REVIEW

Inflammation and the Silent Sequelae of Stroke

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Published online: 20 June 2016

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Abstract Depression and fatigue are common after stroke and negatively impact the quality of life of stroke survivors. The biological bases of these symptoms are unknown, but an abundance of data point to a role for inflammation. This review highlights evidence supporting the contribution of inflammation to poststroke depression and poststroke fatigue. Potential treatments for poststroke depression and poststroke fatigue are explored, with a special emphasis on those that modulate the immune response.

Keywords Depression · Fatigue · Inflammation · Stroke

Introduction

Stroke affects approximately 795,000 persons each year in the USA and is the leading cause of permanent adult disability [1]. The physical consequences of stroke are generally obvious to an observer, but there are less perceptible consequences of stroke that may be more incapacitating than the physical disabilities. Poststroke depression (PSD) and poststroke fatigue (PSF) are both common and interfere with a person's ability to reintegrate into daily activities, even in patients with no apparent neurological deficits. Despite the high prevalence of PSD and PSF, the biological underpinnings of these symptoms are unknown. Based on data regarding depression and fatigue in other disease processes, as well as emerging data for stroke, it is possible that the genesis of PSD and PSF might be related to dysregulation of the immune response after stroke.

This paper will review the importance of PSD and PSF, explore the literature that supports an immunological connection to these symptoms, and speculate about the development of potential therapies.

PSD and PSF are Prevalent

At least one-third of patients who suffer stroke report depression in the poststroke period [2, 3]. These estimates vary based on the population studied and how depression was defined. Most studies of PSD are cross-sectional; the longitudinal studies that have been done tend to be small and have limited follow-up [4]. Fatigue, defined as a feeling of weariness, tiredness, or lack of energy, affects up to three-quarters of patients who suffer stroke [5–12]. Similar to PSD, most studies of PSF are cross-sectional in design and do not adequately address the natural history of PSF [13].

Fatigue is a manifestation of depression, but multiple lines of evidence suggest that fatigue and depression are distinct clinical entities. First, PSF is more prevalent than PSD, meaning that there is a subset of patients with stroke who develop fatigue without being depressed. For instance, in a study of patients who were at least a year poststroke, only 38% of the patients with fatigue were depressed [9]. Second, effective treatment of PSD by pharmacologic means does not eliminate PSF [14, 15]. And, finally, fatigue is more common in patients with stroke who have completely recovered as compared with patients with transient cerebral ischemia (without infarction), despite similar levels of depression and anxiety [16]. This observation suggests that tissue injury might set into motion biochemical changes that lead to fatigue but that anxiety and depression are more related to the psychological aspects of the event. The overlap between PSD and PSF is depicted in Fig. 1.

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Fig. 1 There is overlap between poststroke depression (PSD) and poststroke fatigue (PSF); most patients with PSD have PSF, but not all patients with PSF have PSD

PSD and PSF Impair Recovery and Decrease Quality of Life

PSD has been linked to decreased quality of life, increased disability, and increased mortality [4, 17–19]. In addition, there is an increase in suicidal ideation and suicide after stroke, especially among those with PSD [20, 21]. Studies also show that individuals with PSD experience a shorter interval to recurrent stroke [22]. And even in patients with minor stroke, PSD is independently associated with disability and poor physical and mental health 1 year after stroke [19].

PSF interferes with physical therapy, and patients identify fatigue as one of the major obstacles to their rehabilitation [23, 24]. The consequences of PSF are further illustrated by the fact that patients who complain of fatigue are more likely to be dependent for their activities of daily living and are more likely to require institutional care; mortality is also higher in patients with PSF [11, 25–27]. Among patients with mild stroke, fatigue is the most common complaint and is identified as the major issue restricting their life style [7, 10]. It is thus not surprising that PSF is more predictive of a lower health-related quality of life after stroke than actual neurological dysfunction [28]. Fatigue also prevents individuals who have experienced otherwise good stroke recovery from returning to work, which means that there are economic, as well as psychological implications to PSF [29, 30].

Assessing PSD and PSF

Studies of PSD use a variety of different rating scales to assess for depressive symptoms, and the distinction between

depressive symptoms and a depressive disorder is often not clear [31]. Further, the cut-off points for defining depressive symptoms using individual scales tend to differ from study to study [31]. A meta-analysis suggests that while some of commonly used scales are helpful in screening for PSD, none are satisfactory for case finding [32].

