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Post-stroke depression: Mechanisms and pharmacological treatment

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ABSTRACT

Depression, the most frequent psychiatric disorder following ischaemic stroke, negatively affects survivals' functional outcome, response to rehabilitation and quality of life. Approximately, one-third of them are affected by post-stroke depression (PSD), making it a serious social and public health problem and anti-depressant preventive and curative therapies worth investigating. However, a two-way association between depression and stroke has been also established: stroke increases the risk of PSD, but depression is an independent risk factor for stroke.

The pathophysiology of PSD is presumably multifactorial, involving a combination of various ischaemia-induced neurobiological dysfunctions in the context of psychosocial distress. The damage of frontal-basal ganglia brainstem pathway suggested alterations of monoaminergic neurotransmitter systems. Several lines of evidence point to a relationship between neuroinflammatory response to acute ischaemic stroke, stress activation of the hypothalamic-pituitary-adrenal (HPA) axis and the impairment of adaptive response (neurogenesis) within a background of altered energy metabolism (*i.e.* mitochondrial dysfunction).

The complexity of PSD mechanisms makes its biologically-based prevention and treatment a difficult task. So far, especially the selective serotonin (5-hydroxytriptamine, 5-HT) reuptake inhibitors (SSRIs) have mainly proved to be clinically active in preventing and treating PSD, although their effects have not been demonstrated unequivocally and they may cause bleeding and intracerebral haemorrhage. Besides the primary pharmacological activity of SSRIs (*i.e.* the inhibition of neuronal 5-HT reuptake) there is evidence supporting their pleiotropic mechanisms of action: anti-inflammatory and enhanced neurogenesis through the up-regulation of neurotrophins, conceivably supported by the stimulation of mitochondrial energy metabolism.

In the future, novel developments might point at anti-cytokine modulators which can improve symptoms of depression, especially in subjects affected by inflammation processes.

This review will address the various areas of epidemiology, pathophysiology, preventive and therapeutic strategies for PSD. The activity of SSRIs in clinical trials, as well as their pharmacology, pharmacokinetics, safety and mechanisms of action, will be examined in detail. A final section will deal with the effect of depression as risk factor for stroke. The literature on PubMed from 1990 to 2017 was reviewed.

1. Introduction

Stroke is the third cause of death worldwide, with 16.9 million first-ever cases, 5.9 million deaths per year and a projected increase to 23 million cases (12 million deaths and 70 million survivors) in 2030. Stroke incidence and prevalence increase sharply with age and the numbers of patients are expected to rise with the growing of the aged population, although the proportion of patients < 65 years is substantially increasing, especially in low- and middle-income countries (Feigin et al., 2014). Even more worrying, stroke is the main cause of chronic, severe adult disability, requiring long-term rehabilitation procedures. Thus, despite the advancement in prevention and therapy (Moretti, Ferrari, & Villa, 2015a, 2015b; Villa, Ferrari, & Moretti, 2017), stroke remains both a serious human problem for patients and families and a dramatic public financial burden.

Among the consequences of stroke for survivors, post-stroke

Abbreviations: ADL, Activities of Daily Living; BDNF, Brain-Derived Neurotrophic Factor; CBF, Cerebral Blood Flow; CI, Confidence Interval; CNS, Central Nervous System; COX, Cyclooxygenase; CSF, Cerebro-Spinal Fluid; DES, Depression-Executive Dysfunction Syndrome; DST cortisol, (overnight) Dexamethasone Suppression Test for cortisol; HPA axis, Hypothalamic-Pituitary-Adrenal axis; HR, Hazard Ratio; 5-HT, 5-Hydroxytryptamine, Serotonin; 5-HTTLPR, Serotonin-Transporter-Linked Polymorphism Region; IL, Interleukin; MDD, Major Depressive Disorders; OR, Odds Ratio; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; PSD, Post-Stroke Depression; RR, Relative Risk; SSRI, Selective Serotonin Reuptake Inhibitors; TCA, Tricyclic Anti-depressants; TNF, Tumor Necrosis Factor; VEGF, Vascular Endothelial Growth Factor

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depression (PSD) is the most frequent psychiatric problem. PSD is strongly associated with further worsening of physical and cognitive recovery, functional outcome and quality of life. Moreover, depression negatively affects patients' ability to engage in rehabilitation therapies.

However, this scenario is complicated by the bidirectional relationship between depression and stroke: stroke increases the risk of PSD, but depression is an independent risk factor for stroke and stroke mortality.

Despite this conceptual complexity, the term post-stroke depression is commonly used to define any depression state present after stroke, regardless of the timing of symptoms onset.

Empirical evidence of pathophysiological factors associated with PSD suggests alterations in ascending monoamine pathways, excess of pro-inflammatory cytokines, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis and alterations in neuroplasticity.

The development of a rational therapy would require an integrated view of these pathophysiological factors. Up to now, this topic is only speculative and the current therapy is mainly based on the monoamine hypothesis of depression. Indeed, various antidepressant medications could be used for PSD, being selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) the classes most widely studied.

This review will address the epidemiology, predictors, pathophysiology, prevention and therapeutic strategies for PSD. We will focus on the treatment with SSRIs, their pharmacology, pharmacokinetics, safety and mechanisms of action (reviews by Hayhow, Brockman, & Starkstein, 2014; Loubinoux et al., 2012; Paolucci, 2017; Robinson & Jorge, 2016; Towfighi et al., 2017; Williams, 2005). The term PSD is used for depression after ischaemic (not haemorrhagic) stroke, because ischaemic stroke has been the subject of the vast majority of the literature. The role of depression as a risk factor for stroke will also be discussed.

