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Altered Hypothalamus-Pituitary-Adrenal Axis Function: A Relevant Factor in the Comorbidity of Atopic Eczema and Attention Deficit/Hyperactivity Disorder?

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Highlights

- Children with attention-deficit/hyperactivity disorder (ADHD) show reduced hypothalamus-pituitary adrenal (HPA) axis responsiveness to stress. HPA axis reactivty was also found to be significantly attenutated in children with atopic eczema scoring high in ADHD-like behavior suggesting HPA axis dysfunction as a potential key factor in AE-ADHD comorbidity

Abstract

Epidemiological data show a significant association between childhood atopic eczema (AE) and an increased risk to develop attention deficit/hyperactivity disorder (ADHD). However, the underlying mechanisms of the comorbidity of AE and ADHD are mostly unknown. We investigated whether alterations of hypothalamus-pituitary-adrenal (HPA) axis function represent a shared feature of AE and ADHD potentiating AE-ADHD comorbidity. Children aged 6-12 years with AE, ADHD, or comorbid AE+ADHD and healthy control (HC) children were examined cross-sectionally (*N* = 145). To evaluate HPA axis function, salivary cortisol in response to psychosocial stress (Trier Social Stress Test for Children, TSST-C), after awakening (cortisol awakening response, CAR), and throughout the day (short diurnal profile) and hair cortisol capturing long-term HPA axis activity were assessed. Quantile regression analyses showed an attenuated cortisol response (% maximum change) to the TSST-C in children with ADHD compared to HC. A diminished cortisol response to acute stress was also observed in the comorbid AE+ADHD group, in which the reduction was numerically even more pronounced. Contrary to our previous findings, no alteration of the cortisol response to the TSST-C was observed in children with AE. However, in children with AE, increased ADHD-like behavior (i.e., inattention, impulsivity, and overall ADHD symptom severity) was associated with a reduced HPA axis response to acute stress. No such associations were observed in children without AE. Groups did not differ in CAR, short diurnal profile, and hair cortisol. These findings underscore the potential relevance of HPA axis function in the pathophysiology of AE and ADHD with emphasis on stress reactivity. Additional studies are required to further explore the separate and joint role of the HPA axis in the pathophysiology of AE and ADHD.

Keywords: atopic eczema, attention deficit/hyperactivity disorder, cortisol, hypothalamus-pituitary-adrenal axis, stress

Introduction

Atopic eczema (AE) is a chronic inflammatory skin disease with key symptoms such as eczematous and inflammatory eruptions of the skin and intense pruritus (Brown, 2016; Lawton, 2014). AE typically manifests in early infancy (with an onset before the age of 5 in 90% of the patients) and represents one of the most common chronic childhood disorders (Weidinger and Novak, 2016). Notably, about 50% of all

individuals with AE have specific allergic sensitization indicating that atopy is not a necessary feature of AE (Flohr et al., 2004). In the last decade, prevalence of AE has been on the rise, particularly in Western societies, and recent epidemiological studies suggest that AE affects up to 20% of children and 3% of adults (Mallol et al., 2013). Although multiple factors seem to be involved in AE, immunoregulatory abnormalities such as hypersecretion of immunoglobulin-E (IgE), increased, mainly type-2 (TH2), inflammatory cytokine levels, and eosinophilia are considered to play a key role in AE pathogenesis (Leung, 2013).

A growing number of epidemiological data support an association between childhood AE and attention deficit/hyperactivity disorder (ADHD) (van der Schans et al., 2017). ADHD represents one of the most common neurobehavioral disorders occurring during childhood and adolescence with increasing prevalence, including a 42% rise in ADHD diagnoses between the years of 2003 and 2011 (Visser et al., 2014). Main symptoms of ADHD are inattention, hyperactivity, and impulsivity. Although there is a decline in the prevalence of ADHD symptoms with increasing age, symptomatology persists into adulthood in half of children diagnosed with ADHD. ADHD is often accompanied by emotional instability, sleep disturbances, substance abuse, and conduct problems (Sharma and Couture, 2014). The pathology of ADHD is not clear, however, alterations in brain morphology and function, particularly in the frontostriatal and mesocortical brain networks, have been shown to play a key role in ADHD (Kieling et al., 2008). The dysfunctional sleeping patterns and the psychological burden caused by ADHD (Peasgood et al., 2016) show similarities with behavioral and psychological sequelae of AE, letting researchers to hypothesize that ADHD and AE may share etiopathological commonalities (Buske-Kirschbaum et al., 2013). In a meta-analysis of 20 observational studies, Schmitt and colleagues (2010) reported that children with AE have an 1.5-fold increased risk for developing ADHD compared to age-matched healthy controls (HC). Similarly, in the 2007 National Survey of Children's Health including 92,642 children aged 0 to 17 years, childhood AE was associated with higher odds of ADHD (odds ratio: 1.87, 95% CI: 1.54-2.27) (Yaghmaie et al., 2013). Using cross-sectional data from 19 population-based surveys, Strom and colleagues (2016) confirmed these findings demonstrating a 46% increased risk of ADHD diagnosis in children with AE. The authors further reported that severity of AE and/or suffering from another atopic disease, such as atopic asthma or allergic rhinitis, independently and synergistically increased the risk for

ADHD. Although most of the studies are restricted to pediatric populations, a positive association between AE and ADHD has also been observed in adults (Cicek et al., 2009; Strom et al., 2016).