Similar to the situation for PSD, evaluation of the PSF literature quickly demonstrates that there is no consensus regarding the use of fatigue scales in patients with stroke—multiple different scales are used by multiple different research groups. Comparison of the various fatigue scales in patients with stroke shows that several are valid and feasible [33], yet none have been agreed upon as a standard for studies of PSF. A case definition has been proposed, however, and it requires that “Over the past month, there has been at least a 2-week period when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities” [34].

Risk Factors for PSD and PSF

Many studies suggest that PSD is associated with a history of prestroke depression. PSD also appears to be related to the degree of neurological disability and functional impairment, as well as to the social support network, socioeconomic status, and education [35, 36]. Identified risk factors for PSF depend upon the study in question, but depression, female sex, and European ethnicity are often implicated [12]. A relationship between age and PSF is unclear given that some studies show PSF to be more common in younger patients and others show it to be more common in older patients [12, 13].

The Contribution of Inflammation to Depression and Fatigue

A role for inflammation in the genesis of both depression and fatigue is implicated by several lines of evidence. First, depressive-like behavior is common in animals subjected to inflammatory insults [37, 38]. Second, mood disturbance is common after infection [39]. In the Third National Health and Nutrition Examination Survey (NHANES III), major depression was associated with higher levels of C-reactive protein (CRP), especially in men [40]. Finally, patients treated with proinflammatory cytokines often develop depression. Treatment with interferon- γ , in particular, is associated with depression [41].

A similar body of evidence exists for the link between inflammation and fatigue. First, it is a common symptom in patients with immune-mediated diseases [42–46]. Second,

the perception of fatigue is common among otherwise healthy individuals who suffer infectious illnesses [47, 48]. And, as with depression, the administration of proinflammatory cytokines [e.g., interleukin (IL)-6] is associated with the perception of fatigue [49]. Further, treatment with cytokine antagonists is associated with a decrease in fatigue—administration of exogenous IL-1ra (anakinra) decreases fatigue in patients with Sjögren's syndrome [50], and the tumor necrosis factor (TNF)- α receptor antagonist infliximab and the IL-6 receptor antagonist tocilizumab reduce fatigue in patients with cancer and autoimmune diseases [51–55].

Inflammation and the Biological Basis of PSD

Most studies that have looked for biological markers of PSD are small and have serious methodological issues. Given that inflammation is common after stroke, inflammation is linked to depression, and depression is common after stroke, there seems as if there should be a link between PSD and inflammation [56]. Unfortunately, the poor quality of the studies done to date do not allow for a definitive connection between PSD and inflammation to be made. In some studies, early markers of inflammation like CRP [57], ferritin [58], and neopterin [59] were associated with the later development of PSD. High serum levels of leptin at days 7 and 30 after stroke have also shown an association with later development of PSD [60]. And low levels of vitamin D, which is important for immunoregulation, have been linked to PSD [61]. Finally, elevated plasma glutamate levels at admission are associated with PSD [62]. Glutamate is an excitatory amino acid which is neurotoxic at high concentrations, but glutamate also possesses inflammatory potential, with glutamate receptors playing a role in immune-mediated diseases of the nervous system [63, 64].

In most studies, psychosocial factors are predictive of PSD [35, 36]. Epigenetics are invoked as a link between psychosocial stressors and the biology that mediates disease onset or outcome [65]. In animal studies, social isolation after stroke leads to behaviors consistent with PSD and is associated with increased serum IL-6 [66].

Inflammation and the Biological Basis of PSF

There are limited data supporting a role for inflammation in PSF. Similar to the studies for PSD, those studies that have looked for biological markers of PSF are small and have methodological issues. The studies that have been done show a link between PSF and increased IL-1 β , decreased IL-1ra, and decreased IL-9 at stroke onset [67, 68]. The data, however, were

not controlled for initial stroke severity, age, or other important covariates. More fundamentally, however, is that for a cytokine to mediate fatigue, that cytokine should be measured contemporaneously with the fatigue assessment instead at the time of the initial stroke. When assessed simultaneously, CRP appears to correlate with PSF in some studies [69] but not in others [70].

