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Stroke depression: a concept with clinical applicability

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ABSTRACT

Stroke is a common neurological condition and among the leading causes of death and disability worldwide. Depression is both a risk factor for and complication of stroke, and the two conditions may have a complex reciprocal relationship over time. However, the secondary effects of depression on stroke are often overlooked, resulting in increased morbidity and mortality. In the previous concept of 'poststroke depression', stroke and depression were considered as two independent diseases. It often delays the diagnosis and treatment of patients. The concept 'stroke depression' proposed in this article will emphasise more the necessity of aggressive treatment of depression in the overall management of stroke, thus to reduce the incidence of stroke and in the meantime, improve the prognosis of stroke. Hopefully, it will lead us into a new era of acute stroke intervention.

EPIDEMIOLOGY OF STROKE

Stroke is the second-leading cause of death in the world, accounting for 11.8% of all deaths. It is also the third most disabling disease, responsible for 4.5% of all disability-adjusted life-years (DALYs).[1] In 2019, there were almost 101 million stroke survivors all over the world. Meanwhile, there are 12.2 million new stroke patients, 6.55 million deaths from stroke and 143 million DALYs due to stroke.[2]

EPIDEMIOLOGY OF DEPRESSION

Currently, the most effective approach to stroke prevention is risk factor control, including hypertension, diabetes and heart disease, etc. Although the use of antiplatelet and antihypertensive agents, as well as statins, is critical for secondary prevention of stroke, management of other risk factors, especially clinical depression, deserves equal attention.[3]

Depression is also a leading cause of disability worldwide and is a major contributor to the overall global burden of disease. It affects an estimated 3.8% of the world's population, including 5.7% of adults over the age of 60. Approximately 280 million people in the world have depression.[4]

According to WHO, in 2016, there were approximately 80.1 million stroke patients worldwide, with 13.7 million new stroke cases each year. As we know, the 5-year prevalence of depression after stroke is estimated to be 31%, which leads to the likelihood that nearly 24 million patients may suffer from stroke-related depression stroke.[5] Moreover, a US study estimated that 3.9% of stroke cases were attributable to depression.[6] Not specific to stroke, depression will more generally lead to poor overall health in multiple domains such as increased risk for dementia, pain, cardiovascular diseases, etc.[7 8]

'POSTSTROKE DEPRESSION': DIAGNOSTIC AND THERAPEUTIC CHALLENGES

For many years, clinicians and scientists have used the term 'poststroke depression' and regarded depression as a sequelae of stroke.[9] In 2016, the American Heart Association (AHA) and the American Stroke Association (ASA) first published a consensus statement on poststroke depression.[10] Then, according to the 2019 Canadian Stroke Best Practice Recommendations for mood, cognition and fatigue following stroke, poststroke depression remains classified as an 'emotional disorder caused by a certain medical disease'. In the fifth edition ofDiagnostic and Statistical Manual of Mental Disorders (DSM-5), it is defined as 'stroke with depressive features, major depressive-like episodes or mixed features'. However, the term is gradually being challenged in clinical practice. First, it has been classified as a disease. Therefore, fulfilment of diagnostic criteria (eg, DSM-5) is required to make a definitive diagnosis. Thus, it is easy to be ignored by neurologists, due to the relatively complex diagnostic criteria. Second, depressive symptoms must last at least 2 weeks to meet the diagnostic criteria, leading to delays in diagnosis. For patients who had an acute stroke, time is brain. It is also the case that many patients are not in the hospital long enough poststroke for physicians to observe symptoms consistent with the DSM criteria for depression for an adequate duration. Third, once diagnosed, antidepressants are used for up to 6 months to 1 year.

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Drug-related adverse reactions increased significantly. Although psychotherapy is recommended, it is usually not available for neurological patients. Fourth, the optimal screening scale and optimal screening time for poststroke depression are not yet clear. If multiple scales are recommended for screening for poststroke depression at multiple time points, it will affect the efficiency of clinical work.[11] Last but not least, the diagnosis is complicated by many cognitive sequelae of stroke (eg, abulia, aphasia).[12] All of the above factors may eventually lead to delays in diagnosis and treatment, and poor prognosis.