While the epidemiological link is well substantiated, the psychobiological mechanisms underlying the comorbidity of AE and ADHD are still unknown. Studying these mechanisms is important in order to improve clinical care for individuals with these conditions. We hypothesize that several neurobiological pathways play a role in the comorbid manifestation of AE and ADHD (Buske-Kirschbaum et al., 2013). In addition to allergic inflammatory cytokines likely impacting development and maturation of ADHD-relevant brain circuits (immuno-psychiatric model), we hypothesized that the hypothalamus-pituitary-adrenal (HPA) axis plays a key role in the biological underpinnings of AE and ADHD and their co-occurrence. In previous studies, our group and others demonstrated that children with AE show significantly attenuated cortisol responses to psychosocial stress when compared to non-atopic controls (Buske-Kirschbaum et al., 1997; Kojima et al., 2013). Hyporesponsiveness of the HPA axis to stress was also found in adult AE, suggesting that HPA axis dysfunction is linked to AE independent of age or disease duration (Buske-Kirschbaum et al., 2002). The assumption of an altered HPA axis function in individuals with AE was further supported by observations of a blunted cortisol response after awakening (CAR) in AE (Ruttle et al., 2014). However, other studies found no evidence for an attenuated CAR or reduced basal cortisol secretion in AE (Buske-Kirschbaum et al., 2002; Wamboldt et al., 2003).

The underlying pathological mechanisms responsible for HPA axis irregularities in AE are still poorly understood. Previous research suggests several factors that might be involved. First, our observation of an altered HPA axis reactivity in newborns with atopic disposition suggests that hereditary factors are potentially relevant (Buske-Kirschbaum et al., 2004). Second, increased levels of inflammatory cytokines in AE might alter the secretory activity of the HPA axis, as cytokines are potent modulators of the HPA axis, and chronic secretion of inflammatory cytokines (e.g. TNF-α, IL-10) can induce HPA axis hypofunction (Morris et al., 2017). Third, chronic stress, especially in early life, may cause long-term alterations in HPA axis responsiveness, including a blunted HPA axis response to stress (von Bodegom et al., 2017). Such a hyporesponsive HPA axis in AE, in turn, could be of significant pathological relevance. Due to its immunoregulatory and anti-inflammatory capabilities, an altered

HPA axis may facilitate and/or consolidate immunological aberrations and thus, may increase the risk of allergic sensitization as well as the exacerbation and chronification of AE symptomatology (Lin et al., 2017; Silverman and Sternberg, 2012).

In addition to its immunoregulatory role, HPA axis activity and resulting glucocorticoid levels have been linked to a variety of cognitive functions, including cognitive control processes that allow for focusing attention, suppressing unwanted impulses and thoughts, and exerting voluntary behavior (Plessow et al., 2011; Shields et al., 2015). Impaired cognitive control represents an endophenotype of ADHD (Aron and Poldrack, 2005; Kieling et al., 2008), and its extent is linked to the severity of ADHD symptoms (Nigg et al., 2005). Based on this link between HPA axis activity and control over attention, thoughts, and behaviors, dysregulation of the HPA axis may be a key candidate when investigating biological underpinnings of the comorbidity of AE and ADHD. This idea is supported by findings of abnormalities in HPA axis function in ADHD patients, such as a dysfunctional circadian rhythm (Kaneko et al., 1993), lower basal cortisol levels (Blomqvist et al., 2007; Ma et al., 2011), or a blunted CAR in ADHD children with co-morbid oppositional defiant disorder (Freitag et al., 2009) or disruptive behavior (Hastings et al., 2009). In contrast, other studies have failed to show a relation of ADHD and cortisol production (Pesonen et al., 2011; Wang et al., 2011).

In this study, we hypothesized that alterations in HPA axis function play a key role in both AE and ADHD and could represent a potentiating factor in the comorbidity of both diseases. We specifically focused on children in the years of high prevalence of developing ADHD by conducting a cross-sectional investigation of children aged 6-12 years with a diagnosis of AE, ADHD, AE+ADHD, and HC, recruited from outpatient clinics and the community. Contrasting HPA axis function in children with AE and ADHD only with a comorbid patient group with AE *and* ADHD provides a unique opportunity to study the occurrence of distinct HPA axis aberrations alterations in the comorbidity of both diseases. To account for the multifacetness of HPA axis function and to provide a more comprehensive picture of adrenocortical functioning in AE and ADHD, we assessed core indicators of basal HPA axis activity and activation in response to a stressor as well as different time scales, including hair cortisol as a cumulative marker of HPA axis function that allowed us, for the first time, to assess whether AE, ADHD, or their co-occurrence is characterized of alterations of basal

HPA function over the period of months rather than singular time points and days. Our study comprised of (a) a well-established stress induction protocol designed to elicit a reliable HPA axis response in children combined with frequent saliva sampling that allows for an evaluation of HPA axis activity in response to an acute stressor (Trier Social Stress Test for Children; TSST-C) (Kirschbaum et al., 1993) designed to elicit a reliable HPA axis response in children combined with frequent saliva sampling that allows for an evaluation of HPA axis activity in response to the stress experience, (b) outside of the laboratory saliva sampling throughout the day to assess the CAR and diurnal HPA axis fluctuations, and (c) analysis of cortisol from hair samples to evaluate HPA axis activity on a longer time scale (i.e., the previous 2 months). We hypothesized that (1) compared to HC, children with a diagnosis of AE or ADHD would show reduced cortisol levels (as markers of HPA axis activity) following the TSST-C, after awakening (CAR), throughout the day (short diurnal profile), and over the past 2 months (hair cortisol); (2) this pattern would be more pronounced in children with comorbid AE+ADHD than those with AE or ADHD only; and (3) a reduced HPA axis function would be associated with severity of ADHD symptoms in children with and without AE.