In a prospective study of patients with ischemic stroke, we assessed biomarkers of inflammation over 1 year after stroke. Patients with severe stroke (National Institutes of Health Stroke Scale Score ≥ 17), had elevations in CRP, IL-6, IL-1ra, and high mobility group box-1 for many months after stroke onset, and in some instances to at least a year (Fig. 2). In a subset of these patients, fatigue was assessed at 1 month, 3 months, and 1 year after stroke using the Fatigue Assessment Scale (FAS). The FAS has been validated in healthy cohorts [71]. FAS scores of 10–21 indicate that the patient is “not tired”, scores of 22–34 indicate that the patient is “tired”, and scores of 35–50 indicate that the patient is “very tired” [72]. We evaluated the relationship between the biomarkers of inflammation shown in Fig. 2, as well as other potential biomarkers, and being “tired” (FAS ≥ 22) in the year after stroke (Table 1). After controlling for stroke severity and the time at which fatigue was assessed, CRP, cortisol, and vascular cell adhesion molecule-1 were predictive of fatigue. After controlling for “feeling sad”, only CRP and vascular cell adhesion molecule-1 remained significant. In this same cohort of patients, we found that single nucleotide polymorphisms (SNPs) in genes that regulate inflammation were also associated with PSF [73]. Specifically, we found that PSF was associated with the C allele of *IL1RN* rs4251961, which is commonly associated with a decrease in IL-1ra and an increase in proinflammatory cytokines like IL-1 β and CRP [74, 75]. Further, we found that functional polymorphisms in Toll-like receptor 4 (TLR4) that render it less responsive to its ligands were associated with less fatigue [73]. These data are shown graphically in Fig. 3.

In attempt to better understand the biological basis of PSD and PSF, we evaluated the behavior and spontaneous activity in Lewis and Sprague-Dawley rats 1 month after stroke. Lewis rats are prone to inflammatory and autoimmune disorders, while Sprague-Dawley rats are more resistant to such diseases [76]. Following stroke, Lewis rats developed “learned helplessness”, which is a proxy for depression [77]. Sprague-Dawley rats, however, evidenced “fatigue-like” behavior with a decrease in the velocity of movement; this strain did not develop behavior consistent with depression [77]. In this study, systemic levels of IL-1 α correlated with “learned helplessness” and were higher in Lewis rats. Lower levels of IL-1ra, however, were associated with a decrease in the velocity of movement and the distance moved [77]. These data show that differences in rat strains can be capitalized upon to study the origins of PSD and PSF, and that the inflammatory milieu

Fig. 2 There is a prolonged inflammatory response after stroke, which is most notable in patients with severe stroke [National Institutes of Health Stroke Scale Score (NIHSS) ≥ 17]. Compared with patients with less severe stroke, (a) C-reactive protein (CRP), (b) interleukin (IL)-6, and (d) high mobility group box-1 (HMGB-1) are still elevated at 180 days after stroke. Compared with healthy controls, IL-6, (c) IL-1ra, and HMGB-1 are elevated to at least 180 days after stroke. Data are shown as the mean with error bars representing the SD. The dotted black horizontal lines in

(b–d) represent the mean value in control patients; the solid horizontal in (a) represents the upper limit of normal for CRP in our laboratory. Differences among stroke patients are represented by horizontal red lines; 1 line indicates $p \leq 0.05$, 2 lines indicate $p \leq 0.01$, and 3 horizontal red lines indicate $p \leq 0.001$. Differences between each tertile of stroke severity and control patients are denoted by * $p \leq 0.05$, † $p \leq 0.01$, or ‡ $p \leq 0.001$

in these strains likely affects the propensity to develop behaviors consistent with depression and fatigue.

Finally, neurochemicals, including glutamate, have also been implicated in the genesis of fatigue [78]. In a small clinical study, plasma glutamate levels correlated with the degree of fatigue in patients with minor stroke [79]. While stroke itself can lead to dynamic alterations in the metabolism of neurotransmitters (e.g., glutamate), inflammation also leads to major changes in the metabolism of these neurochemicals [80–82]. Cytokines (like IFN) alter the metabolism of monoamines (including dopamine and serotonin) and may contribute to fatigue [83, 84]. Based on these kinds of data, it appears that all of the major potential causes of fatigue following stroke are therefore intimately related and may share a common denominator in the immune system [85–88].

Therapeutic Approaches to the Treatment of Depression: A Focus on Inflammation

One of the most common pharmacological treatments for depression is modulation of 5-hydroxytryptophan through the use of selective serotonin reuptake inhibitors (SSRIs). There are ample data that show that this class of drugs also modulates inflammation [89]. For instance, treatment with SSRIs decrease CRP in patients with depression [90]. And in experimental models, SSRIs attenuate lipopolysaccharide-induced inflammation [91]. A variety of more traditional anti-inflammatory therapies has also been used for the treatment of depression, including aspirin and other nonsteroidal anti-inflammatory drugs, statins, and cytokine inhibitors like etanercept (which blocks TNF) [92–95]. Agomelatine is a

Table 1 Biomarkers of poststroke fatigue (Fatigue Assessment Score ≥ 22) from 1 month to 1 year after ischemic stroke

