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Is poststroke depression the same as major depression?

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What causes PSD versus major depression?

In the United States, it is estimated that 11 million strokes occurred within 1 year (1998).^{1,2} Poststroke depression (PSD) is a common outcome following stroke, with 30% of patients poststroke having comorbid major depression and 80% of patients having milder forms of depression.^{3,4} Patients with PSD show increased likelihood of recurrent stroke and depression, and increased mortality compared with nondepressed patients.⁵ Major depression is a chronic disorder that is often comorbid with anxiety.⁶ Environmental stressors, including having a stroke, contribute to predisposition and can trigger episodes of major depression.⁶ Both PSD and major depression are diagnosed according to the same set of criteria that combine diverse and sometimes opposite symptoms, which contributes to the heterogeneous nature of major depression.⁷ One of the goals of psychiatry today is to move toward precision medicine by elucidating biomarkers for better characterization of mental illness and its treatment.⁸ Identifying the underlying molecular, cellular or circuit changes leading to behavioural phenotypes can be used to target therapeutic interventions to specific mechanisms driving mental illness. This raises the question of whether PSD and major depression should be considered the same or separate mental illnesses.

Poststroke depression appears to be triggered by or linked to the ischemic event, as depression occurs within three months of a stroke.³ How stroke triggers depression is unclear. The sudden physical handicap and loss of personal independence following stroke may trigger a chronic state of depression. However, there is evidence that lesions associated with stroke or vascular ischemic events, particularly in cases of covert stroke where no evident impairment presents, can lead to depression. The size, number of ischemic lesions, and whether the lesions disrupt the midbrain, limbic and medial prefrontal cortical (mPFC) circuitry are implicated in depression.⁹ In particular, white matter lesions are associated with metabolic alterations in this circuitry¹⁰ and are correlated with major depression.¹¹ Several independent studies have indicated that in patients with ischemic stroke, lesions in the left frontal cortex, left basal ganglia or brainstem are correlated with affective and apathetic symptoms of depression.^{12,13}

Thus, an emerging concept that remains to be tested is that strokes leading to PSD may disrupt the anxiety or depression circuitry at several locations.¹⁴

Detecting PSD and vascular depression

Poststroke depression is a form of vascular depression related to large vessel occlusion.¹⁴ Covert (or "silent") strokes include small brain infarcts or microbleeds (lacunae or white matter infarctions) that do not result in obvious sensorimotor impairments. Covert strokes are five-fold more frequent forms of stroke, with one stroke every nine minutes (62 000/yr) and one covert stroke each two minutes in Canada.^{2,15} Recently, vascular depression has been associated with the presence of covert strokes.¹¹ Thus, the prevalence of vascular depression is potentially five-fold higher than that of PSD.¹⁶ On the other hand the incidence of covert stroke in depressed patients is 46%,² consistent with a strong bidirectional connection between the two.¹⁷ However, the "silence" of covert stroke presents a challenge in detecting vascular versus major depression. Presently, covert stroke is often detected only once a more severe condition arises requiring imaging, at which time the presence of lacunae or white matter hyperintensities may be evident. Typically, patients presenting with depression are not referred for imaging, but the need for imaging may be important, particularly in patients with risk factors for cerebrovascular disease (e.g., cardiovascular disease, hypertension, diabetes).^{2,17} Recently, imaging has been applied with repetitive transcranial magnetic stimulation (rTMS), which is recommended as second-line treatment for major depression in patients who do not respond to antidepressant treatment.¹⁸ It remains unclear what proportion of patients with major depression show stroke pathology that may suggest vascular depression. Based on the prevalence of covert stroke, this proportion may be substantial.

Does PSD/vascular depression respond to antidepressant treatment?

Assuming we can distinguish PSD and vascular depression from major depression, how does this impact treatment? It remains unclear. Like major depression, PSD is mainly

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treated with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs).¹⁴ There is evidence that in addition to improving anxiety and depression symptoms, SSRIs also enhance poststroke cognitive ability and recovery.^{9,14,19} However, most antidepressants require chronic treatment (3–4 weeks) to produce improvement.²⁰ For major depression, the STAR*D study found that although about 50% of patients responded to SSRIs, remission occurred in only 30%.²¹ It remains unclear whether the same can be said for PSD or vascular depression; notably, chronic SSRI treatment increases the risk of hemorrhage.^{22,23} However, to examine treatment outcomes for vascular depression, it will be necessary to first detect it using imaging, as mentioned earlier.

What can preclinical studies tell us about treatment for PSD? Most rodent models of PSD have used middle cerebral artery occlusion, which produces a large and variable lesion, leading to sensorimotor impairments and altered behaviour.²⁴ The sensorimotor impairments may confound behavioural tests that are often based on intact sensorimotor function. Thus, in order to obtain a robust depression phenotype, middle cerebral artery occlusion has been combined with chronic stress, which itself induces depression-like behaviour. Although chronic SSRI treatment is effective, this raises the question of whether stroke- or stress-induced depression is being studied. One recent study used photothrombosis to elicit an anterior cortical stroke and waited until sensorimotor function recovered before testing behaviour.²⁵ The researchers showed that chronic SSRI treatment is effective to reverse the anxiety- and depression-like phenotypes, involving increase in hippocampal brain-derived neurotrophic factor.²⁵ Another model used endothelin-1 microinjection to induce a small lesion of the left medial prefrontal cortex, resulting in anxiety- and depression-like behaviour, as well as cognitive impairment, with no sensorimotor impairment.^{26,27} In this model, chronic SSRI treatment, but not free running wheel exercise, reversed the behavioural and cognitive phenotypes. Interestingly, the small lesion became refilled with neurons, which may be recruited by SSRI treatment. These findings suggest that chronic SSRI treatment is effective to reverse PSD, in part through growth factor induction. In this regard, chronic SSRI treatment may trigger neuroplasticity to promote recovery from depression, including PSD. However, clinical studies of the effectiveness of SSRI treatment in human PSD or vascular depression need to be done and will require a dedicated pretreatment imaging screen to detect vascular lesions in drug-naïve, depressed patients.

Etiology of PSD and depression: inflammation link?

The pathology underlying PSD and major depression differs. Stroke leads to neuronal and glial cell death due to hypoxic lesion, whereas major depression is not always associated with detectable cell death. However, postmortem studies of brains from depressed individuals who committed suicide show loss of glia and neurons.^{28,29} Chronic stress is known to induce neuronal atrophy,³⁰ particularly in the hippocampus, and reductions in hippocampal volume can be seen in depressed

humans.³¹ It has been suggested that neuroinflammatory processes involving cytokine and microglial mobilization underlie some forms of depression,^{29,32} and inflammatory processes may be important in the pathology of PSD and vascular depression.^{33,34} Therefore, vascular depression may fall into a “neuroinflammatory” depression phenotype.¹⁴

Hence the question remains: how much of major depression is really undiagnosed PSD? It can be argued that increased effort to diagnose both systemic inflammation and small-vessel disease in depressed individuals is warranted, since many of the risk factors leading to stroke (e.g., diabetes, atherosclerosis, stroke, heart failure) are also tied to depression.^{2,16,35} The good news is that these risk factors, if recognized early enough, can be controlled to prevent or reverse the depression phenotype.³⁶

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