Methods

Participants

Children aged 6-12 years with AE (*n* = 42), ADHD (*n* = 34), or AE+ADHD (comorbid; *n* = 31) as well as HC (*n* = 47) were recruited at the University Allergy Centre and the Department of Child and Adolescent Psychiatry at the University Hospital Carl Gustav Carus in Dresden (Germany) and via announcements in local newspapers.

During a screening visit ($visit_0$, V_0), all participants were clinically examined by a dermatologist and a child and adolescent psychiatrist to evaluate their health status and to validate AE and/or ADHD diagnoses. AE was diagnosed using the UK Working Party criteria (Williams et al., 1994). All AE children were free of steroid treatment or anti-inflammatory medication for ≥ 4 weeks and had used only topical application of steroids with low to moderate potency during this time period, as it is well documented that topical treatments with low to moderate potency have no detectable effects on HPA axis activity (Ellison et al., 2000; Lucky et al., 1997). ADHD children were diagnosed according to the ICD-10 criteria following the guidelines of the German Association of Child and Adolescent Psychiatry,

Psychosomatics, and Psychotherapy (DGKJP) (Organization, 1992). Severity of the ADHD core symptoms (inattention, hyperactivity, impulsivity) was assessed using the German ADHD Rating Scale FBB-ADHS (Erhart et al., 2008). All participants with a diagnosis of ADHD were free of medication (methylphenidate, dextroamphetamine, atomoxetine) for ≥ 48 h prior to testing. Based on studies on the pharmacokinetics and pharmacodynamics of methylphenidate (Swanson et al., 2011; Swanson et al., 1999), a wash-out period of 24 or 48 h is considered the gold standard when studying neurobiological processes in ADHD patients. Children were diagnosed as comorbid with AE+ADHD, if the diagnostic criteria of AE and ADHD were fulfilled. Healthy children were recruited as control group. None of the HC children had a history of atopy or neuropsychiatric disease. Children with current infection, other dermatologic disorders, current medical treatment known to affect the HPA axis, or an intelligence quotient < 80 (HAWIK-IV) were excluded from the study. This cross-sectional investigation was conducted as part of a larger cross-sectional and longitudinal clinical trial investigating psychoimmunological and psychoneuroendocrine mechanisms in the comorbidity of AE and ADHD. From this clinical trial, a previous publication reports the role of history of antihistamine use for occurrence of ADHD symptoms in AE (Schmitt et al., 2018). For the analyses reported in this manuscript, only participants who provided saliva and/or hair samples for analysis of cortisol were included, resulting in a sample of 145 participants, including 37 patients with AE, 33 patients with ADHD, 28 individuals with AE+ADHD, and 47 HC.

Clinical characteristics

AE symptom severity

AE symptom severity was assessed at the screening visit (V_0) using the SCORAD Index. The SCORAD is a well-validated composite measure of the intensity and extent of AE signs (percentage of skin affected) and the intensity of pruritus and sleeping problems due to AE (Oranje et al., 2007). A dermatologist conducts the assessment, and the resulting SCORAD Index ranges from 0 to 83. Comparisons of SCORAD Indices across 10 trained dermatologists showed an intra-class correlation of 0.66 and a coefficient of variation of 28.1, indicating good inter-rater reliability (Bozek and Reich, 2017). In addition, self-reported symptom severity was assessed using the Patient-Oriented Eczema Measure (POEM). The POEM allows the patient

to indicate the frequency of the seven most important symptoms of AE (i.e., itch, sleep disturbance, skin bleeding, skin weeping or oozing clear fluids, skin cracking, skin flaking, skin dryness or roughness) during the preceding week with scores ranging from 0 (no symptoms) to 28 (most frequent symptoms). The POEM shows high internal consistency (Cronbach's α = 0.88) and good test-retest reliability with 95% of scores falling within 2.6 points on repeated testing (difference score = 0.04, SD = 1.32) (Charman et al., 2004).

ADHD symptom severity

ADHD symptom severity was evaluated at V_0 using the well-established ADHD rating scale Fremdbeurteilungsbogen Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (FBB-ADHS). Using the FBB-ADHS, parents rated the severity and associated burden of 20 behaviors as observed in their children. Raw values were combined into the three scales of inattention, hyperactivity, and impulsiveness as defined by the ICD-10 (World Health Organization, 1992) as well as a total score and transformed into stanine scores (mean = 5, SD = 2; range: 1-9) for each scale. The FBB-ADHS has been shown high internal consistency (Cronbach's α = 0.90) and factorial and convergent/discriminative validity (Erhart et al., 2008).

