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ORIGINAL COMMUNICATION

Serum cytokine and glucose levels as predictors of poststroke fatigue in acute ischemic stroke patients

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Abstract Fatigue is a common but often overlooked symptom after stroke. This study investigated whether stroke type, infarct volume, and laterality, as well as the levels of various cytokines and other blood components in the acute phase of acute ischemic stroke (AIS), can predict the level of fatigue at 6, 12, and 18 months after its onset. In 45 patients with acute stroke, serum levels of C-reactive protein, hemoglobin, glucose, and 13 cytokines were measured within 72 h of stroke onset. The cytokine measurements were performed using BioPlex XMap technology (Luminex). The acute serum levels of interleukin (IL)-1β and glucose were positively correlated with the score on the Fatigue Severity Scale (FSS) at 6 months after the stroke ($r = 0.37$, $p = 0.015$, and $r = 0.37$, $p = 0.017$, respectively). The acute serum levels of IL-ra and IL-9 were negatively correlated with FSS score at 12 months after the stroke ($r = -0.38$, $p = 0.013$, and $r = -0.36$, $p = 0.019$, respectively). The FSS score at 12 months after stroke was significantly lower in patients with radiologically confirmed infarction than in those without such confirmation ($p = 0.048$). The FSS score at 18 months was not correlated with any of the measured variables. High acute serum levels of glucose and IL-1β, and low IL1-ra and IL-9 may predict fatigue after AIS, indicating that the development of poststroke fatigue can be accounted for by the proinflammatory response associated with AIS. These novel findings support a new cytokine theory of fatigue after stroke. However, more research is needed to validate the results of this study.

Keywords Acute ischemic stroke · Inflammation · Cytokines · Proinflammatory · Anti-inflammatory

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Introduction

Stroke is the second most common cause of death and is a major cause of disability worldwide [1]. Many stroke survivors cope with chronic health problems that require a long-term process of recovery and rehabilitation. Fatigue is a common but often overlooked symptom after stroke [2]. Indeed, there are several reports of fatigue being a common difficulty after stroke, with a frequency ranging from 29 to 68% (compared to 20% in control groups) [3]. This significant variability in the prevalence of poststroke fatigue (PSF) is probably related to varying definitions and methods of assessing fatigue, as well as sampling of different populations [4].

PSF represents a complex interaction of biological, psychosocial, and behavioral phenomena, and is, therefore,

challenging to define [4]. However, some definitive characteristics of PSF have been reported: it is qualitatively different from the fatigue experienced by patients before stroke, it is exacerbated by stress and physical exercise, and it responds well to rest, sleep, and low temperatures—the last three being rarely described in association with either chronic fatigue syndrome (CFS) or depression [3]. Although fatigue and depression are unquestionably related, fatigue can reportedly occur in the absence of depression, with one study finding that only 38% of patients with severe fatigue after stroke met the criteria for depression [5].

The best way to treat PSF is uncertain. A recent Cochrane study that evaluated different interventions for PSF by reviewing three trials found that there is currently insufficient evidence to guide the management of fatigue after stroke [6]. Furthermore, despite the high clinical relevance, there are few studies on the pathophysiology of PSF. It has been postulated that fatigue is related to an immune dysregulation with cytokine abnormities in CFS [7–10], Parkinson's disease [11], multiple sclerosis [12], fibromyalgia [13], and cancer [14].

There is considerable evidence that cytokines contribute to inflammation in both the central and peripheral nervous systems associated with stroke [2, 15, 16]. Several studies performed in recent decades have examined the relationship between cytokines and outcome in stroke. It has been found that elevated levels of inflammatory markers, and especially interleukin (IL)-6, are associated with poor outcomes in stroke [17–21].

We are not aware of previously published data on the relationship between serum cytokine levels and the severity of fatigue following stroke. This study investigated whether serum levels of various cytokines, C-reactive protein (CRP), hemoglobin and glucose, and stroke lateralization, subtype, and infarct volume in acute ischemic stroke (AIS) patients can predict the level of PSF, as measured using the score on the Fatigue Severity Scale (FSS) at 6, 12, and 18 months after stroke onset.

