) Grass pollen (++) Hazelnut (++) Peanut (++) Apple (++)

Table 4 (continued)

Course types compared to course type 5	Significant differences		
	Stigmata	Numerical values	Allergen-specific IgE
31	Flexural lichenifications (++) Flexural eczema (++) Immediate (type I) skin test reactivity (++) Nipple eczema (++) Cheilitis sicca (++) Pulpitis sicca (++) Facial pallor/facial erythema (++) Pityriasis alba (++) Intolerance to wool and lipid solvents (++) Food intolerance (++) Tendency towards cutaneous infections (++) Perlèche (++) 'Dirty neck' (++) Asthma allergicum (++) Intolerance to metal (‡) Ear eczema (++) Crusta lactea (++) Rhinitis (++) Dennie–Morgan infraorbital fold (++) Hertoghe sign (++) Orbital darkening (++) Course influenced by environmental/emotional factors (++) White dermographism (++) Xerosis (++)	Age (mean) (‡) Diepgen Criteria (++) Total IgE (++)	Dermatophagoides pteronyssinus (++) Dermatophagoides farinae (++) Cat dander (++) Hen's egg (++) Cow's milk protein (++) Wheat (++) Codfish (++) Peanut (++) Hazelnut (++) <i>C. albicans</i> (++) <i>Pityrosporum orbiculare</i> (++) <i>A. fumigatus</i> (++) Birch (++) Grass pollen (++) Apple (++)

patients (2513.4 ± 4748.0 kU/l vs 1111.7 ± 3532.1 kU/l; $P < 0.0001$, $n = 718$) and significant differences in the severity of the skin lesions (objective SCORAD 33.2 ± 17.7 vs 29.9 ± 16.8 ; $P = 0.0138$, $n = 693$) and the affected body surface area (SCORAD A 24.0 ± 25.1 vs 19 ± 22 ; $P = 0.0092$, $n = 629$). In terms of the intensity of the skin lesions (SCORAD B), no significant differences between male and female patients with AD could be detected.

Atopy signs and concomitant atopic diseases are significantly more present in patients with early onset and chronic persisting course than in patients with onset of AD after the age of 20 years

Because the criteria of Hanifin and Rajka and the Diepgen score are important parameters to diagnose and possibly to stratify AD, we evaluated these criteria within the different course types. A comparison of course type 5 with the other

four most frequent course types showed significant differences in the manifestation of food intolerance according to the Diepgen score criteria with a higher percentage of patients suffering from food intolerance in course type 5 (Table 2).

Interestingly, 90.5% of the patients of course type 5 reported an impact of psychic factors on the course of their disease in contrast to patients of course type 31 who reported worsening of AD due to psychic factors only in 78.9% ($P = 0.0105$).

Patients with early onset of AD and a chronic persisting course (type 5) had more often flexural eczema (compared to course type 30; $P = 0.0003$ and course type 31 $P < 0.0001$). Amongst others, in comparison with course type 31, course type 5 showed a significantly higher occurrence of rhinoconjunctivitis ($P < 0.0001$), milk crust ($P < 0.0001$), Hertoghe sign ($P = 0.0091$), Dennie–Morgan infraorbital fold ($P = 0.001$), orbital darkening ($P = 0.0007$), white

dermographism ($P = 0.0031$) and asthma bronchiale ($P < 0.0001$) (Table 2).

Patients with an early onset and chronic persisting course develop the highest level of total serum IgE and a high frequency of allergen-specific IgE

Atopic dermatitis in adult patients often coincides with elevated IgE serum levels and allergen-specific IgE against several food- and aeroallergens. The highest total serum IgE level was detected in patients with course type 5 (2468.25 ± 4436.27 kU/l), course type 30 (2215.18 ± 7100.52 kU/l) and course type 20 (2075.58 ± 6029.44 kU/l), while the lowest IgE serum level occurred in AD patients with course type 27 (1177.48 ± 1858.29 kU/l) and course type 31 (918.95 ± 1847.17 kU/l). Comparison of the total serum IgE between course type 5 and the other four most frequent course types showed significant differences ($P = 0.0165$) when comparing with course type 20, ($P = 0.0069$) with course type 27, ($P = 0.0397$) with course type 30 and $P = 0.0001$ with course type 31.

Allergen-specific IgE towards peanut and apple allergen was more frequent in patients of course type 5 than in the other four most frequent course types (Table 3). The highest percentage of patients with allergen-specific IgE against *C. albicans* and *A. fumigatus* was detectable in AD patients with course type 5 and 20. Comparing the level of allergen-specific IgE against birch and grass pollen, the highest levels were detected in patients with course type 5.