	Uncontrolled		Controlled for NIHSSS		Controlled for NIHSSS and time point		Controlled for NIHSSS, time point, and “feeling sad”	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Inflammatory biomarkers								
CRP (per 10 mg/l)	5.42 (1.30–22.58)	0.02	8.74 (1.81–42.24)	0.007	8.72 (1.80–42.26)	0.007	7.38 (1.39–2.26)	0.02
TNF- α (per pg/ml)	1.26 (0.92–1.71)	0.15	1.34 (0.95–1.90)	0.09	1.35 (0.95–1.92)	0.09	1.33 (0.90–1.98)	0.16
IL-6 (per pg/ml)	1.06 (0.95–1.20)	NS	1.09 (0.95–1.25)	NS	1.09 (0.95–1.25)	NS	1.10 (0.96–1.26)	0.17
IL1ra (per 100 pg/ml)	1.03 (0.99–1.08)	0.13	1.04 (0.99–1.09)	0.11	1.04 (0.99–1.09)	0.11	1.04 (0.99–1.10)	0.14
HMGB-1 (per ng/ml)	1.02 (0.86–1.21)	NS	1.01 (0.84–1.21)	NS	1.08 (0.88–1.32)	NS	1.16 (0.91–1.46)	NS
IL-10 (per pg/ml)	23.40 (0.51–1073.23)	NS	34.68 (0.76–1589.81)	0.07	33.91 (0.72–1599.65)	0.07	32.96 (0.42–2619.50)	0.12
Endocrine biomarkers								
Cortisol (per μ g/dl)	1.21 (1.04–1.42)	0.02	1.19 (1.01–1.39)	0.04	1.19 (1.01–1.39)	0.04	1.15 (0.96–1.37)	0.13
ACTH (per pg/ml)	0.98 (0.94–1.02)	NS	0.99 (0.95–1.03)	NS	0.99 (0.94–1.03)	NS	(0.93–1.03)	NS
α -MSH (per pg/ml)	1.02 (0.99–1.06)	0.12	1.03 (1.00–1.07)	0.07	1.04 (1.00–1.07)	0.05	1.03 (0.99–1.06)	0.15
Adhesion molecules								
VCAM-1 (per 100 pg/ml)	0.85 (0.72–0.99)	0.04	0.84 (0.72–1.00)	0.04	0.84 (0.72–1.00)	0.04	0.83 (0.70–0.98)	0.03
ICAM-1 (per 100 pg/ml)	1.00 (0.51–1.97)	NS	0.84 (0.40–1.78)	NS	0.84 (0.40–1.77)	NS	0.69 (0.30–1.60)	NS
FKN (per 100 pg/ml)	1.02 (0.78–1.34)	NS	1.08 (0.81–1.43)	NS	1.08 (0.81–1.44)	NS	0.96 (0.70–1.33)	NS

NIHSSS = National Institutes of Health Stroke Scale Score; OR = odds ratio; CI = confidence interval; CRP = C-reactive protein; TNF = tumor necrosis factor; IL = interleukin; NS = nonsignificant; HMGB = high mobility group box; ACTH = adrenocorticotrophic hormone; MSH = melanocyte-stimulating hormone; VCAM = vascular cell adhesion molecule; ICAM = intercellular adhesion molecule; FKN = fractalkine

member of a novel class of new antidepressants which are melatonin agonists; it has been approved by the European Union, after being shown to have similar efficacy to SSRIs for the treatment of depression [96, 97]. Melatonin agonists have numerous effects on the immune system, most of which serve to limit inflammation [98]. Finally, nonpharmacologic

approaches are also used to treat depression; these approaches include vagal nerve stimulation and exercise. Vagal nerve stimulation, approved for the treatment of resistant depression, leads to immunomodulation in animals [99]. Exercise also appears to decrease systemic markers of inflammation [100, 101] and lessen depression [102].