2. Epidemiology

Currently approximately half of stroke survivors suffer from persisting disability and need institutional care and rehabilitation (Bonita, Solomon, & Broad, 1997; Go et al., 2013). To further complicate the complex rehabilitation process, a substantial proportion of survivors may develop PSD after stroke onset.

2.1. Prevalence and incidence

Approximately one third of survivors suffer from PSD, with a cumulative incidence of 55%. The prevalence of PSD varied across studies depending on population characteristics, diagnostic criteria, inclusion/exclusion criteria (*e.g.* the presence/absence of aphasia), time after stroke and the clinical setting where the patients were examined (acute or rehabilitation hospital settings, community, outpatient clinics) (reviews by Paolucci, 2008; Robinson, 2003; Truelsen et al., 2006).

In their meta-analysis of 43 studies Ayerbe, Ayis, Wolfe, and Rudd (2013) reported a cumulative incidence of depression of 39–52% within 5 years following stroke and a pooled prevalence of 29% at any time within 10 years. Interestingly, a significant fraction of those patients who became depressed early after the acute event recovered in subsequent assessments.

A meta-analysis of 61 studies by Hackett and Pickles (2014) reported a pooled frequency of depression of 31% at any time up to five years following stroke, consistently with results found in a 10-year earlier review where the pooled frequency was 33% (Hackett & Anderson, 2005). This emphasises the need for better evidenced-based strategies of screening, prevention and therapy. Indeed, PSD remains relatively under-diagnosed, under-treated and under-researched.

A limitation of most studies was the lack of diagnostic criteria for specific mood disorders, thus missing important clinical variables. A previous review by Robinson (2003) on pooled data of hospital studies found prevalence rate of 19.3% of major depression (MDD) and 18.5% of minor depression (MnD).

Recently, a thorough meta-analysis of 108 studies on mood disorders observed 147 cases from 2 days to 7 years post-stroke and demonstrated a 33.5% prevalence of any depressive disorder. MDD accounted for 17.7%, MnD for 13.1%, dysthymia for 3.1%. Adjustment disorder was present in 6.9% of patients and anxiety in 9.8% (Mitchell et al., 2017).

2.2. Natural history

Longitudinal studies provided conflicting results as to the time course of PSD. According to the meta-analyses by Ayerbe et al. (2013) and Hackett and Pickles (2014) the prevalence rate was stable in the first year but declined thereafter. However, the review by Werheid (2016) based on 10 prospective longitudinal studies, observed a biphasic pattern, with a rise in depressive symptoms within the first six months, a slight drop at about one year and a new increase within the second year after stroke.

2.3. Outcome

PSD is associated with severe disability, anxiety, lower Quality of Life, speech and language dysfunction, anhedonia, feeling of despair, functional and cognitive impairment, greater dependency with regard to activities of daily living (ADL), lack of medication compliance (Ayerbe, Ayis, Crichton, Wolfe, & Rudd, 2014; De Ryck et al., 2013). PSD and even more the depression-executive dysfunction syndrome (DES), *i.e.* the clinical entity defined as late-life depression *plus* executive dysfunctions, were associated with earlier recurrence of stroke: 8.15 years for PSD and 7.15 years for DES *versus* 9.63–9.75 years in non-depressed and non-DES patients (Sibolt et al., 2013). Not surprisingly, PSD was associated with increased costs of stroke hospitalization (Husaini et al., 2013).

Increased mortality is the most dramatic clinical event following PSD. In a meta-analysis of 13 studies Bartoli et al. (2013) reported an OR of 1.46 (95% CI 0.76–2.80, NS) with a follow-up < 2 years, 1.21 (95% CI 1.12–1.32) at 2–5 years and 1.37 (95% CI 0.95–1.97) for > 5 years. A recent study, lasting 10 years on all-cause of mortality in a large population of stroke patients stratified by age, documented a HR of 1.56 (95% CI 0.49–5.02, NS) at the ages between 25 and 74 years, and 2.28 (95% CI 1.79–2.90) for patients aged 65–74 years (Razmara et al., 2017). Increased mortality in PSD patients might be the result of cardiovascular mortality linked to decreased heart rate variability, caused by the alteration of autonomic functions (Robinson, Spalletta, et al., 2008).

2.4. Predictors

The most frequent predictors cited in the vast (but somehow divergent) literature are female gender, a personal history of pre-stroke depression, physical disability, anxiety, aphasia, stroke severity, cognitive and physical impairment, level of independence, dysphagia and psychosocial factors like pre-stroke life events and lack of perceived family and social support (De Rick et al., 2014; Hackett & Anderson, 2005; Kutlubaev & Hackett, 2014; Shi, Yang, Zeng, & Wu, 2017).

3. Pathophysiology

Pathophysiology of PSD is complex and multifactorial, resulting from the combination of ischaemia-induced neurobiological dysfunctions and psychosocial distress. Indeed, the current evidence indicates the neurobiological factors (rather than the psychological response to disability) as the main factors associated with PSD.

This heterogeneity may result from the subtype of depression (major, minor), the post-stroke onset (early or late), the cerebral area