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Atopic dermatitis and psychosocial comorbidities

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Summary

Atopic dermatitis (AD) is a chronic inflammatory disease that may be associated with a number of comorbidities including psychosocial disorders, which are the primary focus of this article. The data presented is based on a literature search in PubMed and subsequent screening of relevant review articles and guidelines.

There is a greater prevalence of depression, anxiety, sleep disorders and suicidal ideation among individuals with AD. The disease negatively impacts patients' quality of life. Children with AD have been shown to more commonly exhibit signs of attention-deficit/hyperactivity disorder. Only little data exists on the association of AD with schizophrenia, eating disorders or obsessive-compulsive disorder.

There is a great need for research in the field of AD-related comorbidities, especially with respect to the question as to whether and how novel treatment options may potentially affect these comorbidities.

Introduction

Typical comorbidities in patients with atopic dermatitis (AD) include allergic asthma, allergic rhinoconjunctivitis, and food allergy [1]. In addition, it has been shown that AD is associated with a number of other diseases, particularly autoimmune disorders such as rheumatoid arthritis, inflammatory bowel disease [2], systemic lupus erythematosus [3], vitiligo [4], and alopecia areata [5–7]. As early as 1942, atopic individuals were described as being tense, nervous, depressed, introverted and anxious [8]. The goal of the present article is to provide an overview of psychosocial comorbidities currently known to be associated with AD.

Methods

Using the terms atopic dermatitis/eczema, comorbidity, depression, anxiety, attention-deficit/hyperactivity disorder, anorexia, obsessive compulsive disorder, quality of life, sleep, schizophrenia, we conducted a literature search in PubMed. Articles published over the course of the past 10 years were included in our analysis. We identified 21 stu-

dies, including cross-sectional studies, case-control studies, and randomized placebo-controlled trials. The number of patients included in the various studies ranged from 30 to 120,508. The diagnostic definitions we used in our discussion of the various psychosocial disorders are based on current guidelines [1, 9–15].

Depression, anxiety disorders and suicidal tendencies (Table 1)

The diagnosis of depression is made when two of the following three main symptoms are present: depressed/subdued mood, loss of interest or pleasure, psychomotor retardation, increased fatigue/low energy. Other possible symptoms include the following: decreased ability to concentrate, low self-esteem/confidence, feelings of guilt/worthlessness, negative/pessimistic views of the future, suicidal ideation, self-injury or suicide attempts, sleep disorders and decrease in appetite [9].

As regards anxiety disorders, a distinction is made between panic disorder, generalized anxiety disorder, social

phobia, and specific phobias [10]. Both depression and anxiety disorders may lead to suicide [11].

In the US, a cross-sectional study revealed that patients with AD significantly more frequently showed symptoms of depression such as loss of interest, hopelessness, decrease in appetite, fatigue, and decreased ability to concentrate [16]. This association is most likely bidirectional: on the one hand, AD increases a patient's risk of depression [17]; on the other hand, stress is a known trigger of AD [18].

A German cross-sectional study showed an increased risk of suicidal ideation and found symptoms of depression, high disease activity, young age and a weak family bond to be significant predictive factors in this context [19]. According to a Korean cross-sectional study, there is a significantly increased risk of suicidal thoughts, plans to commit suicide, and suicide attempts among adolescents with AD as well [20].

A Danish cross-sectional study found that patients with moderate-to-severe AD were significantly more often treated with anxiolytic agents and antidepressants than control subjects [21]. Female AD patients have been shown to significantly more frequently develop depression than men [22]. Twins of AD patients are thought to be at increased risk of having anxiety disorders and depression, irrespective of their own atopic status [23]. In their 2018 meta-analysis, Rønnstad et al. demonstrated a significant association of AD with depression and anxiety. However, their analysis was limited in that the various studies had used different definitions of depression and anxiety. Moreover, only few studies had included an assessment of disease severity and of its impact on psychosocial disorders [24].

Depression seems to be associated with the presence of proinflammatory cytokines, in particular tumor necrosis factor (TNF)- α , interleukin 6 and CRP [25].

In a randomized, placebo-controlled trial, treatment with the interleukin 4 receptor antagonist dupilumab resulted in improvement in quality of life (DLQI) as well as a decrease in depressive symptoms and anxiety (HADS). Interleukin 4 and interleukin 13 are key cytokines in Th2-mediated inflammation in patients with AD [26]. In summary, the evidence currently available strongly suggests an association of AD with depression, anxiety disorders, and suicidal tendencies. However, more research is needed to corroborate this association and to evaluate the impact disease severity and treatment may potentially have.