Subjects and methods

Patients

The cohort comprised 45 patients who were part of a longitudinal study of first-ever stroke patients admitted to Buskerud Hospital, a regional hospital in Norway. The recruiting procedure is described in detail elsewhere [22]. In short, the inclusion criteria were clinical presentation of first-ever stroke, age 18 years or older, and exhibiting sufficient cognitive functioning to participate. Stroke was defined as the presence of rapidly developing focal neurological signs or symptoms of vascular origin that persisted for >24 h. The exclusion criteria were no serum samples collected, uncertain diagnosis of AIS, presence of cancer, receiving thrombolysis therapy, and uncertain symptom onset.

Clinical and instrumental evaluation

A general medical history was collected, and physical and neurological examinations, standard laboratory tests, 12-lead electrocardiogram, and cerebral computed tomography (CT) imaging were performed in all patients upon admission. Patients without clear radiological findings on admission but with persistent clinical symptoms indicative of AIS after 2–4 days submitted to a secondary CT or magnetic resonance imaging (MRI) scan. The imaging used for measurement of infarct volume was performed within 1–7 days after stroke onset. The type of AIS was determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification: cardioembolic infarct (CEI), large-artery atherosclerosis (LAAS), lacunar infarct (LAC), stroke of undetermined etiology (UDE), and stroke of other determined etiology [23]. Lateralization of the stroke was determined by clinical findings and imaging results, or on a clinical basis (only in patients without conclusive CT or MRI findings). Location of the stroke, supra- or infratentorial respectively, was determined by radiologically findings.

Imaging and volumetric analysis

When possible, infarct volumes were measured on either MRI (24/34 cases) or CT (10/34 cases). In MRI, diffusion sequences were used in the axial plane, combined with sagittal T2 turbo spin-echo and/or coronal fluid-attenuated inversion recovery imaging, using an on-screen measuring technique. In CT, measurements were made on axial slices in combination with thickness data.

Blood collection and serum preparation

Blood samples were taken at <24, 24–48, and 48–72 h after stroke onset in 35, 7, and 3 of the 45 patients, respectively, and collected into 7.5-ml serum S-Monovette gel tubes (Sarstedt, Nümbrecht, Germany). Samples were stored for 30–120 min at room temperature prior to centrifugation at $1{,}400 \times g$ for 12 min. Serum samples were aliquoted at 500 µl into Eppendorf tubes and subjected to instant freezing at −70°C, within 5 h of blood sampling.

CRP, glucose, and hemoglobin measurements

Serum levels of CRP, glucose, and hemoglobin were all determined using clinically validated assays: a standard latex immunoassay (CRP Vario, Abbott Diagnostics),

Architect cSystems (Abbott Diagnostics), and the Advia 120 Hematology system (Siemens Health Care Diagnostics), respectively.

Cytokine measurement

Cytokine levels were measured using a Luminex IS 100 instrument (Bio-Rad, Hercules, CA, USA). Based on a screening of representative serum samples using the Bio-Plex human cytokine 27-plex assay (catalog no. 171A11127, Bio-Rad), the following custom plex was purchased to screen all samples: Bio-Plex Pro Human Cytokine Group I—IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, tumor necrosis factor (TNF)-α, and interferon-γ; Bio-Plex Pro Human Cytokine Group II; growth-related oncogene (GRO)-α (CXCL1); and IL-18 (Bio-Rad). All samples were thawed on ice, vortexed, spun down at 14,000$\times g$ for 10 min at 4°C, and then diluted at 1:4. Longitudinal controls were used to assess the interassay variation. The coefficient of variation for controls ranged from 9 to 19% on the exponential phase of the standard curve.

Clinical measurements

Barthel Index

Functional disability was measured using the Barthel-20 Index (BI-20) [24] at admission, and then again at 6, 12, and 18 months thereafter. This index is currently regarded to be the most reliable disability scale for stroke, and is highly correlated with the immediate poststroke condition [25].