Experimental protocol

Testing (visit$_1$, V_1) took place < 5 days after the screening visit (V_0) between 3 PM and 5 PM. First, the children completed a set of cognitive tests, while their accompanying parent filled in questionnaires. The children were then guided to the experimental room and exposed to the TSST-C, which has been described and evaluated in detail elsewhere (Buske-Kirschbaum et al., 1997). Briefly, the TSST-C is a standardized laboratory stressor that includes a free speech (5 min) and mental arithmetic tasks (5 min) in front of an audience. For the free speech, the children received the beginning of a story and were asked to finish the story making it as exciting and interesting as possible. The children were prompted to perform better than the other participants. The mental arithmetic task consisted of a serial subtraction task according to age. The TSST-C represents an adapted version of the original Trier Social Stress Test (TSST) that has been documented to be a reliable instrument to induce significant HPA axis activation (Kirschbaum et al., 1993). The experimental protocol was approved by the local ethics committee, and written

informed assent and consent was obtained from the children and their parents, respectively before performance of any study-related procedures. Careful debriefing was provided at the end of the session. The children received a compensation of €70 on completion of the experimental protocol.

Salivary cortisol

Psychological stress test (TSST-C). To assess cortisol levels in response to the TSST-C, saliva samples were obtained 1 min before and 1, 15, 30, and 60 minute(s) after the TSST-C using the Salivette sampling device (Sarstedt, Rommelsdorf, Germany).

CAR and short diurnal profile. One day before the study visit (V_1), participants collected saliva at home after awakening and 30 and 45 minutes after waking up for analysis of morning cortisol levels. In addition, saliva was sampled at 4 PM, and 8 PM to allow for determining a short diurnal cortisol profile.

All samples were stored at -20^{o}C before analysis. After thawing, saliva samples were centrifuged for 10 min for 4,000 rpm. Saliva cortisol concentrations were analyzed using a commercially available luminescence assay (LIA, IBL Hamburg, Germany). The intra- and interassay coefficients for cortisol were below 8%.

Hair cortisol

Hair strands (~3 mm diameter) were obtained at V_1 scalp-near from a posterior vertex position. Hair cortisol concentrations in the proximal 2-cm hair segment reflect integrated cortisol secretion over the 2-month period to hair sampling (Kirschbaum et al., 1993). Hair cortisol concentrations were determined via liquid chromatography tandem mass spectrometry. Detailed description of the analytical protocol can be found elsewhere (Gao et al., 2016).

Data analysis

Cumulative measures. As a measure of HPA axis response to the TSST-C, the percent change in salivary cortisol from baseline to each individual's cortisol peak following the TSST-C was calculated. From the saliva samples collected throughout the day, the CAR was calculated as area under the curve with respect to ground (AUC_G) from waking up to the +45 min measure. The short diurnal cortisol profile was calculated as AUC_G from waking up to 8 PM saliva samples.

Statistical analysis. Statistical analyses were performed using JMP Pro 13 (SAS Institute, Inc., Cary, NC, USA) and the quantreg package version 5.35 in R (Koenker, 2005). Analyses of variance (ANOVAs) and χ^2 tests were conducted to compare age, sex, and FBB-ADHS scores across the four groups. Where applicable, ANOVAs were followed up by post-hoc pairwise comparisons using the Tukey-Kramer honestly significant difference test. In addition, POEM Score and SCORAD Index were compared between the AE and AE+ADHD groups using *t*-tests. Multiple linear quantile regression analyses with the factors AE, ADHD, the comorbid group (AE+ADHD, and sex (male/female) were conducted for percent change in salivary cortisol following the TSST-C, CAR, short diurnal cortisol profile, and hair cortisol concentrations. A quantile regression approach was chosen, as the dependent variables were not normally distributed and characterized by a wide data range. Quantile regressions do not use distributional assumptions, are robust against outliers, and allow for analysis of the impact of the independent variable on the outcome beyond simple shifts in the mean (Koenker and Bassett, 1978), namely statistical relationships between the independent and dependent variable within a specific range of the data distribution of the dependent variable. To test for associations between ADHD symptomatology and HPA axis function among individuals with and without AE, nonparametric correlations (Kendall's Tau-b to adjust for ties) were performed between FBB-ADHS scores and percent change in salivary cortisol following the TSST-C, CAR, short diurnal cortisol profile, and hair cortisol concentrations within each group.

Results

Participants' characteristics

Participants' characteristics are summarized in in Table 1. Data analysis indicated no differences between groups for age. However, a significant group difference in the percentage of boys and girls was found (p = .026), reflecting the typically higher prevalence of AE and ADHD in boys. As indicated by the POEM score and SCORAD Index, participants with AE showed a mild and sometimes even almost clear disease activity. Most importantly for the study design, the AE and the AE+ADHD groups did not differ with regard to AE symptom severity (p = .209 and .622 for POEM score and SCORAD Index, respectively). As per study design, ADHD symptomatology (FBB-

ADHS Total Score and all subscale scores) was most pronounced in the ADHD and AE+ADHD groups, who did not differ from each other, but significantly differed from both the AE and the HC group. However, compared to the HC group, children with AE showed significantly higher values in FBB-ADHS impulsivity, inattention, and Total scores, indicating a more pronounced ADHD-like symptomatology in AE children that falls in-between the HC group and the ADHD and AE+ADHD groups.

