Inflammation in Patients With Rheumatoid Arthritis and Fibromyalgia Associated with Pronociceptive Brain Connections

For patients with rheumatoid arthritis (RA), peripheral inflammation affects measures of brain functional connectivity as well as fibromyalgia (FM) status. These alterations in brain connectivity center on the insula, which is a multimodal sensory processing region that is critically involved in pain perception. In this issue, Kaplan et al (p. 41) report the results of their investigation into how peripheral inflammation, the principal nociceptive stimulus in RA, interacts with brain connectivity in RA patients with FM.

The group had previously identified the inferior parietal lobule (IPL) cluster as a region linked to levels of peripheral inflammation in patients with RA. In their current research, they expanded their investigation to the connectivity of the IPL and insula in patients with concomitant RA and FM. Their new results are the first neurobiologic evidence that FM in RA may be linked to peripheral inflammation via pronociceptive patterns of brain connectivity.

In this study, investigators examined patients with RA, some of whom had FM and some of whom did not. The 2 groups did not differ by age, sex, or erythrocyte sedimentation rate (ESR). They found that FM+ RA patients had increased functional connectivity of the insula–left IPL, left IPL–dorsal ACC, and left IPL–mPFC regions, and that these changes correlated with higher ESR levels. By performing post hoc interaction analyses, researchers were able to confirm the relationship between ESR and connectivity changes that occurred as FM scores increased. The findings suggest that, in patients with such “bottom-up” pain centralization, concomitant symptoms may partially respond to antiinflammatory treatments.

Tocilizumab Cardiovascular Risk Similar to That of Etanercept

Giles et al (p. 31) report the results of a cardiovascular (CV) safety trial of tocilizumab versus etanercept in rheumatoid arthritis. The ENTRACTE trial was designed to determine whether it was possible to rule out a relative risk for major adverse cardiovascular events (MACE) of 1.8 or higher in the tocilizumab group compared to the etanercept group. The investigators found that, by week 4, patients receiving tocilizumab had higher levels of low-density lipoprotein cholesterol (11.1% increase), high-density lipoprotein cholesterol (5.7% increase), and triglyceride (13.6% increase), compared to patients receiving etanercept. During a mean follow-up of 3.2 years, researchers documented 83 MACE in the tocilizumab group and 78 MACE in the etanercept group, with an estimated hazard ratio for MACE of 1.05 (95% confidence interval 0.77–1.43). Sensitivity analyses and an on-treatment population analysis revealed similar results.

The investigators’ results rule out a relative risk of 1.43 or higher for the occurrence of MACE in patients treated with tocilizumab. The investigators did note that adverse events such as serious infections and gastrointestinal perforation occurred more frequently in the tocilizumab group and concluded that their results should be interpreted in the context of the clinical efficacy and non-CV safety of tocilizumab.
As many studies measure serum uric acid (UA) levels in patients with gout, monosodium urate (MSU) deposits are central to the pathology of gout. In this issue, Choi et al (p. 157) report the results of their nationally representative study of men and women that investigated the role of 4 modifiable risk factors in hyperuricemia. They found that body mass index, the Dietary Approach to Stop Hypertension (DASH) diet, alcohol use, and diuretic use could be used to individually account for a substantial proportion of hyperuricemia cases. The investigators calculated the population attributable risks (PARs) of hyperuricemia cases for overweight/obesity (prevalence 60%), nonadherence to a DASH-style diet (prevalence 82%), alcohol use (prevalence 48%), and diuretic use (prevalence 8%) as 44%, 9%, 8%, and 12%, respectively. The researchers determined that the corresponding serum urate variance explained by these risk factors was very small and, paradoxically, masked their high prevalences. For example, the serum urate variance explained by adherence to the DASH diet was just 0.1%, a finding that was similar to one previously reported in an analysis of 5 U.S. cohorts. These patients also had antibodies to HisRS (anti-Jo-1) in BAL fluid and it was possible to identify germinal center-like structures in lung biopsy samples. The results suggest that immune activation against HisRS might take place within the lungs of patients with IIM/antisynthetase syndrome.

To investigate whether the presence and functionality of antigen-specific CD4+ T cells may vary in different compartments, the investigators analyzed T cell responses by measuring changes in CD40L expression in cells stimulated with HisRS protein or a HisRS-derived peptide (HisRS_{11-23}) compared to unstimulated cells. When they examined BAL fluid, they found that the highest frequencies of CD4+CD40L+ T cells were found in BAL fluid after stimulation with HisRS_{11-23} with a median fold change of 7.8% (IQR 1.37-29.9%), whereas in PBMCs, the median fold change was 0.38% (IQR 0.02-5.89), suggesting an enrichment of antigen-specific T cells in the lung. Further experiments revealed that HisRS-specific CD4+CD40L+ T cells in BAL fluid presented a proinflammatory Th1 phenotype with an increased production of IFNγ, when compared to the corresponding CD4+CD40L+ T cells from PBMCs. The researchers concluded that there is an increased reactivity against the HisRS protein, and in particular the HisRS-derived peptide HisRS_{11-23} in lung-derived T cells compared to blood-derived T cells. Taken together, the results suggest that immune activation against HisRS might take place within the lungs of patients with IIM/antisynthetase syndrome.

Characterization of CD4+ T Cells in Patients with Idiopathic Inflammatory Myopathies

In this issue, Galindo-Feria et al (p. 179) compare the peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) fluid cells from patients with idiopathic inflammatory myopathies (IIMs) and antisynthetase syndrome to those from patients with sarcoidosis and healthy controls. They report the presence of histidyl-transfer RNA synthetase (HisRS)-reactive CD4+ T cells in blood and BAL fluid cells of patients with IIM/antisynthetase syndrome relative to the comparator groups in both compartments. These patients also had antibodies to HisRS (anti-Jo-1) in BAL fluid and it was possible to identify germinal center-like structures in lung biopsy samples. The results suggest that immune activation against HisRS might take place within the lungs of patients with IIM/antisynthetase syndrome.

Gout: Primary Importance of Modifiable Risk Factors for Hyperuricemia, Uric Acid–Lowering Therapy Works

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The researchers determined that the corresponding serum urate variance explained by these risk factors was very small and, paradoxically, masked their high prevalences. For example, the serum urate variance explained by adherence to the DASH diet was just 0.1%, a finding that was similar to one previously reported in an analysis of 5 U.S. cohorts. The researchers also calculated corresponding variances of 8.9% for overweight/obesity, 0.5% for alcohol intake, and 5% for diuretic use. When they performed a simulation study, the variance nearly 0% as exposure prevalence nearly 100%. The authors concluded from real-life empirical evidence that these common modifiable risk factors have an important place in the primary prevention of hyperuricemia.

Also in this issue, Ellmann et al (p. 150) report that lifestyle intervention and xanthine oxidase inhibitors decrease MSU deposit burden. The team performed baseline and follow-up dual-energy computed tomography scans on 83 subjects with gout. Six subjects discontinued treatment, 24 underwent a lifestyle intervention, 29 were treated with allopurinol, 22 were treated with febuxostat, and 2 were treated with benzbromarone over the observation period. The investigators found that the mean serum UA level decreased from 7.2 to 5.8 mg/dl in the overall population. The patients who discontinued treatment had no change in MSU deposits or serum UA levels. In contrast, the burden of MSU deposits decreased in patients undergoing lifestyle intervention and in those treated with allopurinol or febuxostat. The results suggest that conventional gout therapy not only lowers serum UA levels but also reduces pathologic MSU deposits.