FSS score

The FSS, which was used to assess the severity of fatigue [26], was originally designed to determine the impact of fatigue in patients with multiple sclerosis [26], but has also been used frequently to assess stroke patients [27–32]. The FSS contains nine items, each of which is scored from 1 to 7, with a higher score indicating a greater impact of fatigue on the patient's daily life. The sum score is the mean of the nine items. The FSS has an internal consistency (Cronbach's α) of 0.89 [31]. The aforementioned studies defined fatigue as being present if the FSS score was above 4 [27–32], indicating a moderate to high impact of fatigue on daily living. The distinction between normal and abnormal fatigue is not clear; linear models treating FSS score as a continuous variable were thus used in the present study when analyzing potential associations between variables. For each of the variables found to be significantly associated with the FSS score ($p < 0.05$), means/medians and proportions of participants falling into groups based on FSS scores are presented in Table 2 (those with FFS ≥ 4 and those with FSS < 4).

Statistical analysis

If more than 50% of the values of a particular cytokine were not detectable, that cytokine was dichotomized as detectable (yes/no) and analyzed using Pearson's chi-square test. Since the distributions of most of the cytokines were markedly skewed, the results are presented as medians and interquartile ranges (IQRs).

The independent-samples *t*-test was used when comparing means from the two FSS groups. Skewed continuous variables are presented as median and IQR values, and the two-tailed Mann–Whitney test was used to compare the median values of cytokines between the two FSS groups. The Spearman correlation coefficient was used to quantify associations between infarct volume and blood components and BI-20. In addition, in order to be a confounder for the relation between glucose or a cytokine variable and later fatigue, the variable must be associated both with glucose or the cytokine variable and be a predictor for fatigue.

All statistical analyses were performed using the SPSS statistical package (version 15).

Results

The study patients comprised 27 males and 18 females aged between 37 and 85 years (mean age 67.7 $\pm$ 11.8 years), of which 22, 21 and 2 had right-, left-sided and bilateral ischemic stroke, respectively.

TOAST classification yielded groups that were too small to allow for more detailed statistical analysis. We thus dichotomized the patients into radiologically confirmed infarctions (merged TOAST criteria for CEI, LAAS, and LAC; $n = 34$) and radiologically unconfirmed infarctions (TOAST criteria for UDE; $n = 11$). Of the 34 patients with radiologically confirmed stroke, 30 had supratentorial, while 4 had infratentorial findings. The stroke volume measured in the 34 patients with radiologically confirmed stroke ranged from 0.5 to 140 cm^3 (median, 2 mm^3; IQR, 1, 17 mm^3).

The following comorbidities were found: hypertension ($n = 28$), atrial fibrillation ($n = 6$), coronary disease ($n = 7$), diabetes ($n = 4$), rheumatism ($n = 2$), psoriatic arthritis ($n = 3$), Bechterew's disease ($n = 1$), and hyperthyroidism ($n = 1$). While 39 patients did not use any immunosuppressant, 3 were medicated with prednisolone and 3 with nonsteroidal anti-inflammatory drugs.

The percent of patients with BI-20 score equal to 20 was 71.2, 70.5 and 78.6%, at 6, 12 and 18 months, respectively.

The mean FFS scores of the 45 patients at the three time points were 4.2 ± 1.4, 4.2 ± 1.4 and 4.4 ± 1.4, respectively.

Associations between various values and FSS scores measured at 6, 12, and 18 months after stroke are presented in Table 1; Table 2 lists the significant findings from Table 1. FSS data are dichotomized as FSS score <4 and ≥4.

The acute serum levels of IL-1β and glucose were positively correlated with FSS score at 6 months after the stroke ($r = 0.37$, $p = 0.015$, and $r = 0.37$, $p = 0.017$, respectively). The glucose level was 7.55 ± 2.73 and 6.25 ± 1.35 mmol/l (mean ± SD) in the FSS ≥ 4 and FSS < 4 groups, respectively. Furthermore, IL1-β was detectable in 32% of the FSS ≥ 4 group and in 13% of the FSS < 4 group. The baseline BI-20 values were negatively correlated with FSS score at 6 months after the stroke ($r = -0.35$, $p = 0.023$).

