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Review article

The risk of ischemic stroke in major rheumatic disorders☆,☆☆

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ABSTRACT

Rheumatic disorders (RD) are a range of conditions associated with inflammation of joints and connective tissue. They can manifest beyond the musculoskeletal system. Recent focus has been placed on the association of ischemic stroke with these conditions. Traditional vascular risk factors seem to be more prevalent in patients with certain types of RD than in the general population, but these factors do not fully explain the enhanced vascular risk in this population. Four major RD will be discussed in terms of their relationship with ischemic stroke: rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and psoriatic arthritis.

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1. Introduction

Rheumatic disorders (RD) include a range of conditions associated with inflammation of joints and connective tissue. Depending on the specific disorder, RD can manifest beyond the musculoskeletal system. There are more than 100 different types of RD; the four major conditions are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) (Table 1) (Altman, 2011; Hajj-ali, 2011). All four disorders feature joint inflammation of some variety, but each condition has a unique set of extra-articular manifestations.

Neurological manifestations of RD have been extensively described (Sofat et al., 2006). Recent investigations have focused on the association of ischemic stroke (IS) with these conditions, but the exact mechanism of IS in these cases has not been delineated. Traditional vascular risk factors seem to be more prevalent in patients with certain types of RD than in the general population (Al Husain and Bruce, 2010). However, these factors do not fully explain the enhanced vascular risk in this population (Tyrrell et al., 2010). This review discusses IS in association with the four major rheumatic disorders.

2. Rheumatoid arthritis

RA is primarily characterized by chronic, progressive inflammation of smaller synovial joints, causing severe pain and deformity. The overall age- and sex-adjusted annual RA incidence is 40.9 per 100,000 (Myasoedova et al., 2010). Other potential features associated with RA are keratoconjunctivitis sicca, interstitial pulmonary fibrosis, and cardiovascular disease (Turesson and Matteson, 2004).

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Table 1
Overview of major rheumatic disorders. ANA = antinuclear antibody, anti-dsDNA = double-stranded DNA antibody, APA = antiphospholipid antibodies, anti-RNP = ribonucleoprotein antibody, AS = ankylosing spondylitis, anti-Sm = anti-Smith, DAMRD = disease-modifying anti-rheumatic drugs, NSAID = non-steroidal anti-inflammatory drugs, PsA = psoriatic arthritis, RA = rheumatoid arthritis, RF = rheumatoid factor, SSA = anti-Ro antibodies, SSB = anti-La antibodies, SLE = systemic lupus erythematosus, TNF-α = tumor necrosis factor alpha.

Condition	Principal clinical features	Serological marker	Typical joints involved	Treatment
RA	Joint swelling and tenderness Morning stiffness Rheumatoid nodules	RF	Interphalangeal Metacarpophalangeal Metatarsophalangeal	NSAID DMARD (methotrexate in particular) Glucocorticoids TNF-α antagonists
AS	Severe back pain Joint pain Axial stiffness Improvement of symptoms with exercise	None	Sacroiliac Zygapophyseal	NSAID DMARD (if peripheral joints are involved) TNF-α antagonists Surgery
SLE	Joint pain Mouth sores Malar (butterfly) rash Fever	ANA Anti-dsDNA Complement Anti-Sm SSA SSB Anti-RNP APA	Interphalangeal Metacarpophalangeal Metatarsophalangeal Wrist Knee	Glucocorticoids (oral or injection) Anti-malarial agents NSAID DMARD
PsA	Psoriatic skin rash Joint pain Morning stiffness	None	Any joint but usually interphalangeal (fingers and toes)	NSAID Glucocorticoid (topical and injection) DMARD TNF-α antagonists

Although some investigations have suggested that the incidence of cerebrovascular events, including IS, is similar in RA and non-RA subjects, accruing data suggest the contrary (Bacani et al., 2012). According to a recent Danish study involving 18,247 RA patients, who were followed for a median of 4.8 years, patients with RA have a 30% higher risk of IS compared to those without RA. The study also reported a 40% higher risk of atrial fibrillation in RA patients (Lindhardsen et al., 2012). In another study of 269 RA patients, the odds ratio (OR) for IS was estimated at 2.66, and the severity of RA and hypertension seemed to correlate positively with the risk of IS (Nadareishvili et al., 2008). Canadian investigators similarly demonstrated that patients with RA have double the rate of myocardial infarction and IS, when compared to the general population. The estimated absolute increase in stroke risk, according to their study, was 2.4 per 1000 person-years (Solomon et al., 2006). RA also has an impact on stroke-related mortality: a meta-analysis of 111,758 RA patients found a 50% increase in the risk of death from stroke, compared to the general population (Aviña-Zubieta et al., 2008; Södergren et al., 2009).