– Insert Table 1 around here –

HPA axis function

Indicators of HPA axis function by group are summarized in Table 2. Regarding the percent change in salivary cortisol following the TSST-C, the difference in percent change values between ADHD and HC groups increased with increasing quantiles, and a significant difference was observed for the 0.8 quantile (β = -366.38, p = .034) with a less pronounced cortisol response in the ADHD group compared to the HC control group (Table 3 and Figures 1 and 2). A similar pattern was observed for the AE+ADHD group, where the cortisol response to the TSST-C was significantly smaller in both the 0.7 and 0.8 quantile when compared to HC (β = -241.50, p = .042 and β = -466.94, p = .007, respectively; Table 3 and Figures 1 and 2). While for the 0.8 quantile, the coefficient was numerically more pronounced in the AE+ADHD group relative to the ADHD group, the interaction between AE and ADHD was not significant (0.8 quantile: p = .373; interaction not shown in table). No significant effects were found for the lower quantiles in the ADHD and AE+ADHD groups or across all quantiles in the AE group. Analyses of CAR, AUC_G diurnal profile, and hair cortisol showed no differences between AE, ADHD, and AE+ADHD groups relative to HC (Table 3 and Figure 1).

– Insert Tables 2 and 3 and Figures 1 and 2 around here –

Association between HPA axis function and ADHD symptoms

In children with AE (with or without an additional diagnosis of ADHD), FBB-ADHS Impulsivity, Inattention, and Total scores were negatively correlated with the percent change in salivary cortisol in response to the TSST-C (r = -.21, p = .031, r = -.29, p = .004, and r = -.23, p = .020, respectively). These associations were not observed in

children without AE (r = -.06, p = .515, r = -.16, p = .069, and r = -.12, p = .150, respectively; Table 4). No other relationships between FBB-ADHS scores and indicators of HPA axis activity were significant (Table 4).

– Insert Table 4 around here –

Discussion

The goal of this study was to test whether HPA axis is altered in children with AE, ADHD, and comorbid AE+ADHD compared to HC and whether altered HPA axis function is linked to ADHD-like behavior. To this end, basal (CAR, short diurnal profile), stimulated (HPA axis activity following an acute psychosocial stressor, i.e., TSST-C), and cumulative cortisol secretion (hair cortisol) were assessed. Results show significantly altered HPA axis activity in children with ADHD and AE-ADHD as indicated by a smaller cortisol response to an acute psychosocial stressor (TSST-C) compared to HC. This finding was numerically more pronounced in children with comorbid AE+ADHD than those with ADHD only. However, this numerical difference was not significant. Our observation of a suppressed cortisol secretion in response to stress in the ADHD group is in line with previous studies showing diminished HPA axis responses in ADHD children in response to mental stressors or to venipuncture stress (Hong et al., 2003; King et al., 1998; McCarthy et al., 2011). Further, attenuated reactivity after dexamethasone treatment (Kaneko et al., 1993), lower basal cortisol levels (Ma et al., 2011), and a flattened diurnal cortisol profile (Isaksson et al., 2012) have been reported. A hypo(re)active HPA axis with low cortisol levels is consistent with the theory of dysfunctional behavioral inhibition in ADHD subjects (Hirshfeld-Becker et al., 2003; Satterfield et al., 1974). Behavioral inhibition refers to a response activated by stimuli of threat or punishment enabling an individual to delay a determined response, to focus attention to relevant environmental cues, and to plan activities to avoid aversive consequences. Behavioral inhibition was found to be associated with increased HPA axis activity (Fox et al., 2005), and poor behavioral inhibition has been described as a core symptom of ADHD (Hirshfeld-Becker et al., 2003). Low circulating cortisol levels, especially in challenging situations, might reflect behavioral disinhibition and could contribute to the maladaptive behavior in ADHD children. We did not find evidence for a concomitant altered basal HPA activity in the ADHD group by means of CAR, short diurnal profile,

and hair cortisol compared to HC children. The lack of an altered CAR in ADHD patients is in line with previous findings (Snoek et al., 2004). However, the data are mixed and studies have reported an increased (Hatzinger et al., 2007) as well as a blunted (Blomqvist et al., 2007) CAR in ADHD patients.

We did not find evidence for an altered HPA axis function in children with AE, which contradicts previous work by our own and other groups demonstrating significantly blunted cortisol responses to stress in both children and adults with AE (Buske-Kirschbaum et al., 2002; Buske-Kirschbaum et al., 1997). Based on these previous findings, it was postulated that due to the anti-inflammatory properties of glucocorticoids, the inability of AE patients to exert an appropriate HPA axis response to stress may be pathologically relevant and may increase the risk of an exaggerated (allergic) inflammatory response leading to the manifestation and exacerbation of AE symptoms (Buske-Kirschbaum, 2009; Lin et al., 2017). However, our study differed from previous investigations in that due to requirements set by the ethics committee, AE patients displayed only mild or very mild AE symptoms, which may have hindered the detection of potential effects that would be observable in samples with more pronounced symptom severity. Supporting this idea, Haeck and coworkers reported significantly reduced cortisol levels only in adults with severe but not with moderate AE (Haeck et al., 2007). Accordingly, others found that attenuated cortisol levels in severe AE normalized with improvement of the disease (Nutan et al., 2011).