Acute serum levels of IL-ra and IL-9 were negatively correlated ($r = -0.38$, $p = 0.013$, and $r = -0.36$, $p = 0.019$, respectively), and those of glucose positively correlated ($r = 0.37$, $p = 0.016$) with FSS score at 12 months after the stroke. The FSS ≥ 4 group had a significantly lower median value of IL-1ra [1,021 μg/ml (IQR, 761–1,364 μg/ml) versus 1,561 μg/ml (IQR, 985–2,023 μg/ml)] and a lower proportion of patients with detectable values of IL-9 (29 vs. 61%) than the FSS < 4 group. The glucose levels in these two groups were 7.8 ± 2.7 and 6.02 ± 1.1 mmol/l, respectively.

Table 1 Factors associated with FSS score at 6, 12, and 18 months after stroke onset; correlation coefficients and p values (based on the FSS score as a continuous variable)

Variable	FSS score at 6 months	FSS score at 12 months	FSS score at 18 months
Gender	$p = 0.991$	$p = 0.752$	$p = 0.952$
Age, years	$r = -0.3$, $p = 0.14$	$r = 0.20$, $p = 0.192$	$r = 0.26$, $p = 0.102$
Radiologically confirmed infarction	$p = 0.311$	**$p = 0.048$**	$p = 0.123$
Yes	4.1 ± 1.4	3.9 ± 1.4	4.2 ± 1.3
No	4.6 ± 1.3	4.9 ± 1.3	4.9 ± 1.5
Infarction side	$p = 0.76$	$p = 0.34$	$p = 0.91$
Right ($n = 22$)	4.3 ± 1.3	4.4 ± 1.4	4.3 ± 1.7
Left ($n = 21$)	4.2 ± 1.3	4.0 ± 1.3	4.4 ± 1.1
Location	*	*	*
Supratentorial ($n = 30$)	4.1 ± 1.3	4.0 ± 1.4	4.2 ± 1.2
Infratentorial ($n = 4$)	4.6 ± 1.7	3.5 ± 1.3	4.1 ± 1.8
Infarct volume (cm^3)	$r = -0.18$, $p = 0.313$	$r = 0.15$, $p = 0.405$	$r = 0.02$, $p = 0.927$
BI-20 baseline	**$r = -0.35$, $p = 0.023$**	$r = -0.18$, $p = 0.263$	$r = -0.2$, $p = 0.224$
Glucose	**$r = 0.37$, $p = 0.017$**	**$r = 0.37$, $p = 0.016$**	$r = 0.27$, $p = 0.09$
Hemoglobin	$r = 0.1$, $p = 0.543$	$r = -0.051$, $p = 0.744$	$r = -0.21$, $p = 0.175$
CRP	$r = 0.02$, $p = 0.882$	$r = 0.01$, $p = 0.935$	$r = -0.7$, $p = 0.664$
IL-1ra (μg/ml)	$r = -0.02$, $p = 0.917$	**$r = -0.38$, $p = 0.013$**	$r = -0.28$, $p = 0.077$
IL-8 (μg/ml)	$r = -0.23$, $p = 0.131$	$r = -0.03$, $p = 0.858$	$r = 0.12$, $p = 0.452$
IL-18 (μg/ml)	$r = -0.04$, $p = 0.795$	$r = -0.05$, $p = 0.730$	$r = -0.28$, $p = 0.072$
GRO-α	$r = -0.09$, $p = 0.551$	$r = -0.19$, $p = 0.226$	$r = 0.05$, $p = 0.755$
IL-1β	**$r = 0.37$, $p = 0.015$**	$r = 0.09$, $p = 0.571$	$r = -0.07$, $p = 0.677$
IL-2	$r = 0.27$, $p = 0.084$	$r = 0.27$, $p = 0.075$	$r = 0.19$, $p = 0.222$
IL-4	$r = 0.09$, $p = 0.556$	$r = -0.17$, $p = 0.289$	$r = -0.004$, $p = 0.981$
IL-6	$r = 0.18$, $p = 0.242$	$r = 0.1$, $p = 0.514$	$r = 0.07$, $p = 0.661$
IL-9	$r = 0.07$, $p = 0.665$	**$r = -0.36$, $p = 0.019$**	$r = -0.02$, $p = 0.882$
IL-10	$r = 0.09$, $p = 0.553$	$r = 0.1$, $p = 0.535$	$r = -0.1$, $p = 0.55$
IL-12	$r = 0.11$, $p = 0.476$	$r = -0.2$, $p = 0.205$	$r = -0.1$, $p = 0.549$
INF-γ	$r = 0.2$, $p = 0.189$	$r = 0.05$, $p = 0.763$	$r = 0.11$, $p = 0.506$
TNF-α	$r = 0.06$, $p = 0.710$	$r = -0.06$, $p = 0.693$	$r = -0.09$, $p = 0.594$