Attention-deficit/hyperactivity disorder (ADHD) (Table 2)

ADHD is characterized by the three symptoms inattention, impulsivity, and hyperactivity [12].

In a case-control study, Tsai et al. showed that children with AD and other atopic diseases (allergic asthma, allergic rhinitis or allergic conjunctivitis) were at a greater risk of developing ADHD. In addition, the risk increased with the number of atopic diseases an individual had; the risk was also greater in individuals living in urban areas [27]. In another case-control study, Schmitt et al. also saw a significant association between ADHD and AD, irrespective of age, gender and other psychiatric disorders. The likelihood of developing ADHD increased with each AD-related doctor's visit [28, 29]. A prospective, non-interventional study has suggested that the risk of developing ADHD increases with the use of antihistamines in early childhood [30]. Moreover, it has been shown that children with AD significantly more often exhibit oppositional defiant behavior and autism spectrum disorders [31]; the longer AD persists, the greater is the association with mental health problems [32].

Schizophrenia (Table 3)

Schizophrenia is a syndrome characterized by various mental impairments, including perception, cognition, ego functions, affectivity, lack of energy, and psychomotor activity [13].

There is only little – and partly controversial – data on the association of schizophrenia and AD. In one study, it was shown that the presence of AD, urticaria, or allergic rhinitis in the absence of asthma significantly increased the risk of schizophrenia [33]. For schizophrenia too, an association with proinflammatory cytokines and Th17 cells has been suggested [34]. Besides, a significant increase in the prevalence of ischemic stroke has been reported in patients with schizophrenia and atopic diseases [35]. In another study, however, seropositivity for specific IgE antibodies was significantly lower in patients with schizophrenia, suggesting a lower prevalence of atopic diseases in schizophrenic individuals [36].

Obsessive-compulsive disorder (Table 4)

Obsessive-compulsive disorder is characterized by recurrent, stereotypic thoughts and behaviors. There are four subgroups: 1) compulsive checking; 2) compulsive repeating and ordering/arranging; 3) compulsive washing and cleaning; 4) hoarding disorder [37, 38].

There are hardly any studies on the correlation of AD and obsessive-compulsive disorder. One study examined the association of obsessive-compulsive symptoms in mothers of children with AD. The disease had no impact on the

Table 1 Data on depression, anxiety disorders and suicidal tendencies in patients with AD.

Author/year	Study design	Parameters	Number of patients	Country	Conclusion
Yu et al. [16] 2015	Cross-sectional study NHANES 2005–2006	– PHQ9 (patient health questionnaire) – SIGECAPS (symptoms related to sleep, interest, guilt, energy, concentration, appetite, psychomotor activity, suicidal tendencies)	5,555 (≥ 18 years)	USA	– Increased prevalence of depression in patients with AD (17.5 vs. 10.5 %; OR 1.89) – Higher risk of moderate (OR 2.24) and severe (OR 5.64) depressive episodes
Kim et al. [17] 2015	Cross-sectional study Survey among military draftees 2008 to 2012	– Survey on depression, anxiety, and somatization based on medical files, history, and psychological tests	120,508; 1,517 (1.2 %) thereof had AD (19–21 years)	South Korea	– Psychological stress significantly more common in draftees with AD – Risk of depression (OR 1.79), anxiety (OR 1.38), and somatization (OR 1.75) significantly higher in AD – Moderate/severe AD significantly more often associated with depression and somatization than mild AD
Dieris-Hirche et al. [19] 2017	Cross-sectional study	– Questionnaires: Pödingger's scale for suicide risk assessment, HADS, DLQI, PO-SCORAD, Skin Satisfaction Questionnaire (SSQ).	181 with AD, 64 control subjects (18–65 years)	Germany	– High prevalence of suicidal ideation in patients with AD (21.3 %) – 3.9 % of patients with acute suicidal tendencies – Predictive factors for suicidal tendencies: depressive symptoms, severe AD, young age, little family support
Lee et al. [20] 2017	Cross-sectional study	– Questionnaires on depression, anxiety, suicide and AD	72,435 students of junior high schools and high schools (12–17 years)	Korea	– Compared to control subjects, adolescents with AD had a higher risk of depressive symptoms (OR 1.27), suicidal ideation (OR 1.34), plans to commit suicide (OR 1.46) and suicide attempts (OR 1.51)

Continued

Table 1 Continued.

