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REVIEW

Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder

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Summary Epidemiological data indicate that atopic eczema (AE) in infancy significantly increases the risk for attention deficit/hyperactivity disorder (ADHD) in later life. The underlying pathophysiological mechanisms of this comorbidity are unknown. We propose that the release of inflammatory cytokines caused by the allergic inflammation and/or elevated levels of psychological stress as a result of the chronic disease interfere with the maturation of prefrontal cortex regions and neurotransmitter systems involved ADHD pathology. Alternatively, increased stress levels in ADHD patients may trigger AE via neuroimmunological mechanisms. In a third model, AE and ADHD may be viewed as two separate disorders with one or more shared risk factors (e.g., genetics, prenatal stress) that increase the susceptibility for both disorders leading to the co-occurrence of AE and ADHD. Future investigation of these three models may lead to a better understanding of the mechanisms underlying the observed comorbidity between AE and ADHD and further, to targeted interdisciplinary primary prevention and treatment strategies.

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Contents

1. Atopic eczema: epidemiology, clinical aspects and pathology

Atopic eczema (AE), allergic rhinitis and allergic asthma are among the most common chronic diseases worldwide and represent the three major clinical manifestations of atopy. Currently more than 30% of the population in Western industrialized countries is suffering from at least one atopic disease and prevalences have been predicted to further increase in the next decade (Bjorksten et al., 2008; Committee, 1998; Shamssain, 2007).

AE is the first manifestation of atopy and represents the most common chronic disorder within the first two years of life (Illi et al., 2004; Schmitt et al., 2009c; Williams, 2005). AE is a multifactorial, chronically persistent or chronically relapsing skin disease characterized by dry skin, intense pruritus, and inflammatory skin lesions. Although often trivialized, AE constitutes a major public health problem not only because of its high prevalence rate and substantial economic costs accrued by health care utilization (Su et al., 1997; Weinmann et al., 2003), but also because of its negative impact on the life quality of the affected patients and their families (Carroll et al., 2005; Lewis-Jones, 2006; Schmitt et al., 2009a; Wittkowski et al., 2004).

Most recently it could be demonstrated that impairment of the epidermal skin barrier is a key feature of AE. Null mutations in the gene that encodes the key epidermal protein, filaggrin, are the strongest known risk factors to date (Barker et al., 2007; Baurecht et al., 2007; Palmer et al., 2006) (see below for more details). Additionally, immunoregulatory abnormalities such as hypersecretion of immunoglobuline-E (IgE), recruitment and activation of eosinophils and T cell dysfunction have been found to be key factors in AE pathology. AE is considered to be biphasic and a switch from a predominant TH2 immune response in the acute phase toward a TH1 polarization in the chronic phase is broadly accepted. The onset of acute AE is strongly associated with increased production of TH2 cytokines such as IL-4, IL-5, IL-10, IL-13, IL-17 and IL-31 while consolidation and aggravation of AE is dominated by a secretion of TH1-derived cytokines, for example IFN-γ, IL-1β, IL-6, IL-8 and TNF-α (Carmi-Levy et al., 2011; Werfel, 2009). TH2-cytokines are important stimulators of IgE secretion by B cells and eosinophil recruitment, both known to be strongly involved in the allergic inflammatory processes of the skin (Del Prete, 1998; Leung and Bieber, 2003; Novak et al., 2003). TH1 cytokines support the function of macrophages, NK cells and keratinocytes (Werfel, 2009). In the majority of AE patients, significant colonization with *Staphylococcus aureus*, probably due to a diminished antibacterial function of the skin is observed. *S. aureus* can induce TH2 responses by endotoxins with superantigenic properties and thereby act as potent trigger factor (Roll et al., 2004). Furthermore, a decreased number of infections during childhood (hygiene hypothesis) and increased psychosocial stress in everyday life are discussed to be relevant in AE. Both factors have been found to induce and consolidate a TH2 immune response and thus, may trigger AE (Arndt et al., 2008; Flohr, 2003). Taken together, in AE a genetically inherited defective skin barrier function and an abnormal predominant TH2 immune response are the hallmarks of AE pathology. Environmental factors are suggestive to influence the development and course of AE, but their individual pathological relevance and their interaction with these hereditary factors are still poorly understood.

2. Attention deficit/hyperactivity disorder (ADHD): epidemiology, clinical aspects and pathology

Both main diagnostic schemata for childhood ADHD — the hyperkinetic disorder in the ICD-10 (WHO, 1996), and the more broadly conceptualized DSM-IV-TR (APA, 2000), are defined by the three core symptoms hyperactivity, inattention and impulsivity that had to be present before school age. ADHD has been recognized in different cultures and countries all over the world (Polanczyk et al., 2007). With a worldwide prevalence of about 5%, the individual regional prevalence rates range from 2% to over 10% depending on the diagnostic criteria applied (Polanczyk et al., 2007). In clinical samples the sex ratio is commonly assumed to be 3—6 boys to 1 girl although epidemiological samples tend to be more evenly distributed. First symptoms usually