Does lupus reduce psychomotor speed?

“...reduced psychomotor speed was an systemic lupus erythematosus-specific characteristic of neurocognitive impairment, and may be added to the symptoms of early systemic lupus erythematosus...”

Keywords: neurocognitive impairment • systemic lupus erythematosus • white matter inflammation

Neurocognitive impairment in lupus
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple systems that has primary and secondary effects on the CNS. Twenty-one to ninety-five percent of SLE patients show neuropsychiatric manifestations [1], a condition known as neuropsychiatric systemic lupus erythematosus (NPSLE). Primary manifestations in those with NPSLE are thought to be a consequence either of microvasculopathy and thrombosis, or of autoantibodies and inflammatory mediators [1]. Among the 19 different NPSLE syndromes identified by the American College of Rheumatology (ACR) [2], studies using standardized neuropsychological tests have shown that cognitive dysfunction presents frequently, with a prevalence ranging from 14 to 79% [3]. Many patients with SLE show mild or subclinical cognitive dysfunction that is accompanied by a decreased quality of life. Despite its high prevalence, the etiology, nature, course and treatment of SLE-associated neurocognitive impairment (NCI) remains elusive.

Although a single pattern of SLE-associated NCI had not been found, SLE-associated NCI that was identified in studies using formal neuropsychological tests included overall cognitive slowing, decreased attention, impaired working memory and executive dysfunction such as difficulty with multitasking, organization or planning [1]. NCI has been reported both in SLE patients with (40–60%) and without (20–30%) overt NP symptoms [4]. This finding suggests that NCI may be a residual factor in patients with previous CNS impairments, or may serve as an early marker of CNS impairments in patients who have not shown NP symptoms. Because there is typically a delay in diagnosing SLE, NCI may occur even before its diagnosis. One study, which focused on patients with newly diagnosed SLE, demonstrated that depression was associated with poor function in several cognitive domains [5]. However, to date, the nature of SLE-associated NCI has been studied mainly in long-term patients.

Secondary NCI including corticosteroid effects
Notably, SLE-associated NCI may result from several conditions other than SLE. These include psychological or psychiatric disturbances, pain, fatigue and sleep disturbance. Some studies also show that medications such as corticosteroids are related to the development of NCI in SLE patients, although these findings are still controversial. Nevertheless, linking corticosteroids to NCI has become increasingly common in recent years [6], and even severe cognitive disorders such as delirium and dementia have been reportedly associated with them [7]. The most extensively reported cognitive changes resulting from corticosteroid treatment involve declarative (verbal) memory, and these changes occur during both short-term (high-dose) and long-term (relatively low-dose) therapies, reflecting a hippocampus-dependent process [6]. Corticosteroid-induced cognitive deficits are thought to be related to dysfunctional hip-
pocampal and frontal cortical neuronal circuits [8]. Thus, corticosteroid therapy may affect the incidence and profile of NCI in patients with SLE.

**SLE-specific pattern of NCI**

To clarify the SLE-specific profile of NCI, we recently investigated NCI in corticosteroid-naive inpatients with early-stage SLE who did not exhibit any overt NP manifestations [9]. In that study, the prevalence of NCI in the patients was much higher than that in healthy control subjects. Furthermore, multivariate analysis showed that the dominant NCI characteristic was slower psychomotor speed (assessed using the Digit Symbol Substitution Test). Verbal memory deficits were not evident among the corticosteroid-naive patients.

“Reduced psychomotor speed... may reflect white matter inflammation in early systemic lupus erythematosus.”

In addition, general SLE disease activity as assessed using the SLE Disease Activity Index 2000 was identified as the only independent risk factor for NCI in those SLE patients. We found no association between NCI and pain, fatigue, mood state or sleep disturbance, although uncomfortable disease-related physical and emotional symptoms derived from high disease activity might have affected cognitive performance.

We concluded that reduced psychomotor speed was an SLE-specific characteristic of NCI, and may be added to the symptoms of early SLE, although further follow-up studies using larger sample sizes are needed [9].

**White matter inflammation in SLE**

Data from recent neuroimaging studies have supported white matter (WM) inflammation, particularly in myelin, as a primary or early CNS pathophysiology in SLE [3]. Indeed, conventional MRI analysis has typically revealed macrostructural changes, including diffuse or regional atrophy, enlarged ventricles and hyperintense lesions in the WM of patients with NPSLE [10]. Recent studies using magnetic resonance spectroscopy [11–13] have shown inflammatory changes in WM even in SLE patients who did not show any WM abnormalities on conventional MRI or who had no NP manifestations. A study using 18fluorodeoxyglucose positron emission tomography revealed inflammation in the WM (most markedly in heavily myelinated tracts) of patients with newly diagnosed SLE [14]. A recent study using diffusion tensor imaging demonstrated widespread WM tract alterations outside overt lesions in patients with diffuse NPSLE [15]. In those patients, decreased fractional anisotropy in the superior WM pathways was significantly correlated with poor executive function.

Furthermore, a recent finding using advanced WM-imaging techniques has highlighted the prominence of cerebral WM abnormalities as a general feature of cognitive slowing [16]. In SLE, the association between such WM microstructural inflammation and NCI, including cognitive slowing, has been found in SLE patients without overt NP syndromes [15]. In that study, NCI correlated with increased frontal WM choline levels, but not with the neuronal marker N-acetyl aspartate or with hippocampal atrophy [13].

**Autoantibodies, inflammatory mediators & SLE-associated NCI**

Autoantibodies and inflammatory mediators are attracting more and more attention as pathogenic factors related to NPSLE. For example, DeGioia et al. demonstrated that a subset of murine anti-DNA antibodies cross-reacts with a sequence within the anti-N-methyl-d-aspartate receptor subunit NR2 [17]. Furthermore, increased permeability of the blood–brain barrier has been thought to allow circulation of potentially pathogenic autoantibodies, such cross-active anti-DNA antibodies, across to the CNS, causing subsequent neuronal damage and cognitive/behavioral impairment [18].

Evidence for involvement of autoantibodies in SLE-associated NCI comes from some studies. Persistent elevation of antiphospholipid antibodies (aPL) has been implicated as a significant risk factor of SLE-associated NCI [4]. Some evidence shows an association between anti-NR2 antibodies and NCI [19], but other studies have failed to do so [20]. Despite a suggested link to NPSLE psychosis, no reports have associated antiribosomal P antibodies and NCI. Proinflammatory cytokines (e.g., IL-6 or IFN-γ) also likely have a role in the pathogenesis of NPSLE. For clarifying the pathogenesis of NCI in early SLE [4], monitoring levels of such autoantibodies and cytokines may be crucial.

**Conclusion**

Reduced psychomotor speed may be a primary characteristic of NCI and may reflect white matter inflammation in early SLE. Further research using advanced neuroimaging techniques such as magnetic resonance spectroscopy, positron emission tomography or diffusion tensor imaging [21] in parallel with immunological investigations may prove useful in explaining the association between microstructural WM abnormalities and NCI at very early stages of disease progression.
Does lupus reduce psychomotor speed? Editorial

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