Rheumatoid arthritis and vascular dementia: do they have common pathogenetic mechanisms?

Fabiola Atzeni, MD, PhD
Rheumatology Unit, L.Sacco University Hospital, Milan

Central nervous system involvement is uncommon in patients with rheumatoid arthritis (RA), and the incidence of cerebrovasculitis (CV) ranges from 1% to 8%. It seems to affect only patients with seropositive RA (it shows a close relationship with RF titres), and may appear as part of a systemic manifestation of vasculitis or (less frequently) only involve the brain. It is mainly found in women aged >50 years with RA long-standing seropositive, and usually presents with polymorphic symptoms of headache, seizures and changes in mental status. Patients may have focal signs such as hemiplegia, partial epilepsy, cranial nerve involvement, or visual field loss, or diffuse manifestations denoting encephalitis, such as altered consciousness, confusion, and cognitive impairment or dementia. The clinical alterations surely reflect the extent of the underlying lesions.

The factors involved in the pathophysiology of the disease include endothelial cell antibodies, tumour necrosis factor (TNF), and anti-phospholipid antibodies. Perinuclear anti-neutrophil cytoplasmic antibodies have been found in 29% of patients with rheumatoid CV, thus suggesting that they may play a pathogenic role, and HLA DRB1 has also been encountered. The diagnosis is based on cerebrospinal fluid and imaging studies, but funduscopy should be used to rule out papilledema before performing a lumbar puncture. Cerebral MRI reveals a strong signal in the white matter and may show signal abnormalities in cortical regions or focal cortical atrophy. Although a definite diagnosis requires a cerebral and leptomeningeal biopsy, this is rarely used and its indications are poorly standardised.

Link between vascular dementia and Alzheimer’s disease

There is a particularly close association between vascular dementia and Alzheimer’s disease (AD).
and vascular risk factors. The pathological hallmark of AD is an accumulation of amyloid plaques and the formation of neurofibrillary tangles, whereas vascular dementia is characterised by ischemic damage and multiple infarctions due to the occlusion of cerebral blood vessels. Although the two diseases have long been considered separate entities, there is increasing evidence that the ischemic damage known to cause vascular dementia is also responsible for the development of AD, which may explain the overlap known as mixed dementia. In animal models, ischemia leads to increased amyloid deposition in the brain cortex, and it is likely similar processes occur in humans. Both high and low blood pressure are strong risk factors for vascular dementia, and obesity, diabetes and high mid-life total cholesterol levels are associated with an increased risk of AD. Cholesterol plays a major role in amyloid aggregation. Cholesterol-derived aldehydes promote the formation of Schiff’s base, thus accelerating the early stages of amyloidogenesis. Cerebral atherosclerosis is closely linked to the formation of neuritic plaques, and cholesterol has also been implicated in their pathogenesis. Inflammatory rheumatic diseases are associated with a substantial increase in accelerated atherosclerosis. It has been shown that mortality is higher in patients with RA than in the general population, and that most of the excess mortality is due to accelerated atherosclerosis. Although RA and atherosclerotic CV share risk factors such as smoking and a poor diet, the increased risk of CV in RA patients cannot be explained by traditional risk factors alone. Various disease-related mechanisms may be involved in the development of premature vascular damage, including an increased synthesis of pro-inflammatory mediators (cytokines, chemokines and adhesion molecules), autoantibodies against endothelial cell components, perturbations in T cell subsets, genetic polymorphisms and iatrogenic factors.

An inverse relationship between AD and RA due to various factors has been described. Like that of RA, the pathogenesis of AD is multifactorial and various findings support the inflammatory hypothesis. Neuro-inflammation seems to be an important step, as suggested by the presence of anti-neuronal antibodies in AD brain, circulating serum anti-A antibodies, higher levels of peptidylarginine-deiminase (PAD) and citrullinated proteins in hippocampal extracts, inflammatory
gene polymorphisms that influence the risk of developing AD, complement proteins co-localising in senile plaques and neurofibrillary tangles, and the increased levels of various inflammatory mediators in serum and brain tissue. The inverse incidence rates between AD and RA may even be explained by the deregulation of intrinsic cellular and molecular regulators of the inflammatory cascade.