The independent-samples t-test was used when comparing means from the two FSS groups

The Spearman correlation coefficient was used to quantify associations between infarct volume, blood components and BI-20

Significant findings ($p < 0.05$) are indicated in bold

*Significance was not calculated due to small group size ($n = 4$)

Table 2 Significant findings from Table 1; data presented for FSS score dichotomized as <4 and ≥4

Variable	At 6 months		At 12 months	
	FSS score <4	FSS score ≥4	FSS score <4	FSS score ≥4
Radiologically confirmed infarction, dichotomized values [*n* yes (% of total)]	–	–	17 (86%)	16 (67%)
Glucose, mmol/l, mean ± SD	6.25 ± 1.35	7.55 ± 2.73	6.02 ± 1.1	7.8 ± 2.7
BI-20 at baseline, mean ± SD	20 ± 0.9	18±3.2	–	–
IL-1ra, μg/ml, median (IQR)	–	–	1561 (985–2,023)	1021 (761–1,364)
IL-1β, μg/ml, dichotomized values [*n* detectable (% of total)]	1 (13%)	9 (32%)	–	–
IL-9, μg/ml, dichotomized values [*n* detectable (% of total)]	–	–	11 (61%)	7 (29%)

The FSS score at 12 months was significantly lower in those with a radiologically confirmed infarction than in those without such confirmation ($p = 0.048$). Moreover, a radiologically confirmed infarction was present in 67% of the FSS ≥ 4 group and 86% of the FSS < 4 group.

FSS scores at 18 months after the stroke was not associated with any of the variables measured.

Age, gender, hypertension, atrial fibrillation, medication, coronary disease and baseline BI-20 were not significant confounders for the significant associations between fatigue at 6 and 12 months and baseline cytokine/glucose levels.

Discussion

We found that neither stroke lateralization nor infarct volume were associated with subsequent fatigue. This finding is in accordance with those of several other studies that have evaluated stroke location [27, 33, 34], and volume [27]. In our study, the group with infratentorial findings was too small ($n = 4$) to allow for detailed statistical analysis on location. Two other studies found no association between TOAST subtype and subsequent fatigue [33, 34]. In our study, TOAST classification yielded groups that were too small to allow a more detailed statistical analysis. However, after dichotomizing our cohort into those with radiologically confirmed infarctions and those without, we found that the latter had significantly higher FSS scores at 12 months after stroke onset ($p = 0.048$). We have previously found that patients with radiologically confirmed infarctions were significantly younger and had significantly higher serum levels of GRO-α than those without such confirmation [35]. However, FSS scores at 12 months were not correlated with either age or GRO-α. Thus, the difference in FSS scores between these two groups cannot be explained by differences in age or GRO-α.

Our finding of more severe fatigue observed among patients with UDE (cryptogenic stroke) is interesting. We did not identify a biological origin for this finding, and it is possible that this phenomenon is of a more psychosocial nature. For example, the diagnosis of "unconfirmed" stroke may confer a lack of acknowledgment upon patients, generating within them a feeling of uncertainty and speculation. More research is needed to investigate this possibility, moving into the interesting field of the biological versus psychosocial aspects of PSF.

We found significantly higher acute levels of IL-β and glucose in stroke patients with more severe fatigue at 6 months after stroke. Significantly higher levels of glucose and lower levels of IL1-ra and IL-9 were found in patients with more severe fatigue at 12 months after stroke. These findings indicate that high levels of glucose and IL-1β and low levels of IL-1ra and IL-9 in the acute phase of AIS may predict subsequent fatigue, indicating that the proinflammatory response in AIS may be responsible for the development of PSF.