As a second key finding, in children with AE but not those without AE, changes in cortisol levels following the TSST-C were related to (clinical and subclinical) ADHD symptoms. The higher ADHD symptomatology, the lower is the cortisol stress response (r = .21, .29, and .23, for impulsivity, inattention and overall ADHD symptom severity, respectively). This specific cortisol pattern in AE patients with increased ADHD-like behavior of small effect size matches HPA axis alterations previously described in our ADHD patient group suggesting that distinct ADHD traits, namely impulsivity and/or inattention, may be particularly linked to HPA axis dysregulation even in absence of a clinical manifestation of ADHD. This finding underscores the importance of focusing future studies on HPA axis when investigating the manifestation of ADHD in children with atopic diseases.

When considering the limitations of the study, several aspects that may influence or limit our data should be discussed. First of all, the number of children included in the

study is rather small. Regarding the non-unitary nature of ADHD, a larger sample size would be necessary to differentiate between ADHD subtypes, allowing for a detailed examination of HPA axis function across varying ADHD dimensions. Second, the local ethics committee requested to limit the enrollment of participants with AE to very mild to mild cases, and low symptom severity might have hindered the detection of alterations in HPA axis function that would be visible with more pronounced AE symptomatology. Future studies are required that include a broader spectrum of symptom severity with regard to AE and consider symptom severity as a factor in the analyses (e.g., by contrasting individuals with low, moderate, and severe AE presentations). Furthermore, recruitment of AE subjects with different disease severity or different type (atopic, non-atopic) would allow for further clarifying the impact of inflammatory state on HPA axis activity and ADHD dimensions. Such investigations should include assessments of inflammatory markers to further complete the picture. Third, there are potential modulating factors that were not assessed in this study but will be interesting to consider in future research. To give an example, changes in both sleep quality and quantity represent a shared feature of AE and ADHD (Camfferman et al., 2010; Diaz-Roman et al., 2016) that have been linked to HPA axis irregularities (Abell et al., 2016). Finally, our cross-sectional investigation provides only correlational data. Future research including experimental approaches, such as studying the effects of HPA axis stimulation or suppression on ADHD (and AE) symptomatology, may help to provide insight into potential causal relationships. The strength of the current work lies in the mixed sample of children, including a group of children with both diagnoses, and a careful assessments of different indicators of HPA axis activity representing different aspects of HPA axis function relevant to its role in everyday life, including basal activity and reactivity to environmental factors as well as varying assessment periods (min following awakening to months), allowing for an investigation of an HPA axis function profile rather than assessment of a single indicator only.

Taken together, our study revealed that in children aged 6-12 years, a diagnosis of ADHD (with or without comorbid AE) is associated with a reduced HPA axis response to an acute stressor. In this study, we did not detect a significantly altered HPA axis activity in AE nor a significant interaction between AE and ADHD, which we discuss in light of the limited variation in AE symptom severity in this sample. However, in children with AE, HPA axis function was linked to (clinical and

subclinical) ADHD symptomatology with specific impact on inattention and impulsivity, while no such associations were observed in children without AE. This finding underscores the potential key role of HPA axis function in the coexistence of both diseases. Future studies are required to build on the reported findings and further explore the separate and joint role of HPA axis function in the pathophysiology of ADHD and AE.

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Table 1. Participants' characteristics

	AE (*n* = 37)	ADHD (*n* = 33)	AE+ADHD (*n* = 28)	HC (*n* = 47)	*p*
Demographics					
Age (years)	9.9±1.6	10.1±1.5	10.5±1.7	9.8±1.8	.346
Gender					**.026**
Male	28 (75.7)	27 (81.8)	17 (60.7)	25 (53.2)	
Female	9 (24.3)	6 (18.2)	11 (39.3)	22 (46.8)	
ADHD symptomatology[a]					
FBB-ADHS Hyperactivity	5.9±1.3^{1,2}	7.6±1.3^{1,3}	7.6±1.4^{2,4}	5.4±1.3^{3,4}	**<.0001**
FBB-ADHS Impulsivity	6.2±1.8^{1,2,3}	8.2±1.1^{1,4}	7.6±1.6^{2,5}	5.2±1.5^{3,4,5}	**<.0001**
FBB-ADHS Inattention	6.0±1.4^{1,2,3}	7.7±0.9^{1,4}	8.1±1.0^{2,5}	4.9±1.8^{3,4,5}	**<.0001**
FBB-ADHS Total Score	6.1±1.3^{1,2,3}	8.1±0.9^{1,4}	8.1±0.9^{2,5}	4.7±2.0^{3,4,5}	**<.0001**
AE symptomatology					
POEM[b]	8.8±5.6		11.0±6.4		.209
SCORAD Index[c]	27.6±17.1		25.3±17.8		.622

Note. Data are reported as mean±SD or *n* (%). *P* values from analysis of variance, $\chi 2$-test, or *t*-test. Identical superscript numbers indicate a significant post-hoc pairwise comparison (Tukey-Kramer honestly significant difference test). [a]Based on 34 individuals with AE, 31 individuals with ADHD, 26 individuals with AE+ADHD, and 45 HC. [b]Based on 33 individuals with AE and 21 individuals with AE+ADHD. [c]Based on 33 individuals with AE and 24 individuals with AE+ADHD. ADHD, attention deficit/hyperactivity disorder; AE, atopic eczema; FBB-ADHS, Fremdbeurteilungsbogen Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (observer-based evaluation questionnaire for ADHD); HC, healthy controls; POEM, Patient-Oriented Eczema Measure.