Author/year	Study design	Parameters	Number of patients	Country	Conclusion
Thyssen et al. [21] 2017	Cross-sectional study Danish study of functional disorders (DanFusnD)	<ul style="list-style-type: none"> Questionnaire on depression, anxiety, symptoms of AD, consumer behavior, suicidal tendencies Criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Rate of hospitalization due to depression or anxiety disorders Suicides in the National Causes of Death Registry Prescription of anxiolytic agents and antidepressants in the Registry of Medicinal Product Statistics 	9,656; 1,044 (13.8 %) thereof had AD (≥ 18 years)	Denmark	<ul style="list-style-type: none"> Significant association between AD and depression (OR 1.92) and anxiety disorders (OR 1.74) Patients with AD significantly more often had depressive symptoms (OR 2.15) Suicidal ideation more common in AD patients (3.4 % vs. 1.7 %) Rate of hospitalization not increased compared to general population Risk of suicide very low in both AD patients and control subjects (n = 4 vs. n = 5) Patients with moderate-to-severe AD were significantly more often taking anxiolytic agents (OR 1.66) and antidepressants (OR 1.24) Patients with mild AD showed only a slight increase in the use of anxiolytic agents (OR 1.08)
Mina et al. [22] 2015	Cross-sectional study	<ul style="list-style-type: none"> Primary Care Evaluation of Mental Disorders (PRIME-MD) 	81 (36 men, 45 women) (10–74 years)	India	<ul style="list-style-type: none"> 15 % had moderate/severe depression; 12 % had anxiety disorders Women: significantly higher scores for depression and anxiety
Brew et al. [23] 2018	Cross-sectional study	<ul style="list-style-type: none"> Screen for Child Anxiety-related Emotional Disorders (SCARED) Shortened Mood and Feelings (SMFQ) 	14,197 children (9 years)	Sweden	<ul style="list-style-type: none"> If a twin had at least one atopic disease, the other twin had an increased risk of developing an anxiety disorder or depression, irrespective of the latter's own atopic status (OR 1.22)
Simpson et al. [26] 2016	Randomized, placebo-controlled phase 3 SOLO 1, SOLO 2	<ul style="list-style-type: none"> DLQI, HADS 	671 in SOLO 1, 708 in SOLO 2 (25–51 years)	USA Europe Asia	<ul style="list-style-type: none"> After 16 weeks of dupilumab therapy, significant improvement in DLQI (by ≥ 4 points) compared to baseline After 16 weeks of dupilumab therapy, significantly higher reduction in HADS (down to < 8 points) compared to baseline

Abbr.: HADS, Hospital Anxiety and Depression Scale, DLQI, Dermatology Life Quality Index, PO-SCORAD, Patient-oriented Scoring Atopic Dermatitis; OR, odds ratio.

Table 2 Data on attention-deficit/hyperactivity disorder (ADHD) in patients with AD.

Author/year	Study design	Parameters	Number of patients	Country	Conclusion
Tsai et al. [27] 2013	Case-control study Longitudinal Health Insurance Database	Medical diagnosis (DSM-5/ICD-9)	4,692 children with ADHD and 18,768 control subjects (< 18 years)	Taiwan	<ul style="list-style-type: none"> Increased risk of developing ADHD in patients with AD (OR 1.80), asthma (OR 1.48), allergic rhinitis (OR 1.81) or allergic conjunctivitis (OR 1.69) Risk increases with number of atopic diseases
Schmitt et al. [29] 2013	Case-control study Secondary data from AOK Plus (statutory health insurance fund) and KV (association of physicians in the statutory health insurance sector) in Saxony, 2003–2004	Medical diagnosis (ICD-9)	1,436 children with AD and 1,436 control subjects (6–17 years)	Germany	<ul style="list-style-type: none"> Significant association between AD and ADHD (OR 1.54, $p = 0.02$) Likelihood of developing ADHD increased with each AD-related doctor's visit (OR 1.06; $p = 0.046$) Association independent of age, gender, and other psychiatric disorders (OR 1.47, $p = 0.046$) Atopic comorbidities not significantly associated with ADHD (asthma OR 1.72, $p = 0.07$; allergic rhinitis OR 1.46; $p = 0.055$)
Schmitt et al. [30] 2017	Prospective, non-interventional	Medical diagnosis (ICD-10), SCORAD, POEM (patient-oriented eczema measure), history, questionnaire	154 children 42 with AD, 34 with ADHD, 31 with AD and ADHD, and 47 control subjects (6–12 years)	Germany	<ul style="list-style-type: none"> Compared to the control group, children with AD only, ADHD only, or AD and ADHD had a significantly increased risk of behavioral problems and lower quality of life Higher risk of ADHD symptoms in children with AD than in control subjects Antihistamine use by children with AD was significantly associated with a higher incidence of ADHD symptoms (OR 1.88; 95 % CI 1.04–3.39). Current severity of AD symptoms had no impact on the severity of ADHD symptoms
Yaghmaie et al. [31] 2013	Cross-sectional study 2007 National Survey of Children's Health	Questionnaire on the severity of AD and the presence of a mental disorder (depression, anxiety disorder, behavioral disorder, autism)	92,642 children (0–17 years)	USA	<ul style="list-style-type: none"> Risk of ADHD significantly increased in children with AD (OR 1.87); increased risk of depression (OR 1.81), anxiety disorder (OR 1.77), behavioral disorder (OR 1.87), and autism (OR 3.04) Correlation between severity of AD and prevalence of mental disorders
Schmitt et al. [32] 2010	Birth cohort GINIplus	Questionnaire; assessment of AD symptoms, comorbidities, environmental factors	2,916 children (1–10 years)	Germany	<ul style="list-style-type: none"> Significantly higher risk of mental problems (OR 1.49) and emotional symptoms (OR 1.62) Strength of association between AD and mental problems increased with the duration of AD