The pathogenic mechanism involved in augmentation of IS risk in RA is complex, and not fully understood. Current evidence suggests that systemic inflammation may play an important role. Elevated inflammatory markers such as the erythrocyte sedimentation rate (ESR) seem to correlate with an increased risk of IS in RA patients (Zhang et al., 2014). Elevated ESR is also a factor associated with accelerated atherosclerosis, when the progression of carotid intima media thickness (CIMT) is assessed (Del Rincón et al., 2014). In the Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program (QUEST-RA), traditional vascular risk factors were highly prevalent in RA patients, extra-articular disease was significantly associated with vascular morbidity, and the presence of hypertension and diabetes increased the risk of IS (hazard ratios (HR) of 2.81 and 2.23, respectively) (Naranjo et al., 2008). Overall, it appears that a combination of traditional and non-traditional risk factors contributes to the increased IS risk.

Disease-modifying anti-rheumatic drugs (DMARD, e.g. methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide) and tumor necrosis factor alpha (TNF-α) antagonists (infliximab, golimumab, etanercept, adalimumab, and certolizumab) show encouraging results for reduction of IS risk, although no randomized study has corroborated this trend. In QUEST-RA, one year of methotrexate therapy was associated with an 11% decrease in the risk of stroke (Naranjo et al., 2008). A longer exposure to TNF-α antagonists also lowered the risk for all vascular events (Naranjo et al., 2008). The use of non-steroidal anti-inflammatory drugs (NSAID) and cyclooxygenase-2 (COX-2) inhibitors had been shown to increase the risk of cardiovascular events, yet more recent data suggests that this risk is modest among RA patients specifically (Johnsen et al., 2005; *Lindhardsen et al., 2013*). After adjusting for age, sex, and socioeconomic status, one study estimated the HR for IS in RA patients exposed to COX-2 inhibitors at 1.154 (95% CI 1.030–1.294, $p = 0.01$), and after adjusting for other factors (including TNF-α antagonists, DMARD, and glucocorticoid use), put it at 1.106 (0.986–1.240, $p = 0.08$) (Bäck et al., 2012). It is therefore reasonable to suggest that, with the exception of rofecoxib, NSAID therapy in RA does not appear to have an additive effect on the risk of IS. The impact of glucocorticoids on this risk—harmful or beneficial—remains uncertain (Nadareishvili et al., 2008).

3. Ankylosing spondylitis

AS is a chronic inflammatory disease characterized by severe back pain and progressive rigidity of the spine (Dakwar et al., 2008). This disorder usually affects young men, and the overall incidence rate is 0.5 to 8.2 per 100,000 people (Sieper et al., 2006). AS primarily involves the sacroiliac joint and the axial skeleton, with gradual cementation of the vertebrae (Dakwar et al., 2008; Bay-Jensen et al., 2012). Extra-articular manifestations of AS include uveitis, aortitis, pulmonary fibrosis, psoriasis, and inflammatory bowel disease (El Maghraoui, 2011). Compared with the general population, AS patients have a 25% higher risk of cerebrovascular disease and IS, and this risk tends to be higher in patients aged 20 to 39 years (Szabo et al., 2011). A study of 4562 AS patients aged 18 to 45 years reported an HR of 1.93 for IS, after controlling for demographic and medical comorbidities (Lin et al., 2014) A population-based matched-cohort study in Taiwan showed that AS patients are also at risk of recurrent IS. A HR of 2.3 has been estimated for recurrent IS (Keller et al., 2014).

The pathogenic mechanism leading to IS is not clear (Nurmohamed et al., 2012). However, accelerated atherosclerosis associated with AS has been confirmed to contribute to an increased risk of vascular morbidity, independent of traditional risk factors (Hamdi et al., 2012). Progressive CIMT is a useful and non-invasive surrogate marker of pre-clinical atherosclerosis in AS patients (Hamdi et al., 2012). Compared to control groups, significantly more extensive CIMT has been observed in AS patients, which positively correlates with age and duration of disease (Gupta et al., 2014). Frequently, AS patients also