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Predictors of autonomic neuropathy in rheumatoid arthritis

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ABSTRACT

Objective: Autonomic dysfunction occurs in rheumatoid arthritis (RA). However, the association between the autonomic dysfunction and inflammation has not been investigated in RA. We investigated the relationship between inflammation and ANS function in RA.
Methods: In this cross-sectional study, 25 RA patients and 25 age and sex-matched healthy controls were recruited. Autonomic function assessed by five cardiovascular reflex tests according to Ewing. Parasympathetic dysfunction established by applying three tests: heart rate response to deep breath (HRD) and standing (HRS) and Valsalva tests. Sympathetic dysfunction examined by applying two tests: BP response to standing and handgrip test. Peripheral sympathetic autonomic function assessed by Sudoscan through measurement of electrochemical skin conductance of hands and feet. Sudoscan investigates the sweat gland activity and used as a surrogate to study the damage of sympathetic sudomotor nerves in neuropathy. It is an indirect assessment tool of sudomotor function. Disease-specific and inflammatory measures (DAS 28, ESR, CRP, TNF-α, IL-6 and IL-1) were determined.
Results: RA patients had significantly impaired HRD, HRS, BP response to hand grip and sudomotor function as compared to healthy controls. Pro-inflammatory cytokines were significantly higher in RA as compared to healthy controls ($p < 0.05$). DAS 28 significantly correlated with HRD in RA. ESR significantly correlated with HRD and HRS. TNF-α significantly correlated with HRD, HRS, BP response to standing and sudomotor function. Significant correlation was found between IL-6 and HRS. Seropositive patients had more pronounced CAN and sudomotor dysfunction.
Conclusion: Autonomic dysfunction in RA is related to disease activity, seropositivity and pro-inflammatory cytokines.

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis known to be associated with autonomic dysfunction (Stojanovich, 2009). In rheumatic diseases the prevalence of cardiovascular autonomic neuropathy (CAN) is 24–100% (Aydemir et al., 2010). The inflammation in RA begins and continues in joints and there is little explanation of why extra-articular manifestations develop in some patients of RA. These include pericarditis, pleuritis, major cutaneous vasculitis, Felty's syndrome, autonomic neuropathy, ophthalmological manifestations, glomerulonephritis, and other types of vasculitis and these extra-articular features vary with the duration and severity of the disease (Gordon et al., 1973; Hart, 1969; Vollertsen et al., 1986). The exact mechanism of autonomic neuropathy in RA remains to be elucidated. It could result from vasculitis, amyloidosis or therapeutic side effect, circulating auto-antibodies directed against nervous structures, represented by superior cervical ganglia and vagus nerve (Maule et al., 1997). Inflammatory products (TNF-α, IL-1, High mobility group B1) produced in the damaged tissues activate afferent signals that are relayed to the nucleus tractus solitaries with subsequent activation of vagus efferent activity. Efferent activity in the vagus nerve leads to Acetylcholine (ACh) release in organs of the reticuloendothelial system which can interact specifically with α7 subunits of nicotinic ACh receptors. The interaction of ACh with macrophage α7 subunits deactivates macrophages, and inhibits cytokine release (Waldburger and Firestein, 2010). This neural control of cytokine production provides an important alternative to the humoral regulation of cytokine responses, because neural regulation is fast, integrated, and not specifically dependent on relatively slow concentration gradients (Czura and Tracey, 2005).

Inflammation can also be relayed to the hypothalamus and the dorsal vagal complex to stimulate the release of adrenocorticotropic hormone, thereby activating the humoral anti-inflammatory pathway. Activation of the sympathetic outflow by pain or by direct signalling,

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can increase local concentrations of adrenaline and noradrenaline, which can suppress inflammation further (Tracey, 2002). Interruption of these homeostatic mechanisms by the disease process aggravates inflammation. If the cytokine response is unbalanced or excessive as occurs in RA, then these mediators can cause disease and its sequelae including autonomic dysfunction.

Parasympathetic autonomic dysfunction in RA, reflected low vagus activity, relates to increased level of IL-1β (Altawil et al., 2012). Heart rate variability, also a marker of vagus nerve tone, is inversely related to levels of inflammatory markers (IL-6 and CRP) (Sloan et al., 2007). Anticytokine therapy with synthetic DMARDs (disease modified antirheumatic drugs) and biologic DMARDs improves cardiovascular autonomic neuropathy in RA and AS (Syngle et al., 2013b, 2015a; Verma et al., 2014). However, more potent treatment with biologic DMARDs improves parasympathetic and sympathetic autonomic dysfunction to a greater extent in RA and AS (Syngle et al., 2015b). IL-6 blockade with tocilizumab also improves autonomic neuropathy in RA (Syngle et al., 2015a). Autonomic dysfunction has not been explored in detail in RA with respect to inflammatory cytokines. Thus, we examined the relationship of pro-inflammatory cytokines, disease activity and disease severity with autonomic neuropathy in Indian RA patients.

2. Materials and methods

2.1. Patients

This was a cross-sectional study in which 25 RA patients (21 female and 4 male, 16 rheumatoid factor (RF) positive, aged 22–57 years) who fulfilled the ACR 2010 classification criteria (Aletaha et al., 2010) and 25 age and sex matched healthy control (20 female and 5 male, aged 23–55 years) subjects without any symptoms of autonomic dysfunction were recruited.

