Clinical and Experimental Rheumatology 2003; 21: 148-150.

Solar light effects on onset/relapses and circannual/circadian symptomatology in rheumatoid arthritis

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Key words: Circardian rhythms, rheumatoid arthritis, solar light effects, circannual rhythms in RA, onset of RA.

Solar light and onset relapses

In an article in this issue, Rozin *et al*. report the results of their study on the possible effect of solar light on the seasonal distribution of relapses in rheumatoid arthritis (RA) and spondyloarthropathy (SpA) (1). The conclusions of the authors are quite stimulating for further analysis of the problem.

In their study the authors found relapses to be more frequent during the summer of the year 2000 in seropositive RA (spRA) but not in seronegative RA (snRA) or SpA patients, while no seasonal predominance was observed during 1998-1999 for any of these patients. As a matter of fact, increased solar activity during the summer of 2000 with the accompanying noxious effect of an increased ultraviolet B/A ratio and the overproduction of heat shock proteins may be inferred to have been the cause of the relapses. A mild inverse correlation was demonstrated for solar activity and the SpA relapse rate during a 3-year assessment period.

The authors concluded after an extended follow-up period that the timing of relapse onset of arthritis was almost independent of solar activity, even if in any given year a correlation may be seen; this could either be coincidental or reflect real relationship. The findings underline the importance of following the dynamics of solar flares and disease relapses in the inflammatory arthritides.

In discussing their results, the authors suggest several possible factors that might link sunlight with the articular inflammatory process. First, the higher absolute level of solar flux in July. Second, the closer proximity of the peaks of solar flux provides a maximal concentration of solar energy during the summer months (solar activity was measured using the "Solar Terrestrial Activity Report Chart 1998-2000" available at www.dxlc.com/solar). Consequently, an increased ultraviolet B/A ratio during the summer months is observed, since the propagation of solar activity may aggravate the negative influence of UVB. Other suggested factors include thermal effects and the overproduction of heat shock proteins (HSP), nucleotide pool activation during the summer season in the T-lymphocytes of RA patients, as well as the biological action of parameters such as relative humidity, barometric pressure, wind speed, and precipitation.

In addition, the seasonal use of chemical agents in agriculture, the interaction of solar radiation with medications, seasonal fluctuations in lysosomal enzyme activity in the synovial fluid of RA patients, and finally the association of seasonal infections are discussed as further possible factors by the authors. However, this study was limited to the role of solar factors in the seasonal distribution of disease relapse.

Concerning the symptoms of the articular inflammatory diseases, it is generally retained that heat acts as a palliative and cold as a local stress factor, even if clinical practice indicates the opposite. Treatment of an inflammatory joint with heat results after a short time in increased inflammation and swelling. Therefore, the summer season in sunny geographic areas with a maximal concentration of solar energy, such as Israel, might well represent a condition for worsening RA if the patient is exposed for a long period of time to such a risk factor.

It is interesting to note that the same vasodilatatory effects induced by high temperatures, which seem to exert a negative influence at the level of the inflamed synovial tissue, on the contrary improve other pathological conditions such as the vascular vasoconstriction in Raynaud's phenomenon (2).

However, the role that solar light may play in disease onset in RA and generally in other autoimmune diseases would seem to be more complex than a simple influence on disease relapse.

Solar light: Role in disease onset and circadian rhythms

As the authors themselves note, the role of sunlight (duration and/or intensity) on disease onset seems to be supported by serveral clinical data. For example, across Canada the appearance of systemic-onset juvenile rheumatoid arthritis was constant across seasons with the exception of one region, with peaks seen in the autumn and early spring (3). On the other hand, there is

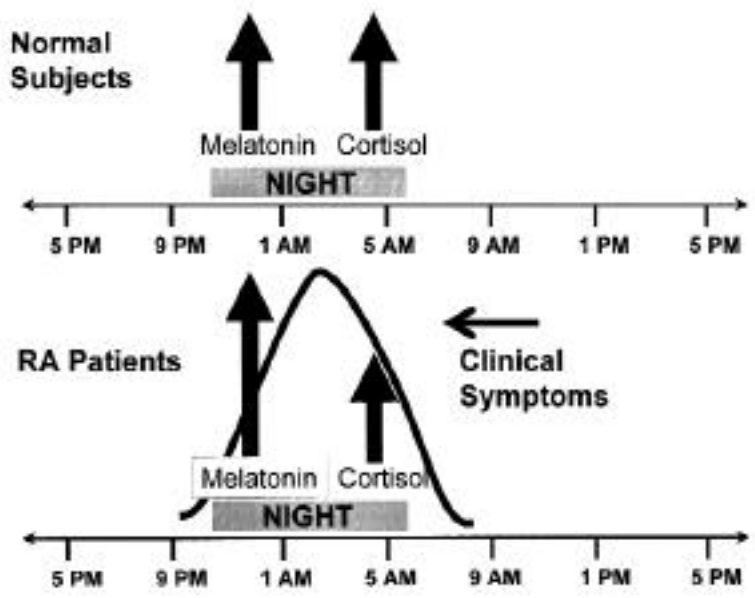

Fig. 1. The role of cortisol and melatonin in clinical circadian rhythms in rheumatoid arthritis patients.

data for the northern hemisphere, where the onset of RA from October to March was found to be twice as frequent as in other months (4). Furthermore, in a cohort of 106 ankylosing spondylitis patients, lumbar spine flexibility and quality of life improved in the summer and deteriorated during the cold season (5).