Table 2. Hypothalamus-pituitary-adrenal axis function by group

	AE (*n* = 37)	**ADHD (*n* = 33)**	**AE+ADHD (*n* = 28)**	**HC (*n* = 47)**
% change in salivary cortisol following the TSST-C[a]	100.1 (4.1-223.0)	42.8 (11.5-178.3)	29.4 (-9.7-107.3)	113.5 (25.8-396.8)
Diurnal salivary cortisol (nmol/L)				
Cortisol awakening response[b]	859 (649-1,142)	795 (690-1,139)	939 (702-1,294)	739 (587-1,104)
AUC_G diurnal profile[c]	7,144 (3,992-8,914)	6,770 (3,923-11,199)	7,546 (5,699-10,309)	6,534 (4,960-8,743)
Hair cortisol (pg/mg)[d]	3.8 (2.4-7.8)	5.7 (3.1-9.4)	4.1 (2.6-8.7)	3.4 (2.3-6.4)

Note. Data are reported as median (interquartile range). [a]Calculated as percent change from baseline to individual peak following the TSST-C. Based on 34 individuals with AE, 31 individuals with ADHD, 26 individuals with AE+ADHD, and 43 HC. [b]Calculated as AUC_G from waking up to +45 min measure. Based on 33 individuals with AE, 21 individuals with ADHD, 16 individuals with AE+ADHD, and 41 HC. [c]Calculated as AUC_G from waking up to 8 PM measure. Based on 24 individuals with AE, 17 individuals with ADHD, 12 individuals with AE+ADHD, and 26 HC. [d]Based on 30 individuals with AE, 24 individuals with ADHD, 27 individuals with AE+ADHD, and 44 HC. ADHD, attention deficit/hyperactivity disorder; AE, atopic eczema; AUC_G, area under the curve with respect to ground; HC, healthy controls; TSST-C, Trier Social Stress Test for Children.

Table 3. Hypothalamus-pituitary-adrenal axis function for the atopic eczema (AE), attention deficit/hyperactivity disorder (ADHD), and comorbid groups (AE+ADHD) against the healthy control group

	Quantiles									
	20th		30th		50th		70th		80th	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
% change in salivary cortisol following the TSST-C[a]										
AE	-8.23	.682	21.25	.510	-22.94	.760	-120.33	.400	-367.22	.177
ADHD	-3.50	.864	15.10	.566	-63.31	.393	-184.42	.137	**-366.38**	**.034***
AE+ADHD	-26.92	.067	-28.20	.212	-81.05	.248	**-241.50**	**.042***	**-466.94**	**.007****
Diurnal salivary cortisol (nmol/L): Cortisol awakening response[b]										
AE	-43.57	.689	95.35	.391	119.20	.229	72.38	.624	10.28	.942
ADHD	103.20	.350	119.76	.210	56.07	.624	63.20	.769	-3.22	.989
AE+ADHD	146.91	.343	163.55	.188	216.15	.106	261.44	.168	178.06	.300
Diurnal salivary cortisol (nmol/L): AUC_G diurnal profile[c]										
AE	-1,226.55	.328	609.22	.643	745.31	.480	656.87	.756	1,266.08	.632
ADHD	-970.00	.531	-820.44	.547	705.29	.695	1,630.43	.506	2,691.44	.358
AE+ADHD	750.50	.504	595.07	.586	929.03	.521	1,884.52	.417	2,265.67	.467
Hair cortisol (pg/mg)[d]										
AE	.219	.780	.00	1.00	.608	.594	1.82	.468	1.10	.735
ADHD	-.275	.724	.675	.501	2.23	.227	4.25	.081	2.79	.444
AE+ADHD	.374	.333	.270	.605	.878	.670	2.93	.225	1.96	.539

Note. Coefficients (β) were estimated from quantile regression analysis with the factors AE, ADHD, sex, and the comorbid group AE+ADHD. The healthy control group served as the reference group. Corresponding *p* values are given for each coefficient with a significance level of *$p < .05$ and **$p < .01$. [a]Calculated as percent change from baseline to individual peak following the TSST-C. Based on 34 individuals with AE, 31 individuals with ADHD, 26 individuals with AE+ADHD, and 43 HC. [b]Calculated as AUC_G from waking up to +45 min measure. Based on 33 individuals with AE, 21 individuals with ADHD, 16 individuals with AE+ADHD, and 41 HC. [c]Calculated as AUC_G from waking up to 8 PM measure. Based on 24 individuals with AE, 17 individuals with ADHD, 12 individuals with AE+ADHD, and 26 HC. [d]Based on 30 individuals with AE, 24 individuals with ADHD, 27 individuals with AE+ADHD, and 44 HC. AUC_G, area under the curve with respect to ground; HC, healthy controls; TSST-C, Trier Social Stress Test for Children.

