Editorial

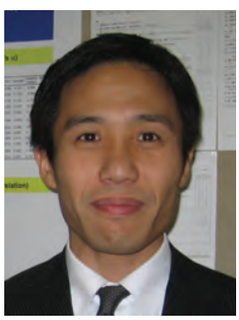
International Journal of Clinical Rheumatology

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

Katsuji Nishimura
Author for correspondence:
Department of Psychiatry, Tokyo Women's Medical University School of Medicine, 8–1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
Tel.: +81 3 3353 8111
Fax: +81 3 3351 8979
nishimura.katsuji@twmu.ac.jp



Yasuhiro Katsumata
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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-

Future Medicine part of fsg

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 ^{18}fluorodeoxyglucose 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 [13]. 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, DeGiorgio *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-α) 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.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Hanly JG. Diagnosis and management of neuropsychiatric SLE. *Nat. Rev. Rheumatol.* 10(6), 338–347 (2014).

2 ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum.* 42(4), 599–608 (1999).

3 Kozora E, Filley CM. Cognitive dysfunction and white matter abnormalities in systemic lupus erythematosus. *J. Int. Neuropsychol. Soc.* 17(3), 385–392 (2011).

4 Kozora E, Hanly JG, Lapteva L, Filley CM. Cognitive dysfunction in systemic lupus erythematosus: past, present, and future. *Arthritis Rheum.* 58(11), 3286–3298 (2008).

5 Petri M, Naqibuddin M, Carson KA *et al.* Depression and cognitive impairment in newly diagnosed systemic lupus erythematosus. *J. Rheumatol.* 37(10), 2032–2038 (2010).

6 Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. *Ann. NY Acad. Sci.* 1179, 41–55 (2009).

7 Varney NR, Alexander B, MacIndoe JH. Reversible steroid dementia in patients without steroid psychosis. *Am. J. Psychiatry* 141, 369–372 (1984).

8 Wolkowitz OM, Burke H, Epel ES, Reus VI. Glucocorticoids, mood, memory, and mechanisms. *Ann. NY Acad. Sci.* 1179, 19–40 (2009).

9 Nishimura K, Omori M, Katsumata Y *et al.* Neurocognitive impairment in corticosteroid-naive patients with active systemic lupus erythematosus: a prospective study. *J. Rheumatol.* 42(3), 441–448 (2015).

10 Appenzeller S, Pike GB, Clarke AE. Magnetic resonance imaging in the evaluation of central nervous system manifestations in systemic lupus erythematosus. *Clin. Rev. Allergy. Immunol.* 34(3), 361–366 (2008).

11 Appenzeller S, Li LM, Costallat LT, Cendes F. Neurometabolic changes in normal white matter may predict appearance of hyperintense lesions in systemic lupus erythematosus. *Lupus* 16(12), 963–971 (2007).

12 Bosma GP, Middelkoop HA, Rood MJ, Bollen EL, Huizinga TW, van Buchem MA. Association of global brain damage and clinical functioning in neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum.* 46(10), 2665–2672 (2002).

13 Filley CM, Kozora E, Brown MS *et al.* White matter microstructure and cognition in non-neuropsychiatric systemic lupus erythematosus. *Cogn. Behav. Neurol.* 22(1), 38–44 (2009).

14 Ramage AE, Fox PT, Brey RL *et al.* Neuroimaging evidence of white matter inflammation in newly diagnosed systemic lupus erythematosus. *Arthritis Rheum.* 63(10), 3048–3057 (2011).

15 Cesar B, Dwyer MG, Shucard JL. Cognitive and white matter tract differences in MS and diffuse neuropsychiatric systemic lupus erythematosus. *Am. J. Neuroradiol* doi: 10.3174/ajnr.A4354 (2015) (Epub ahead of print).

16 Filley CM. White matter: organization and functional relevance. *Neuropsychol. Rev.* 20(2), 158–173 (2010).

17 DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat. Med.* 7(11), 1189–1193 (2001).

18 Diamond B, Volpe BT. A model for lupus brain disease. *Immunol. Rev.* 248(1), 56–67 (2012).

19 Omdal R, Brokstad K, Waterloo K, Koldingsnes W, Jonsson R, Mellgren SI. Neuropsychiatric disturbances in SLE are associated with antibodies against NMDA receptors. *Eur. J. Neurol.* 12(5), 392–398 (2005).

20 Lapteva L, Nowak M, Yarboro CH *et al.* Anti-*N*-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. *Arthritis Rheum.* 54(8), 2505–2514 (2005).

21 Appenzeller S. Magnetic resonance imaging in systemic lupus erythematosus: where do we stand? *Cogn. Behav. Neurol.* 26(2), 53–54 (2013).