Analogously, the prevalence of rheumatic diseases, and particularly of RA, is much higher in northern than in southern Europe. Values include a prevalence of 0.9 in Denmark, Sweden and Finland as opposed to 0.2 in Greece and 0.3 in Italy (6). Recently a north-south gradient has been described (7). The incidence of autoimmune diseases decreases from north to south in the northern hemisphere and the contribution of the environment to this gradient seems to be important (7).

It is furthermore well established that some of the clinical signs and symptoms of RA vary during the course of 24 hours and between days, and indeed the morning stiffness observed in RA patients has become one of the diagnostic criteria of the disease (8). Among the signs of joint inflammation in RA patients, the intensity of pain varies consistently as a function of the hour of the day: pain is greater after waking up in the morning than in the afternoon or evening (9) (Fig. 1).

The production of important circadian hormones such as the adrenal hormone cortisol and the pineal hormone melatonin (MLT), have been implicated in the control of the inflammatory reaction, at least in RA. Recently, intact ACTH secretion but an impaired cortisol response in patients with active RA has been described and this observation was consistent with a relative adrenal glucocorticoid insufficiency (10, 11). On the contrary, basal concentrations and the nocturnal rhythm of MLT in RA patients show peak levels earlier and of longer duration in the early morning when compared to normal subjects (12,13) (Fig. 1). Notably, cortico-steroids exert anti-inflammatory and immunosuppressive activities whereas MLT is characterized by immunoenhancing and pro-inflammatory activities, partially related to a modulation of cytokine production, at least in RA (14-16). In particular, the IFN-γ/IL-10 ratio peaks during the early morning and correlates negatively with plasma cortisol and positively with plasma MLT (17). IFN-γ and IL-10 might be considered markers of cellular (type 1) and humoral (type 2) immunity, respectively.

Several studies suggest that there is a bias towards cellular (Th 1) immunity during the night and early morning (peak of MLT), when the IFN-γ/IL-10 ratio is high and conversely a relative bias towards humoral (Th 2) immunity during the rest of the day (18). Therefore RA, which is considered to be a Th1 disease, might well worsen during the night and early morning.

Possible modulatory role of sunlight on the neuroendocrine network in RA

In adult primates only visible light (400-700 nm) is received by the retina. This photic energy is then transduced and delivered to the visual cortex and, by an alternative pathway, to the suprachiasmatic nucleus (SCN), the hypothalamic region that directs circadian rhythms. Visible light exposure also modulates the pituitary and pineal glands, leading to neuroendocrine changes. MLT, norepinephrine, and acetylcholine decrease with light activation, whereas cortisol, serotonin, GABA, and dopamine levels increase (19). Thus, ocular light appears to be the predominant time cue and major determinant of the circadian rhythm for many neurohormones. Cortisol and MLT show an opposite response to the light.

Light conditions in the early morning have a strong impact on the morning-cortisol peak, whereas MLT is synthesised in a strictly nocturnal pattern. Direct inhibitory effects of light on pineal activity may contribute to the phasing of the onset and termination of MLT production (20, 21). An imbalance between the anti-inflammatory effects of cortisol and the proinflammatory effects of MLT during the night seems to be evident in RA patients and suggests that this imbalance might play a crucial pathogenic role in RA onset, as well as in driving the circadian rhythm of the clinical symptoms (i.e., morning stiffness and pain) (Fig. 1) (22).

Of great interest are both the higher prevalence of RA in the northern hemisphere and the higher frequency of onset in the winter characterised by prolonged darkness. Therefore, several studies have been planned between northern and southern European populations to evaluate whether different climatic conditions (i.e., prolonged daily darkness) might interfere with the circadian rhythm of MLT and cortisol

production as well as with RA symptoms. One large study involving RA patients from Italy and Estonia has already been launched to elucidate the role of these factors, and in particular prolonged darkness.

Conclusions

In conclusion, the study by Rozin *et al.* is of great interest and represents a strong stimulus to further investigate another environmental factor involved in the pathophysiology of RA, namely the effects of sunlight on the neuroendocrine immune system. This aspect has been neglected for many years. Finally, we agree with the suggestions of the authors that "the solar factor and other possible contributory factors should be further investigated" to better understand their real influence on the circannual rhythm, as well as on disease onset and circadian disease rhythms, in RA and other arthritides (i.e., SPA).

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