Editorial

The Interface Between Medicine and Psychiatry: Neuropsychiatric Aspects of Systemic Lupus Erythematosus (SLE)

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Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterised epidemiologically by the preponderance of women, and pathologically by the loss of immunological tolerance to self-nuclear antigens and aberrant B- and T-cell responses.[1,2] Similar to that of other regions around Southeast Asia, the prevalence of SLE in Singapore is 40/100,000.[3] Amongst various organ involvement, neuropsychiatric SLE (NPSLE) is one of the most devastating presentations of the condition.[4] NPSLE is likely the result of the interplay amongst the immunopathological actions of autoantibodies, intrathecal inflammatory mediators and cerebral microvasculopathy.[5] The American College of Rheumatology (ACR) Ad Hoc Committee devised case definitions for 19 neuropsychiatric syndromes in SLE which comprise central and peripheral neurological, and psychiatric syndromes such as anxiety, depression and cognitive dysfunction.[6] Irreversible organ damage, which potentially occurs when lupus-induced damage persists for more than 6 months, does not spare the neuropsychiatric system. Indeed, damage to the neuropsychiatric system has been dragging down the 5-year and 10-year survival rates of lupus patients over the past 50 years,[7] in addition to the substantial socioeconomic burden it entails for those who survive.[8]

Historical Understanding of the Psychiatric Aspects of SLE

In the 1950s, reports of acute anxiety, depression, delusions and hallucinations in lupus patients started to emerge in the literature.[9,10] Owing to the increased awareness and liaison with psychiatrists, the reported frequency of psychiatric symptoms amongst lupus patients increased from less than 20% before 1960 to 40% thereafter.[11] Forty-one percent of the lupus patients suffered from non-organic, non-psychotic psychopathology as compared to psychotic pathology such as paranoid delusion and visual hallucinations.[12] Depression (39%) and anxiety (24%) are the commonest psychiatric comorbidities of SLE.[13] Patients with SLE are susceptible to depression as a result of psychological reaction to the disease, the direct impact of inflammatory mediators on the brain, and the side effects of high-dose glucocorticoids.[14,15] As compared to patients with other common rheumatic conditions, lupus patients are more likely to suffer from anxiety which is predicted by damage accrual, higher cumulative glucocorticoid dose and the presence of depression.[16] Cognitive impairment, one of the commonest neuropsychiatric lupus manifestations, was found in 14% to 75% of lupus patients[17] and associated with significant functional impairment. The ACR developed a set of standard neuropsychological tests to assess cognitive function which chiefly includes attention, executive function, memory and visuoconstructional abilities. Patients with SLE have been demonstrated inferior performance in all of these domains as compared to healthy individuals.[18]

In general, Asian lupus patients have more serious organ manifestations including NPSLE than their Caucasian counterparts.[19] Locally, neuropsychiatric symptoms were found in 21% of Chinese lupus patients, with a female predominance and tendency to manifest early in the course of SLE.[20,21] In this study, disturbances of orientation, perception and memory were the commonest lupus-related psychiatric comorbidities.

Some Recent Advances in the Understanding of Neuropsychiatric Aspects of Lupus

Cerebral atrophy, which can be caused by the reduction of the white and/or grey matter volume, is commonly described in lupus patients.[22] Intriguingly, inflammation and atrophy of the white matter have been found to be more pronounced than those of the grey matter in lupus

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patients, especially in those with short disease duration.[23,24] The involvement of white matter atrophy was generally correlated with anxiety, cognitive impairment, the duration of SLE and cumulative glucocorticoid dose.[24-26] It is currently believed that the inciting impact of inflammation on the white matter precedes grey matter damage in lupus patients.[24,26] Nevertheless, the differential clinical implications of white and grey matter damage remain to be elucidated in lupus patients.

A number of recent functional magnetic resonance imaging (fMRI) studies in lupus patients has generally revealed deactivations of various cortical areas responsible for working memory and executive function, accompanied by compensatory activations in other cortical areas for preserving cognitive functioning. For example, patients with childhood-onset SLE showed compensatory activations in the visual association area and the dorsolateral prefrontal cortex (attention area) but deactivations in the cingulate gyrus during the N-back working memory task.[27] Our recent fMRI study using the Wisconsin Card Sort Test (WCST) which probes cognitive set-shifting found that the cortico-basal ganglia-thalamic-cortical circuit, which is involved in response inhibition, was dysfunctional in adult lupus patients.[28] With the compensatory activations in the contralateral cerebellar and frontal areas, the performance of the WCST amongst the patients remained equivalent to that of healthy subjects despite the dysfunctional neural circuit.[28]

The pathogenetic role of some autoantibodies in NPSLE remain controversial. For instance, high anti-ribosomal P titres were found to be associated with depression and psychosis,[29,30] and anticardiolipin IgG was found to be related to cognitive impairment.[31] While depression and memory impairment were noted in lupus patients with elevated serum titres of anti-NR2,[32] most of the other similar studies refuted such relationships except those which studied the antibodies in the cerebrospinal fluid.[33,34] Currently, the breach of the blood-brain barrier (BBB) is believed to be essential for the entry of pathogenic autoantibodies into the central nervous system which trigger neuropsychiatric symptoms.[35]

Current Knowledge Gaps and Future Research Directions

The pathogenesis of neuropsychiatric symptoms in patients with SLE is still not fully elucidated. The major challenges in diagnosing and monitoring NPSLE stem from its diversity and protean clinical feature, and the lack of reliable lupus-specific neuropsychological assessment tools as well as valid diagnostic and prognostic biomarkers.[33] Targeted exploration of pathogenic autoantibodies and inflammatory mediators leading to NPSLE coupled with longitudinal structural and functional imaging in tandem with prospective neuropsychological assessment of lupus patients are obviously paramount. Additionally, non-invasive assessment of the integrity of the BBB and its associations with neuropsychiatric symptoms and serum autoantibodies will shed more light on the pathophysiology of NPSLE.

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