Non-allergic variant of AD is most frequent in patients with an onset of AD after the age of 20 years

The nonallergic subtype of AD is defined by low IgE serum levels (<150 kU/l) and no detectable sensitizations against aero- and food allergens. The highest number of patients with the nonallergic subtype of AD (25%) was found in course type 31, which was significantly higher than in course type 5 (6.4%, $P < 0.0001$). About 14.3% of course type 20, 15.5% of course type 27, 16.9% of course type 30 and 6.4% of course type 5 had a nonallergic type of AD. Compared to course type 5, these results were significant (Fig. 1).

Different predilection of the skin lesions in the different course types

Distribution of the AD skin lesions was shown to vary between age classes of AD; therefore, we compared the predilection of the skin lesions according to the different course types of AD. We observed a significantly higher predilection of skin lesions in the neck region ($P = 0.0206$) in patients with course type 5 than in patients with course type 31 of AD. Interestingly, 63.2% of the patients of course type 20 had hand eczema, whereas in the other four most frequent course types, hand eczema was detected in about 50% of the cases. In regard to the SCORAD value, no significant differences between the different course types were found.

Considering the classification used in this study, five of the 31 course types occurred most often in our study population. Patients with early onset and a chronic persisting course of AD (course type 5) are at the highest risk for severe complications of AD. We summarized the most important differences of this course type compared to the other four most frequent course types (Table 4).

Discussion

Atopic dermatitis is a complex skin disease, which varies in its clinical picture, the level of sensitizations and course (5, 35, 36). However, long-time follow-up studies documenting the course of this disease and its distribution especially in adulthood are rare. In contrast to a previous study that was limited to AD patients with an early age of onset within the first 2 years of life (37), our study considered a larger spectrum of age of onset. Subgroups were defined according to the study of Wuthrich and were based on the different stages of age classified by EMA and FDA. Patients with a chronic persistent course of AD had more often concomitant respiratory allergic diseases. The observation of a portion of patients with an onset of AD during the first 2 years of life and a chronic persistent course until adulthood (course type 5; 31.1%) confirms the results of other studies (7, 9). In regard to the predilection of the skin lesions, the neck area was significantly more often involved in patients with an early type of onset of AD and a chronic persistent course (course type 5) than in patients with a late type of onset of AD (course type 31).

Interestingly, most of the atopy signs were much more pronounced in patients with a chronic, long-lasting course (comparison of course types 5 vs 31). This might mirror a stronger genetic background in these patients. In addition, similar to the observation of the group of Illig et al. (9), the patients with a chronic persisting course since early childhood had a higher level of total serum IgE and were more often sensitized against aero- and some food allergens in our collective. Particularly in patients of course type 5, sensitization to hen's egg allergen and apple was observed, but sensitization towards cow's milk protein was slightly more frequent in patients with course type 20, 27 and 30.

The highest proportion of patients with high IgE serum levels and strongly pronounced sensitizations classified as allergic variant of AD could be detected in the subgroup of patients with course type 5. This goes along with the findings of a prospective cohort study in Germany with adolescent patients with AD in which sensitization against allergens seemed to be one of the predictors for a course persisting during puberty (38). The highest rate of patients belonging to the nonallergic variant of AD without any sensitizations and low total IgE serum levels was determined in patients with course type 31. This leads to the conclusion that two variants of the nonallergic form of AD might exist, one occurring as a rather transient form early in childhood, which in most of the cases develops into the allergic form later in life and a second adult variant in adult patients with a late type of onset of AD. At the

present, it is unclear which factors such as changes in hormonal regulation, profession with great skin strain, psychological trigger factors, vitamin D3 levels (39), fatty acid intake in breast milk (40) or other unidentified parameters contribute to the manifestation of AD in particular in non-allergic adult patients with AD.

The identification of causative factors of nonallergic AD in adulthood would be of major importance for effective therapeutic strategies in this subgroup of patients. Common preventive measures, which are reasonable in children at risk, such as allergen avoidance or elimination diet, most likely do not have any beneficial effect for these patients. This finding indicates that both environmental and genetic factors might determine and influence the course type of an individual. However, factors contributing to the decay of AD and clear-out of sensitizations during the natural course of AD are far from being known.

Taken together, this is the first study providing a systematic overview about the course of AD in adolescence and adulthood and summarizing the clinical characteristics of the different subgroups in elder patients. Our data strongly support the assumption of a broad heterogeneity of AD in adolescence and adulthood. This heterogeneity might be, amongst other factors, the reason for the high number of variations of the results of different genetic, clinical and

research studies on AD conducted in this collective of patients. Moreover, the data emphasize the need for careful stratification of patients with AD in the clinical practice as a first approach to individualized therapy and more careful definition of AD subtypes in clinical and research studies to achieve better comparable results.

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Authors' contributions

T.H., N.N., T.D. and T.B. contributed to the study design. R.F., I.M.D., D.U.G., T.H. and N.N. performed data analysis. T.H., D.U.G., T.B. and N.N. wrote the manuscript. N.N. gained funding.

Conflict of interest

The authors have no conflict of interest.

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