Fig. 3 Poststroke fatigue is more prevalent in those with the C allele of *IL1RN* (a), which is generally associated with increased inflammation [74, 75], and less prevalent in those with single nucleotide

polymorphisms (SNPs) in *TLR4* (b) that render the Toll-like receptor less sensitive to its agonists. FAS Fatigue Assessment Scale

If inflammation contributes to depression, the increased inflammatory state following stroke would suggest that anti-inflammatory therapies may be particularly beneficial in treating PSD. Studies show that traditional antidepressants, like the SSRIs, have some benefit for the treatment of PSD [14, 15, 103–105]. The quality of these studies, however, has been suboptimal and the evidence is not yet compelling enough to suggest that antidepressants be prescribed to all patients with PSD [106]. Non-SSRI antidepressants have not been widely studied in stroke, but drugs like agomelatine may be particularly attractive given that melatonin decreases central nervous system inflammation [107] and improves outcome in experimental models of cerebral ischemia [108, 109]. Additional evidence for the role of inflammation in the genesis of PSD and as a viable target for the treatment of PSD includes the fact that treatment with pioglitazone, as opposed to metformin, decreases PSD in patients with diabetes [110]. Peroxisome proliferator-activated receptor- γ agonists like pioglitazone have both anti-inflammatory and neuroprotective properties [111, 112]. And in a recent trial of secondary stroke prevention, pioglitazone decreased CRP in patients with insulin resistance [113]. Exercise, which is known to decrease CRP, has also been shown to be of benefit in PSD [114, 115]. And perhaps most exciting is that fact that treatment with natalizumab, an antibody to the $\alpha 4$ component of very late antigen-4 expressed on monocytes and lymphocytes, was associated with less depression after stroke [116]. This finding suggests that the inhibition of the immune response after stroke can prevent PSD.

Therapeutic Approaches to the Treatment of Fatigue: A Focus on Inflammation

Fatigue is common in patients with cancer and in patients with autoimmune disease. Inhibiting proinflammatory cytokines in these patients appears to lessen fatigue. Treatment with exogenous IL-1ra (anakinra), for instance, decreases fatigue in patients with Sjögren's syndrome [50]. Similarly, the TNF- α receptor antagonist infliximab and the IL-6 receptor antagonist tocilizumab reduce fatigue in patients with cancer [51] and a variety of autoimmune diseases [52–55]. Fatigue is a particularly prevalent problem for patients with multiple sclerosis (MS) [117]. While a number of different drugs are used to treat MS-related fatigue, the data providing support for pharmacologic interventions are, at best, weak [118]. Exercise therapy may help treat fatigue in patients with MS, but the quality of most of these trials is limited [119]. Predicated on the belief that MS-related fatigue may be related to inflammation, studies were undertaken with aspirin; this nonsteroidal anti-inflammatory drug was shown to improve fatigue in patients with MS in 2 different clinical studies [120, 121].

Given that there is not a clearly defined etiology for PSF, there are no rationally informed interventions. To date, very few trials have been done to address therapies for PSF. In fact, the most recent Cochrane review concluded that “there is insufficient evidence available to guide the management of fatigue after stroke” [122]. What we do know is that antidepressants do not seem to improve PSD [14]. Modafinil, which is approved for the treatment of fatigue in shift workers and patients with MS, failed to improve the Multi-dimensional Fatigue Inventory-20 score in a relatively small randomized controlled trial of patients with stroke, although it did have an effect on some secondary endpoints [123]. Cognitive therapy with graded activity training, however, was associated with a decrease in PSF [124]. (As mentioned previously, exercise and fitness training lead to a reduction in circulating proinflammatory cytokines [125–127].) All of these intervention trials are small and the results need to be confirmed.

If dysregulation of the immune response is an important contributing factor to PSF, interventions that lessen inflammation would be appropriate treatment strategies. Based on the studies that show a decrease in MS related fatigue with aspirin [120, 121], and as aspirin is prescribed to virtually all patients with ischemic stroke (who do not need to be anticoagulated), it would be reasonable to consider aspirin, albeit at a higher dose than is normally used for secondary stroke prevention, as a treatment for PSF. For example, at doses of 300 mg a day, aspirin decreases plasma concentrations of CRP, TNF- α , and IL-6 [128, 129]. Data regarding the effects of even higher doses of aspirin on these biomarkers of inflammation are limited. Other pharmacologic interventions using drugs that modulate the immune response could also be considered to treat PSF. For instance, treatment with natalizumab, which inhibits lymphocytes and monocytes, is associated with decreased fatigue in patients with MS [130]. This same drug is now being explored as a therapy for acute stroke, and assessing PSF in randomized controlled trials that evaluate acute stroke therapeutics may provide insight into the etiology, as well as the treatment, of PSF.

Summary

PSD and PSF are common sequelae of stroke and are more predictive of quality of life than actual neurological disability. There are data which suggest, but do not prove, a link between systemic inflammation and PSD and PSF. And while there is overlap between PSD and PSF, these symptoms appear to be distinct. It seems very unlikely that a single cytokine or other biological substrate causes either PSD or PSF, but rather it is likely that the overall systemic milieu after stroke that leads to these symptoms.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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