Table 4. Relationship between attention deficit/hyperactivity disorder (ADHD) symptomatology and hypothalamus-pituitary-adrenal axis function for individuals with and without atopic eczema (AE)

FBB-ADHS Score	% change in salivary cortisol following the TSST-C[a]	Cortisol awakening response[b]	AUC_G diurnal profile[c]	Hair cortisol (pg/mg)[d]
Individuals with AE				
Hyperactivity	-.10	.01	-.02	.04
Impulsivity	**-.21***	-.11	-.005	.08
Inattention	**-.29****	.15	.23	.18
Total Score	**-.23***	.11	.20	.20
Individuals without AE				
Hyperactivity	-.05	-.12	-.14	.02
Impulsivity	-.06	-.09	-.17	.04
Inattention	-.16	-0.03	-.003	.08
Total Score	-.12	-0.09	-.09	.05

Note. Data represent Kendall's Tau-b. $^{**}p < .01$; $^{*}p < .05$. [a]Calculated as percent change from baseline to individual peak following the TSST-C. Based on 55 individuals with AD/AD+ADHD and 70 individuals with ADHD/HC. [b]Calculated as AUC_G from waking up to +45 min measure. Based on 44 individuals with AD/AD+ADHD and 60 individuals with ADHD/HC. [c]Calculated as AUC_G from waking up to 8 PM measure. Based on 31 individuals with AD/AD+ADHD and 42 individuals with ADHD/HC. [d]Based on 52 individuals with AD/AD+ADHD and 65 individuals with ADHD/HC. AUC_G, area under the curve with respect to ground; FBB-ADHS, Fremdbeurteilungsbogen Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (observer-based evaluation questionnaire for ADHD); TSST-C, Trier Social Stress Test for Children.

Figure 1. Quantile (black line) and linear regression (gray line) with 95% confidence intervals (ribbon and dotted lines) for percent change in salivary cortisol following the Trier Social Stress Test for Children (TSST-C) for attention deficit/hyperactivity disorder (ADHD), atopic eczema (AE), and comorbid groups (AE+ADHD) and sex against the healthy control group for different levels of the quantile.

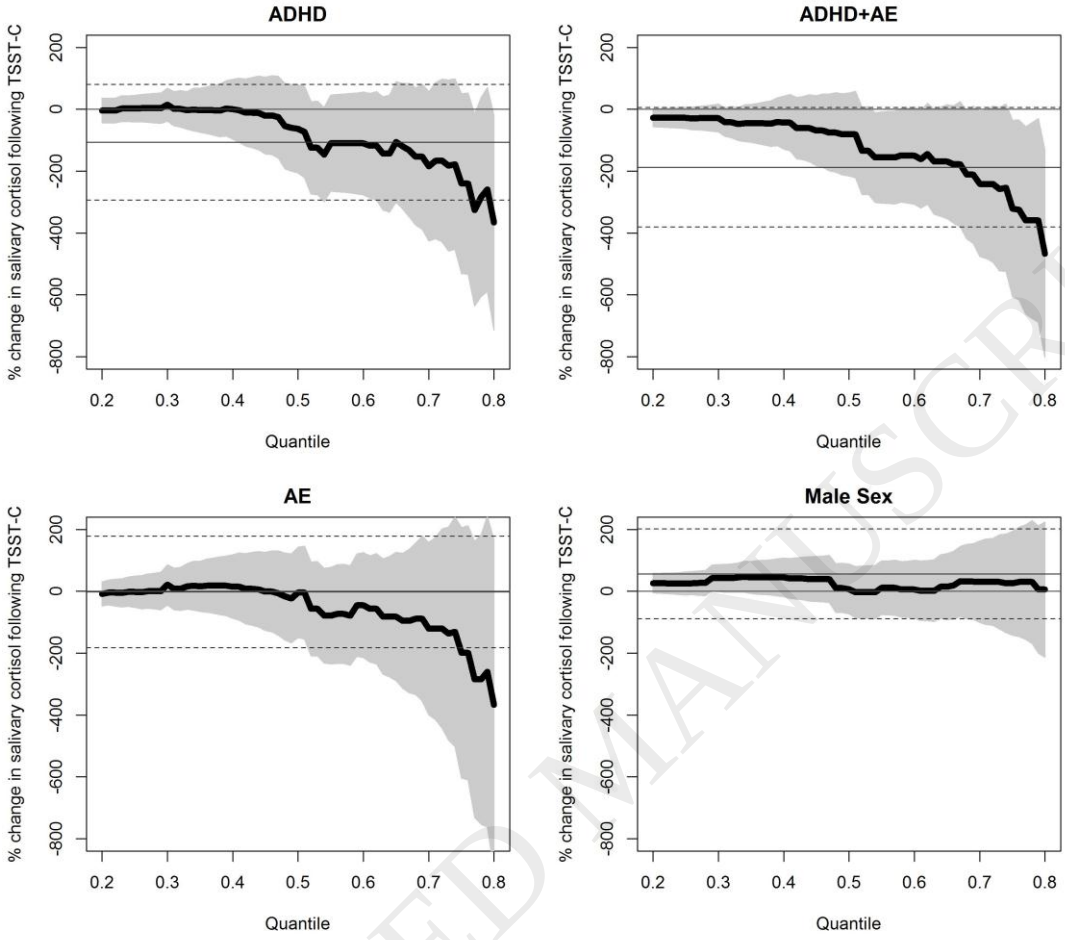

Figure 2. A. Salivary cortisol prior to and following the Trier Social Stress Test for Children (TSST-C) for children with atopic eczema (AE), attention deficit/hyperactivity disorder (ADHD), both diagnoses (AE+ADHD), and healthy controls (HC). Data represent means and SEM. **B.** Percent change in salivary cortisol from baseline to individual maximum following the TSST-C for children with AE, ADHD, AE+ADHD, and HC. Data represent medians and interquartile ranges.