In particular, it should be noted that according to DSM-5, the diagnosis of poststroke depression requires experienced psychiatrists to make a clinical diagnosis based on clinical manifestations. The scale is for screening and assessment of disease severity only. To make matters worse, currently available depression rating scales have not been adequately validated in poststroke depression.[13] Then, in clinical practice, who should manage 'poststroke depression'? When a neurologist first recognises the emotional disturbance of a patient who had a stroke, according to the diagnostic criteria, a psychiatrist is often consulted to assist in diagnosis and treatment.[14] At present, the lack of psychiatric specialists in community hospitals and even general hospitals in most low-income and middle-income countries, is very common. Even in general hospitals with psychiatric specialties, there is an obvious shortage of psychiatrists.[15] Therefore, the initial problem faced by most neurologists is that there are no psychiatrists to consult. The consulted psychiatrist may either attribute the depression to an organic affective disorder, or major depression, independent of the stroke. In either case, neurologists may become less involved. Thus, there are depressed patients in strokes underrecognised and undertreated.

Another concern is whether all patients received equal attention. First of all, from the perspective of 'stroke', in the current concept of 'poststroke depression', 'stroke' refers to acute symptomatic stroke. Therefore, all relevant epidemiological studies have only included first time, symptomatic stroke patients.[16] That is, patients with previous strokes were excluded from most studies. There is also a larger part of the population with asymptomatic cerebrovascular disease.[10 17] Asymptomatic cerebrovascular disease refers to asymptomatic infarcts, white matter lesions and microbleeds found by brain imaging. These asymptomatic patients are currently thought to be predisposed to depression as well.[18] Therefore, in 2017, AHA/ASA issued a joint statement stating that for asymptomatic cerebrovascular disease, primary prevention of stroke is required.[10] As a result, patients with previous strokes and asymptomatic cerebrovascular disease are largely underdiagnosed, according to the current diagnostic criteria of 'poststroke depression'.[13] Furthermore, from the perspective of 'depression', quite a few patients have a history of major depression before the acute stroke attack. In the current concept of 'poststroke depression', this part of the patient is also likely to be ignored.[13] To sum up, the clinical application of term 'poststroke depression' has been greatly challenged.

STROKE AFTER DEPRESSION: CONCEPTUAL UPDATE

Depression is one of the most common accompanying symptoms after a stroke. Depressive symptoms increase the risk of death from stroke by 50%.[19] It is associated with delayed improvement in motor and cognitive functions, increased functional disability and reduced quality of life in stroke survivors.[20] Moreover, patients who had a stroke with depression had a 1.49-fold higher risk of stroke recurrence compared with those without depression.[21] Depression can occur at any time after stroke, with the highest risk in the first year and a 5-year cumulative incidence of approximately 31%.[20 22] The course of poststroke depression is dynamic. Although symptoms may resolve spontaneously in some patients, some other patients may develop new-onset depression. Overall, the prevalence remained stable.[5]

So, does depression only occur after stroke? As early as 2005, it was found in separate studies, that baseline depressive symptoms increased stroke mortality.[19] Participants were followed for 18 years (N=12 866), and those with higher baseline depression scores were more likely to die from stroke (risk ratio: 2.03; 95% CI 1.20 to 3.44; p<0.01).[19] In 2007, Framingham study followed subjects for 8 years. It was found that the risk of first stroke and transient ischaemic attack (TIA) increased by 4.21 times in those with depressive symptoms at baseline. The study, for the first time, suggested that depression is an independent risk factor for stroke and TIA in individuals younger than 65.[23] In 2010, the INTERSTROKE study confirmed this conclusion that depression is a risk factor for all types of stroke (OR 1.35; 99% CI 1.10 to 1.66) and ischaemic stroke (1.47; 99% CI 1.19 to 1.83) in the general population.[24]

Data from these prospective studies were further supported by epidemiological investigations. In a 13-year follow-up of 1703 individuals from the Baltimore Epidemiologic Catchment Area Study, those with a history of depressive disorder were 2.6 times more likely to have first stroke, after controlling other risk factors.[25] The NHANES survey then followed patients for 29 years and showed a 50% increase in stroke-related deaths among patients who reported more than five depressive symptoms at baseline.[6] These studies demonstrated that the risk of stroke incidence and mortality is substantially increased in populations with previously diagnosed clinical depression or with depressive symptoms identified either by depression rating scales or self-rating scales.[25] Therefore, depression can not only occur after stroke, but also earlier than stroke. It affects the entire course of stroke. The two interact. Stroke is a risk factor for depression. Depression is also a risk factor for stroke.