Our finding that IL-1β is a predictor of PSF may be explained by the concept of cytokine-induced sickness behavior, whereby sickness behavior is induced by physiological concentrations of proinflammatory cytokines acting in the brain after infection, the symptoms being loss of appetite, sleepiness, withdrawal from normal social activities, fever, aching joints, and fatigue [36]. IL-1β is one of the two main proinflammatory cytokines involved in sickness behavior, the other being TNF-α [37]. The most plausible mechanism by which proinflammatory cytokines could induce mental fatigue is disturbance of glutamate signaling, which is crucial for information gathering and processing within the brain. The hypothesis is that proinflammatory cytokines TNF-α, IL-1β, and IL-6 act in the pathophysiology of mental fatigue via their ability to attenuate the astroglial clearance of extracellular glutamate, their disintegration of the blood–brain barrier, and their effects on astroglial metabolism and the neuronal metabolic supply, thereby attenuating glutamate transmission [38].

IL1-ra, the naturally occurring antagonist of IL-1β, is known to be neuroprotective [39], and, relevant to the focus of our study, attenuates sickness behavior in

experimental models (as measured by a reduction in social interaction or food intake) [40]. Furthermore, Emsley and coworkers [41] identified recombinant human IL-1ra (rhIL-1ra) as a potential new therapeutic agent for acute stroke, after they found that clinical outcomes at 3 months among patients with cortical infarcts were better in the rhIL-1ra-treated group than in the placebo-treated group. To the best of our knowledge, our finding that IL-ra is negatively correlated with the severity of PSF is novel and also supports the previous findings and approaches discussed above.

Elevated blood glucose is common in the early phase of stroke; hyperglycemia (blood glucose level >6.0 mmol/l) has been observed in two-thirds of all ischemic stroke subtypes on admission [42]; in our study, 60% of the patients had blood glucose levels >6.0 mmol/l. High levels of glucose were found to predict fatigue after 6 and 12 months. Hyperglycemia is associated with impaired clinical outcome [43–45], and significantly worsens both cortical intracellular brain acidosis and mitochondrial function in the ischemic penumbra, which supports the hypothesis that the evolution of acidosis in the ischemic penumbra is related to glucose utilization [46]. Hyperglycemia most probably effects direct membrane lipid peroxidation and cell lysis in metabolically challenged tissue by provoking anaerobic metabolism, lactic acidosis, and free-radical production [47]. We have found no previous data on the relationship between hyperglycemia and PSF, or any other type of illness-related fatigue, and thus believe these findings to be novel.

The role of IL-9 in AIS remains unclear, although we have previously found a significant elevation of serum IL-9 levels in AIS patients (unpublished results). We, therefore, believe that we are the first to show that IL-9 is negatively correlated with FSS at 6 months after stroke onset. It has been shown that the IL-9/IL-9 receptor signaling pathway represents a novel endogenous anti-apoptotic mechanism for cortical neurons [48]. We therefore speculate that IL-9 protects against stress-induced neuronal damage. Further research on the role of IL-9 in AIS is required.

The relationships between cytokines and fatigue found at 6 and 12 months disappeared after 18 months. The fact that the mean fatigue score had not declined at this time point, leads us to speculate that other, most probably psychosocial, factors have contributed to the sustained level of fatigue this late after stroke. Qualitative research of post stroke fatigue indicates that lack of information and knowledge about the fatigue problem following stroke, which may generate a feeling of lack of acknowledgment, leads to additional distress for the patients [49–51]. We hypothesize that this may be a contributing factor for the prolonging of fatigue post stroke.

Considering the relatively high number of significant tests performed in our study, the possibility of at least one false significant result is relatively high. This should be taken into account when interpreting the results.

Conclusion

To the best of our knowledge, this is the first analysis of cytokines and glucose as possible predictors of fatigue following AIS. Thus, our study should be regarded primarily as a hypothesis-generating one (i.e., the findings must be verified in future studies before being interpreted as valid). Our study supports the notion that PSF may be attributable to cytokine activation, most probably by disturbing glutamate signaling. Our findings regarding IL1-β and IL-1ra support this theory.

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Conflict of interest The authors declare no conflict of interest.

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