Correspondence on 'Blood–brain barrier leakage in systemic lupus erythematosus is associated with gray matter loss and cognitive impairment'

We read the article by Kamintsky *et al*[1] with great interest. The study used dynamic contrast-enhanced MRI to calculate cross Blood–brain barrier (BBB) leakage rates in patients with neuropsychiatric systemic lupus erythematosus (NPSLE). This article reported that patients with SLE had higher BBB leakage compared with controls. Almost a quarter of patients with SLE showed extensive BBB leakage and this SLE group had smaller cerebral grey matter volumes and impaired global cognitive function. The study provided objective evidence of impaired BBB in NPSLE. However, the exact mechanisms resulting in BBB leakage in NPSLE remain elusive. The authors have suggested a role of antiribosomal P and anti-NR2 antibodies and complement activation products as possible contributing factors to BBB leakage.[2 3] Also, some non-SLE-related factors, such as smoking, hypertension and systemic infections, can increase BBB permeability.[4]

Here, we want to mention other potential mechanisms to explain higher BBB leakage in NPSLE. The central nervous system (CNS) was previously considered to not have a classical lymphatic drainage system.[5] However, several studies using tracers injected into cerebrospinal fluid (CSF) revealed lymphatic drainage from CNS into cervical lymph nodes (CLNs).[6 7] A study using animal models discovered functional lymphatic vessels lining dural sinuses which are connected to deep CLNs and are able to carry fluid and immune cells from CSF.[8] These discoveries challenged the concept of lack of lymphatic drainage system in the CNS. The immune cells may contribute to neuroinflammation by reaching the brain via lymphatics from deep and superficial lymphatic systems. One study showed that excision of the CNS-draining lymph nodes reduced the CNS inflammation in experimental autoimmune encephalomyelitis.[9] A recent study using animal models of focal cerebral ischemia revealed that ischaemic stroke triggered activation of lymphatic endothelium in CLNs via vascular endothelial growth factor (VEGF)-C/VEGF receptor (VEGFR)-3 signalling, while surgical excision of superficial CLNs improved poststroke inflammation and reduced brain injury.[7] These studies suggest that the lymphatic systemic and CLNs play an important role in CNS inflammation.[7 9] In addition, another study in living zebrafish using high-resolution optical imaging of the meninges confirmed a meningeal lymphatic network draining interstitial fluid from the brain. The study also showed that neutrophils could be readily trafficking within this lymphatic vessel lumen.[10]

Studies in lupus prone mice (MRL/MpJ-Fas$^{lpr/lpr}$) showed tertiary lymphoid structure formation in the choroid plexus and a site for lymphocyte trafficking into the brain. Increased leucocyte migration via choroid plexus was shown in histological analysis of brain in human NPSLE patients.[11]

We suggest that a dysfunctional CNS lymphatic system and increased immune cell trafficking via CLNs play an important role in the neuroinflammation associated with NPSLE. In addition, it may contribute to impaired BBB by increased production of pro-inflammatory cytokines and complement activation in NPSLE. The exact role of the CNS lymphatic system in neuroinflammation and BBB permeability requires further research to better understand the pathogenesis of NPSLE and finding a potential therapeutic target.

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