How exactly do depression and stroke interact? Several potential mechanisms have been proposed. First, depression can enhance adrenergic activity. Thus, the increased

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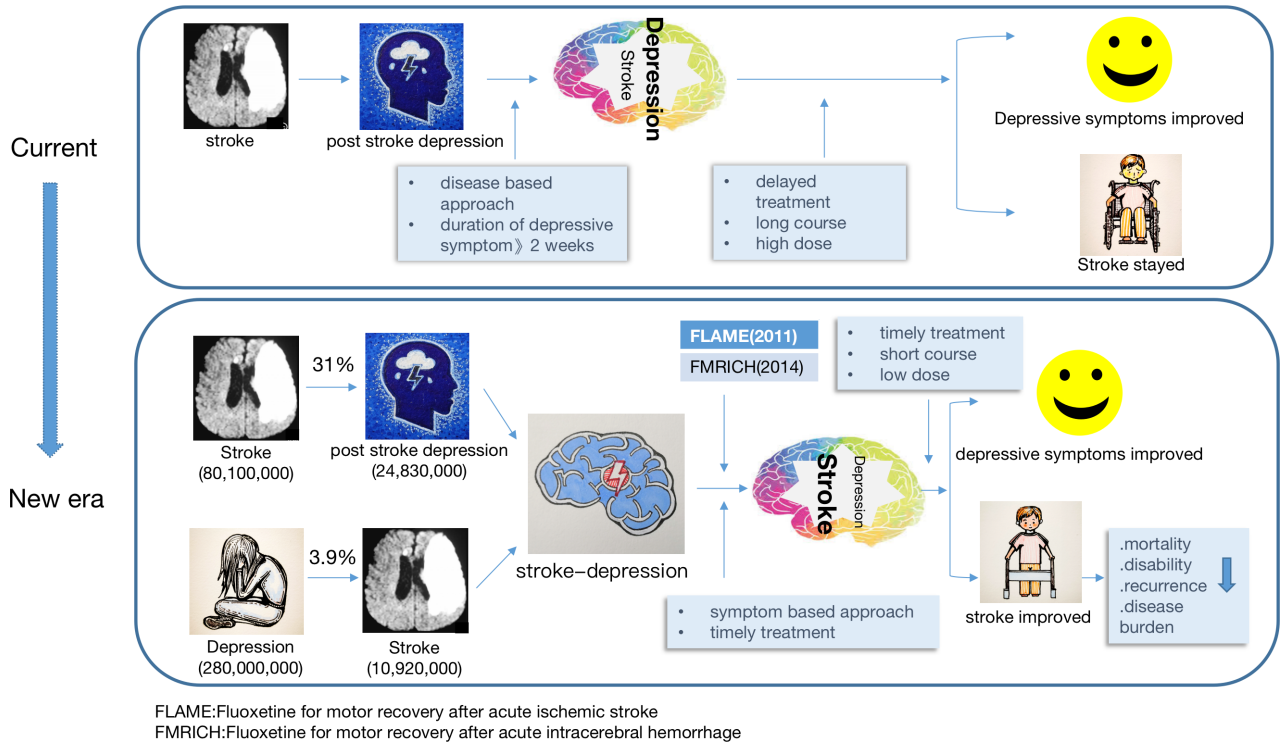

Figure 1 The translation from 'poststroke depression' to 'stroke depression'.

incidence of hypertension and/or diabetes indirectly leads to the occurrence of stroke.[26 27] Depression, through increased inflammation, results in hypercoagulability and increased platelet aggregation.[28] Third, depressive symptoms, even if transient, influence other stroke risk factors, such as smoking, unhealthy eating habits and obesity, as well as lack of physical exercise or medication non-adherence.[29 30] Fourth, there is also evidence that in part due to their anti-platelet effect, antidepressants may increase risk of bleeding complications, increased inflammation, weight gain, cardiotoxicity and hypertension. Therefore, it may cause strokes by damaging cerebral blood vessels. Both a large case–control investigation and a case-crossover study have shown that the risk of stroke increased by as much as 20%–50% with antidepressants use.[31–33]

A NEW ERA OF STROKE DEPRESSION

In summary, stroke and depression are causal and interactive. The term 'poststroke depression' inappropriately regards stroke and depression as independent co-occurring conditions, thereby, delaying diagnosis and treatment. Therefore, we propose the concept of 'stroke depression', emphasising the bidirectional association between depression and stroke (figure 1). Hopefully, this will help usher in a new era of acute stroke management.

