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Review article

Seasonality and autoimmune diseases: The contribution of the four seasons to the mosaic of autoimmunity

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ABSTRACT

Autoimmune diseases (ADs) are a heterogeneous groups of diseases that occur as a results of loss of tolerance to self antigens. While the etiopathogeneis remain obscure, different environmental factors were suggested to have a role in the development of autoimmunity, including infections, low vitamin D levels, UV radiation, and melatonin. Interestingly, such factors possess seasonal variation patterns that could influence disease development, severity and progression. Vitamin D levels which reach a nadir during late winter and early spring is correlated with increased disease activity, clinical severity as well as relapse rates in several disease entities including multiple sclerosis (MS), non-cutaneous flares of systemic lupus erythematosus (SLE), psoriasis, and rheumatoid arthritis (RA). Additionally, immunomodulatory actions of melatonin secretion ameliorate the severity of several ADs including MS and SLE. Melatonin levels are lowest during spring, a finding that correlates with the highest exacerbation rates of MS. Further, melatonin is postulated to be involved in the etiopathogenesis of inflammatory bowel diseases (IBD) through it influence on adhesion molecule and therefore transcription factor expression. Moreover, infections can mount to ADs through pro-inflammatory cytokine release and human antigen mimicry. Seasonal patterns of infectious diseases are correlated with the onset and exacerbation of ADs. During the winter, increased incidence of *Epstein-Barr* virus (EBV) infectious are associated with MS and SLE flares/onset respectively. In addition, higher *Rotavirus* infections during the winter precedes type 1 diabetes mellitus onset (T1DM). Moreover, *Escherichia coli* (*E. coli*) infection prior to primary biliary cirrhosis (PBC) and T1DM disease onset subsequent to *Coxachievirus* infections are seen to occur during late summer, a finding that correlate with infectious agents' pattern of seasonality. In this review, the effects of seasonality on the onset, relapses and activity of various ADs were discussed. Consideration of seasonal variation patterns of ADs can possibly provide clues to diseases pathogenesis and lead to development of new approaches in treatment and preventative care.

Contents

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1. Introduction

Autoimmune diseases (ADs) are chronic conditions that occur due to a loss of immunological tolerance towards self-antigens, causing an immune response against self-tissues [1]. The pathogenesis of ADs comprises a series of complex interactions between genetic, environmental and hormonal factors [2–4]. Various environmental variables, either conferring protective or deteriorating effects, can be associated with ADs, including infectious agents, vaccines, smoking, and dietary factors, among the others [5–7]. Levels of vitamin D, exposure to Ultraviolet (UV) radiation, levels of melatonin and infections exhibit a seasonal variation pattern [8–11]. Recent studies have demonstrated the potential role of seasonality in the incidence/prevalence and disease activity of various ADs [12–17].

In particular, infections are a well-known environmental factor in the world of autoimmunity, and specific pathogens were previously associated with different ADs [18,19]. Several studies described the variability of infection incidence/prevalence in different seasons [20–22], bacterial pathogens of the respiratory tract, such as *Mycoplasma pneumoniae* (*M. pneumoniae*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Chlamydia psittaci* (*C. psittaci*), and *Coxiella burnetii* (*C. burnetii*), are more prevalent during spring time [23], while various viral infections, such as *Enterovirus*, are more prevalent during late summer and early autumn [24,25].

Body levels of vitamin D are documented to fluctuate with changing seasons, due to the influence of UV radiation exposure during different times of the year and to location [26]. Seasonal relapses of ADs could also be explained by low UV exposure, and, therefore, low levels of vitamin D, a well-known immunomodulator [27,28].

Moreover, melatonin is a hormone responsible for the circadian rhythms of different physiological functions. Its secretion from the pineal gland changes according to daylight time and night length and with seasons [29]. Melatonin has anti-inflammatory properties mediated by its inhibition of inflammatory cytokines as well as its influences on different arms of the immune system [30,31].

Other environmental factors such as dietary intake have yet not been firmly established, its impact has been suggested by the higher prevalence of ADs in certain geographical areas as compared to other regions [32]. Western diet, which is based on high fat and sodium diet, is postulated to perturb the immunologic balance, influence the gut microbiota and as a result heightens the risk of ADs in western countries [33,34]. A steep incline in the former lower prevalence areas of ADs is being explained by the westernization of these regions [35]. Therefore, diet appear to rather affect geographical spread of disease. Up till now, the influence of diet alterations and availability of food throughout the year on AD nature have not been studied.

In this review, we report the current knowledge on the association between seasonal factors and relevant ADs (Fig. 1), such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), type 1 diabetes mellitus (T1DM), inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), autoimmune liver diseases (ALDs), autoimmune thyroid disease (AITD), celiac disease, Sjögren's syndrome (SS), systemic sclerosis (SSc) and psoriasis (Tables 1–5).

2. Multiple sclerosis and seasonality

MS is an autoimmune, inflammatory disease, targeting the myelin of the central nervous system (CNS) [36]. MS is a complex disease with an unclear etiology, even though epidemiological studies seem to support the potential role of genetic and environmental risk factors [11,37,38].

In the first pioneering study on the topic, carried out in 1987, a higher susceptibility to developing MS was observed in individuals who were born in the spring, as contrasted to births during the winter months [39]. These findings were also replicated and supported by later studies that demonstrated a higher observed-to-expected ratio of MS in individuals born in April (odds ratio, OR, 1.21 [95% confidence interval, CI, 1.08–1.36]) [40]. Additionally, in a population-based study performed in Northern Europe, a lower risk of disease development in individuals born in November was reported, as compared to births during the month of May [41]. Interestingly, the association between the birth month and the occurrence of MS was stronger in patients possessing the HLA-DRB1 haplotype [42,43], which is a haplotype that confers an increased risk of MS development [44]. These studies, along with others, suggest a possible interaction between seasonal factors during the prenatal as well as perinatal period, and risk for MS. It is postulated that reduced maternal sun exposure, and, thus, decreased levels of vitamin D, during this critical period, may increase the risk of disease development in births during the spring [45].

The association between vitamin D levels and MS has been extensively studied. Higher levels of circulating vitamin D were associated with lower risk for developing MS as compared to low levels of vitamin D [46]. These results were replicated in another study which also showed a significant inverse relationship between plasma vitamin D levels and the risk of MS development (OR 0.59 [95% CI 0.36–0.97]) [47].

UV light, which is essential for vitamin D production in the skin, is usually higher near the equator and lower in latitudes far away from the equator. In epidemiological studies investigating MS