Abbr.: OR, odds ratio.

Table 3 Data on schizophrenia in patients with AD.

Author/ year	Study design	Parameters	Number of patients	Country	Conclusion
Pedersen et al. [33] 2012	Cross-sectional study	Medical diagnosis (ICD-8)	808,559; 3,539 thereof had schizophrenia (15–31 years)	Denmark	<ul style="list-style-type: none"> – Asthma significantly increased the risk of schizophrenia (OR 1.59) – Combination of any atopic disease increased the risk of schizophrenia (OR 1.35) – Presence of AD, urticaria, or allergic rhinitis in the absence of asthma significantly increased the risk of schizophrenia (OR 1.27)
Chen et al. [35] 2015	Case-control study	Medical diagnosis (ICD-9)	63,913 with schizophrenia (mean age 37.29 ± 14.32 years) 63,913 control subjects (mean age 36.51 ± 14.13 years)	Taiwan	<ul style="list-style-type: none"> – Patients with schizophrenia are at increased risk of ischemic stroke – Risk of ischemic stroke increases with number of atopic comorbidities
Okusaga et al. [36] 2014	Case-control study	Phadiatop multi-allergen	66 with schizophrenia (mean age 42.2 ± 12.8 years) 34 control subjects (mean age 41.5 ± 14.1 years)	Germany USA	<ul style="list-style-type: none"> – Prevalence of Phadiatop seropositivity was significantly lower in schizophrenic patients – Lower prevalence of atopy in schizophrenic patients (OR 0.40)

Abbr.: OR, odds ratio.

severity of the mothers' mental disorder and health-related quality [39].

Anorexia nervosa

Self-induced weight loss in combination with body dysmorphic disorder is the hallmark of anorexia nervosa [14].

For the time period analyzed, no data was found on anorexia nervosa in patients with AD.

Sleep disorders (Table 4)

Cardinal symptoms include difficulties falling and/or staying asleep and daytime drowsiness. As a consequence, patients experience fatigue that may cause impairment of both motor and mental functions as well as psychosocial performance (for example, dealing with stress) [15]. Sleep disturbances are problematic as they severely impair the quality of life of patients with AD [40, 41].

Several studies have shown sleep disturbances to occur not only in affected patients but also in the parents

of children with AD. In particular, shorter sleep duration, difficulties falling asleep, early morning waking, and low sleep efficiency have been reported [40–42]. Poor sleep quality may result in impaired linear growth of atopic children [43].

Quality of life (Table 5)

Quality of life is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [44]. The Dermatology Life Quality Index (DLQI) is one of the most widely used questionnaires on health-related quality of life (HRQoL), specifically developed for patients with skin diseases [45]. The Dermatitis Family Impact (DFI) questionnaire is a disease-specific tool to assess the impact of AD on the quality of life of the parents and family members of affected children [46].

Patients with AD have been shown to have a significantly lower quality of life and a higher level of stress than healthy

Table 4 Data on obsessive-compulsive and sleep disorders in patients with AD.