'STROKE DEPRESSION': FOCUS ON 'STROKE' AGAIN

In the term 'poststroke depression', neurologists focus on 'depression', whether the symptoms of 'depression' can be improved by drugs or psychotherapy, and whether the outcome of 'depression' can be adequately evaluated with scales. However, the depression that occurs after a stroke is essentially the same as the changes in blood pressure, blood sugar and blood lipid levels that occur after a stroke. Taking blood pressure as an example, it is well known that post stroke blood pressure fluctuations have adverse effects on stroke, such as an increased proportion of haemorrhagic transformation in acute cerebral infarction, haematoma expansion in acute cerebral haemorrhage, aggravated atherosclerosis and increased risk of stroke recurrence. Therefore, actively stabilising blood pressure levels after stroke is not just to reduce or increase blood pressure, but more importantly, to reduce the adverse effects of blood pressure fluctuations on stroke. Similarly, the benefit of statins demonstrated by the landmark SPARCL study has now become standard protocol for risk reduction of stroke by as much as 23%. The use of statins is not aimed on the specific reduction of blood lipid levels, but rather protection of cerebral vascular vessels. Likewise, the main goal of antidepressant treatment is to restore neurological function, while reducing depressive symptoms. In the term 'stroke depression', 'stroke' has become the focus of attention, and the purpose of improving depressive symptoms is to reduce stroke mortality, disability and recurrence risk. Furthermore, since depression can occur before, during and after a stroke, it is no longer necessary to emphasise the temporal concept of 'poststroke'.

Fortunately, a number of large-scale clinical studies have shown that in addition to a significant reduction in symptoms, antidepressants can improve motor function (especially flexibility) as well as normalise cognitive

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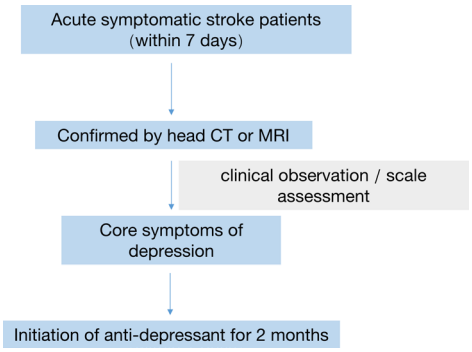

Figure 2 Diagram of antidepressant treatment after stroke.

deficits.[11 34 35] Recent clinical trials also show the benefit of antidepressants in stroke patients, even in the absence of significant depressive symptoms.[36] Although the underlying mechanism remains unclear, the use of antidepressants after stroke is no longer limited to improve depressive symptoms. As we suggest, early initiation of antidepressants after an acute stroke, will be as important as antiplatelet drugs and statins, in stroke prevention and treatment.

IN 'STROKE DEPRESSION': DEPRESSION SEEN AS A SYMPTOM NOT A DISEASE

Studies suggested the estimated rate of misdiagnosis for post stroke depression is between 50% and 70%.[11 35] In a recent article published in the *Chinese Journal of Internal Medicine*, 'depression' has already been proposed as a symptom in stroke.[37] If depressive symptoms are identified by clinical observation or scale assessment, neurologists can start antidepressant treatment immediately. And only short-term use of antidepressants is required.

To summarise, we believe that the concept of 'stroke depression' better interprets the bidirectional relationship between stroke and depression, and is with promising clinical applicability. The concept of 'stroke depression' emphasises early comprehensive management of depression, with the aim of reducing stroke mortality, disability and recurrence. Neurologists can work collaboratively with psychiatrists to develop algorithms (figure 2). At any stage in the evolution or trajectory of a stroke, following a positive screen for depressive symptoms, interventions can initiate. Similarly, for those who have depressive symptom, there is probably no need for long-term maintenance treatment, thereby avoiding the possible side effects of long-term use of antidepressants. Intervention can be initiated at any stage of stroke when core symptoms of depression (depressed mood and/or lost of interest) are identified. And the short course of treatment also avoids the possible side effects of long-term use of antidepressants. The first-line antidepressants effective in major depressive disorder are suggested. Monotherapy starts with a small dose and increases gradually, for a total of 2 months.[34 38]

A possible problem with the application of the current framework is that the recommended first-line antidepressants are all borrowed from the treatment of major depression. The management of major depression has been updated a lot in recent years.[39] Therefore, we need large-scale randomised controlled trials studies, and even with the help of big data to further determine the type and course of drugs.[40] And the choice of drug should be personalised for the subgroup stroke populations. For example, the optimal drug will be recommended based on the severity of the stroke, the location of the lesion and the presence or absence of complications. At the same time, the effects of non-drug treatments for depression, such as neuromodulation and psychological interventions, on stroke should also be investigated. Further, the development of effective predictive models for stroke and depression may further advance our proposed framework from clinical treatment to prevention in the near future. The general population, especially those at high risk for stroke or depression, will receive more attention. Last but not least, when this 'stroke depression' framework is clinically applied, neurologists need to be familiar with depressive symptoms and the use of antidepressants. Neurologists should work closely with psychiatrists to resolve issues that may arise during the treatment.

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