The patients with renal or liver insufficiency, diabetes mellitus, thyroid, skin and vascular disorders, vitamin B_{12} deficiency, anaemia, paraneoplastic neuropathy, alcoholism, cardiac failure, cardiac arrhythmia, acute thrombosis, pericarditis or nephritis, smokers, patients taking medications likely to affect autonomic neuropathy and sudomotor function (anticholinergics, antihypertensive drugs, neuroprotective drugs and steroids) and pregnancy were excluded from the study. Patients with disorders responsible for neuropathy and neurological disorders other than rheumatoid arthritis were excluded.

The study protocol was approved by institutional clinical ethics committee of Punjabi University, Patiala, India and was performed in accordance with the declaration of Helsinki and the code of Good Clinical Practice. All patients provided written informed consent to participate after a full explanation of the study.

In all subjects, blood was drawn in the morning and the following variables were determined: a complete blood count, liver function tests, renal function test, thyroid stimulating hormone, fasting blood sugar and vitamin B_{12}. All these investigations were analysed on the same day as the autonomic system analysis.

2.2. Assessment

Cardiovascular autonomic neuropathy (CAN) was diagnosed by applying five cardiovascular reflex tests, described by Ewing and Clarke (1986). Parasympathetic dysfunction was established by applying three tests: heart rate response to deep breathing and standing and Valsalva tests. Sympathetic dysfunction was examined by applying two tests: blood pressure response to standing and handgrip test. CAN was considered to exist if at least two tests were positive out of five (Aydemir et al., 2010). Peripheral sympathetic autonomic function was assessed by FDA approved Sudoscan (Impeto Medical Device, EZS 01750010193, Paris, France) (Mayaudon et al., 2010).

2.2.1. Cardiovascular autonomic function assessment

2.2.1.1. Parasympathetic function was diagnosed by applying.

A. Heart rate response to deep breaths (HRD): Participants lay flat. After the pulse had steadied, the pulse rate was recorded during six slow maximal deep breaths. In normal subjects the pulse rate should fall by ≥15 beats, borderline 11–14 beats and with autonomic disturbances ≤10 beats per minute (Ewing and Clarke, 1986).
B. Heart rate response to standing up (HRS, 30:15 ratio): Participants were asked to stand up after a 10 minute resting period in supine position while simultaneous ECG and beat-to-beat blood pressures were recorded. The quotient of the shortest RR interval around the 15th beat just after standing and the longest RR interval around the 30th beat after standing is considered as the 30:15 ratio.
C. Heart rate response to Valsalva manoeuvre: The test was performed by asking the subject to sit quietly and then blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg for 15 s. The ratio of the longest RR interval shortly after the manoeuvre (within about 20 beats) the shortest RR interval during the manoeuvre was then measured. The result was expressed as the Valsalva ratio which is taken as the mean ratio from three successive Valsalva manoeuvres. In normal subjects, the Valsalva ratio is ≥1.21 and with autonomic disturbances ≤1.20 (Ewing and Clarke, 1986).

2.2.1.2. Sympathetic function was diagnosed by applying.

A. Blood pressure response to standing (BPS): Participants were asked to stand up for 3 min after a 10 minute resting period in a supine position. The systolic and diastolic blood pressure (SBP and DBP), just before standing and 3 min after active standing were determined to define postural change in blood pressure.
B. Blood pressure response to handgrip (BPH): Three consecutive (within 5 minute resting periods) handgrip tests were performed by the patients for 2 min while beat-to-beat blood pressure was recorded simultaneously. The absolute difference between the highest DBP during handgrip and the basal DBP just before the handgrip is noted. A rise in DBP ≥16 mm normal, 10–15 mm borderline and ≤10 mm abnormal (Ewing and Clarke, 1986).

2.2.2. Evaluation of peripheral sympathetic autonomic function by Sudoscan

Peripheral sympathetic autonomic function was assessed by using simple non-invasive device Sudoscan (Impeto Medical Device, EZS 01750010193, Paris, France) which facilitates easy, quick and quantitative assessment of sudomotor function (Mayaudon et al., 2010).

It is designed to perform the precise evaluation of sweat gland function based on sweat chloride concentrations through reverse iontophoresis and chronoamperometry. The body's sweat glands are linked to the autonomic nervous system via sympathetic C fibers. These fibers are long, thin, unmyelinated or thinly myelinated fibers. Because of these characteristics, they are prone to damage early in many neuropathic processes; assessing sweat gland nerve function, or dysfunction, therefore, can be used as a surrogate for the damage imparted to small caliber sensory nerves in neuropathy. In addition, as the recovery of autonomic nerve fibers is quicker than that of sensory nerves, sudomotor function testing (SFT) could be used as an early indicator of treatment efficacy in neuropathy. Evaluation of CAN must assess the 3 components of the autonomic system: cardiovagal (parasympathetic), adrenergic (sympathetic), and sudomotor (sweating) functions. Sudoscan, may allow wider clinical screening for CAN and assessment of treatment response (Vinik et al., 2013).

It consists of two sets of electrodes for the hands and feet which are connected to the computer for recording and data management. The subject places the palms of the hands and the soles of the feet on the