Author/year	Study design	Parameters	Number of patients	Country	Conclusion
Gunduz et al. [39] 2017	Cross-sectional study	– SCORAD, Maudsley Obsessive Compulsive Inventory (MOCI), SF-36	120 children (mean age 1.5 ± 0.6) and their Mothers	Spain	– AD of children had no impact on the severity of the obsessive-compulsive disorder of their mothers in terms of obsessive-compulsive symptoms and HRQoL
Yu et al. [40] 2016	Cross-sectional study National Health and Nutrition Examination Survey	– Questionnaire on AD and sleep disturbances	5,563 (≥ 18 years)	USA	– AD patients more frequently reported sleep disturbances (OR 1.62); shorter sleep duration (OR 1.61); difficulties falling asleep (OR 1.57); early morning waking (OR 1.86)
Chamlin et al. [41] 2005	Cross-sectional study	– Questionnaire on sleep quality among parents of children with AD	Parents of 300 children (0–6 years) with AD	USA	– More than 60 % of parents stated that AD affected their sleep or their children's sleep – Cosleeping was reported by 30 % of families; the majority of these parents (66 %) reported to be bothered by the cosleeping – Sleep disturbances were directly associated with disease severity and family's happiness
Chang et al. [42] 2014	Case-control study	– Polysomnography – Actigraphy – 6-sulfatoxymelatonin urine levels – Total IgE levels	72 patients, 32 control subjects (1–18 years)	Taiwan	– Lower sleep efficiency; difficulties falling asleep; increased sleep fragmentation; decrease in non-rapid eye movement sleep – SCORAD ≥ 48.7 was predictor for impaired sleep efficiency (p = 0.001) – Sleep disorder associated with low nocturnal melatonin secretion – Correlation between sleep disorder and pruritus, scratching, total IgE, sensitization to house dust mites

Abbr.: SF-36, Short-Form Health Questionnaire; OR, odds ratio.

individuals. Quality of life decreases with increasing severity of AD [47]. The presence of a filaggrin mutation has been associated with impaired HRQoL [48]. Adequate treatment of AD has been shown to improve quality of life [49, 50].

Conclusions

Patients with AD may have a number of psychosocial comorbidities that need to be observed in their clinical care.

Table 5 Data on quality of life in patients with AD.

Author/year	Study design	Parameters	Number of patients	Country	Conclusion
Kwak et al. [47] 2017	Cross-sectional study	– EuroQoL Visual Analogue Scale	11,913 (≥ 19 years)	Korea	– HRQoL was significantly lower – Increased risk of stress (OR 1.74), depression (OR 1.69) and suicidal ideation (OR 1.66)
Heede et al. [48] 2017	Cross-sectional study	– Questionnaire on skin symptoms, DLQI, mental/atopic diseases – Testing for filaggrin mutations	520 (≥ 18 years)	Denmark	– Filaggrin mutations were detected in 16.9 % of patients; significant association with reduced HRQoL but not with anxiety disorders or depression – 19.7 % of patients with AD and filaggrin mutations reported severe or very severe impact on their lives; prevalence twice as high as in AD patients without filaggrin mutations (9.6 %)
Coutanceau et al. [49] 2014	Cross-sectional study	– SCORAD – PO-SCORAD – Patient-oriented Eczema Measure (POEM) – Self-administered Eczema Area and Severity Index (SA-EASI) – DLQI – Dermatitis Family Impact (DFI) questionnaire	4,222 (0.1–97 years)	Europe	– PO-SCORAD, SCORAD, POEM correlated with DLQI ($r = 0.67$) and DFI ($r = 0.56$) – After 5 weeks of treatment, there was a significant decrease in SCORAD and PO-SCORAD by 60 % and 56 %, respectively ($p < 0.0001$); improvement in quality of life

Abbr.: DLQI, Dermatology Quality of Life Index; HRQoL, Health-related Quality of Life; OR, odds ratio.

Based on current data, there is an unequivocal association with depression, anxiety disorders and ADHD. However, the data currently available is by no means conclusive and further research is required to corroborate the association of AD with psychosocial comorbidities. For patients with moderate-to-severe disease in particular, it is recommended to assess the DLQI on a regular basis and, if necessary, to employ specific questionnaires on depression (for example, HADS). Other medical specialties should be involved in the management of these comorbidities as early as possible. More research is needed, especially with respect to the question as to how novel treatment options for AD may affect not only the cutaneous inflammation but also psychosocial comorbidities.

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