Possible Biomarker for an Important Yet Neglected Symptom After Stroke

— Metalloproteinase-9 and Post-Stroke Depression —

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The incidence and prevalence of stroke increase with age, and the number of stroke patients is highly expected to rise with the ageing of populations. Despite recent advancements in stroke treatment such as thrombolytic therapy and mechanical thrombectomy, stroke continues to be a leading cause of chronic and severe adult disability, resulting in a serious human problem, both for patients and caregivers, and a dramatic public financial burden. After stroke, many survivors are faced with a veritable array of physical and neuropsychiatric deficits. The sudden functional deficits and concomitant effect on motivation, the fear of emotional instability and death, and the demands of rehabilitation may result in hopelessness and helplessness leading to stress and depression.

Post-stroke depression (PSD) is the most common emotional disorder after stroke. Approximately one-third of stroke survivors are affected by it.¹ Depressive symptoms are most common in the first 3–6 months after stroke, and the prevalence of PSD remains at a high level in the following several years.² PSD is known to have an important effect on the course, recovery, and prognosis of stroke. The depression negatively affects a patient's ability to engage in rehabilitation therapies, and is strongly associated with further worsening of physical and cognitive recovery, functional outcome, and quality of life, and imposes a heavy burden on society and the family.³ Moreover, PSD is associated with earlier recurrence of stroke.³ Therefore, early accurate diagnosis of PSD is very important and should be taken seriously by clinicians.

However, although a high proportion of stroke patients develop PSD, and PSD is more predictive of quality of life than actual neurological disability, PSD has received little attention in the field of stroke until now, presumably because the pathogenesis of PSD is very complex, involving both biological and sociopsychological mechanisms, and appropriate and reliable diagnostic criteria for PSD have not been developed yet.⁴ As a result, PSD is often underdiagnosed and under-treated.⁵ In addition, populations at risk for PSD are yet to be identified.⁶ Thus, it is necessary to explore the pathogenesis and related influencing factors for PSD, and to establish appropriate screening, assessment, and diagnostic criteria, and determine the best preventive

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and therapeutic scales.

In this issue of the Journal, Che et al⁷ report that the serum level of matrix metalloproteinase (MMP)-9 in the acute stage of stroke is a possible biomarker for predicting

Figure. Role of matrix metalloproteinase (MMP)-9 in the pathogenesis of post-stroke depression (PSD). In the acute phase of ischemic stroke, neurons, astrocytes, microglia, and oligodendrocytes can produce several pro-inflammatory mediators, including TNF- α , IL-1, and NF- κ B. These pro-inflammatory mediators promote MMP-9 expression and enhance MMP-9 activity. Activated MMP-9 degrades extracellular matrix and leads to disruption of the blood brain barrier, which is considered to be involved in the pathogenesis of depression. Activated MMP-9 can also induce an inflammatory response. Tissue inhibitor of metalloproteinase (TIMP)-1 is an endogenous inhibitor of MMP-9.

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PSD in patients with ischemic stroke. The rationale of their study was that MMP-9, which is a key determinant of extracellular matrix degradation, is implicated both in brain injury after stroke and in development of depressive symptoms, and there has been no evidence shown of an association between serum MMP-9 levels in patients with acute stroke and PSD. These authors examined the association between serum MMP-9 levels in patients with acute ischemic stroke who were enrolled in a multicenter cohort study in China, the CATIS study, and who developed PSD within 3 months of the index stroke. Their multivariable adjusted analysis found that high levels of serum MMP-9 (odds ratio 4.36, 95% confidence interval 2.49–7.65) (highest MMP-9 quartile vs. lowest quartile) were an independent predictor of PSD within 3 months after stroke onset, and there was a dose-dependent relationship between serum MMP-9 levels and the occurrence of PSD. These findings were consistent in subgroup analyses according to possible confounding factors, including baseline stroke severity. Furthermore, the authors also report that adding the serum MMP-9 level to conventional risk factors substantially improved risk prediction for PSD. Their findings suggest that serum MMP-9 levels could provide predictive information for PSD, and assist in the identification of stroke patients for whom special attention is needed to identify the development of PSD.

The pathogenesis of PSD is extremely complex and may be the result of multiple factors and multiple pathways. Although there are still many uncertainties in the neurobiological mechanisms of depression, several lines of evidence support the role of inflammatory responses as well as dysfunction of the blood brain barrier (BBB) in the etiology of depression. A recent systematic review and meta-analysis suggests the presence of neuroinflammation in patients with depression, which is mainly characterized by increased levels of pro-inflammatory cytokines in brain parenchyma and a subsequent reduction in the density of astrocytes.⁸ The reduced number of astrocytes may lead to dysfunction and disruption of the BBB, with increased monocyte recruitment and infiltration.⁹ Likewise, other clinical and experimental studies have shown an association between BBB damage and depression.^{10,11} Studies have also shown a significant association between MMP-9 and depression. MMP-9 levels in the peripheral blood increase in patients with major depression, and the levels also correlate with the severity of depression.¹² MMP-9 is a zinc-dependent protease that is upregulated and activated by inflammatory mediators and is involved in the degradation of the extracellular matrix. MMP-9 is also known to be upregulated in the acute phase of ischemic stroke and to participate in BBB breakdown.¹³ Cumulatively, it seems reasonable to

consider that MMP-9 is significantly associated with and involved in the pathogenesis of PSD through BBB disruption, and that serum MMP-9 levels could be a possible biomarker for predicting the risk of PSD (Figure).

Considering the high prevalence and incidence of PSD, it is recommended to assess and manage PSD in stroke patients. Serum MMP-9 could be a possible biomarker for identifying patients at risk for PSD even in the acute stage of ischemic stroke, however, further studies are required to validate the association between MMP-9 and PSD in other cohorts, and to elucidate the causal mechanism underlying the association between them.

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