Higher Plasma Fractalkine Is Associated With Better 6-Month Outcome From Ischemic Stroke

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Background and Purpose—Fractalkine (CX3CL1) is a unique chemokine that is constitutively expressed on neurons where it serves as an adhesion molecule for lymphocytes and monocytes. CX3CL1 may also be cleaved from the surface of these cells and enter the circulation to act as a traditional chemokine. CX3CL1 could thus influence the inflammatory response after stroke. We hypothesized that patients with higher plasma CX3CL1 after stroke would have a more robust inflammatory response and experience worse outcome.

Methods—Plasma CX3CL1 concentrations were assessed in 85 patients who were part of a larger study evaluating immune responses after ischemic stroke; CX3CL1 values were available from Day 1 to Day 180 after stroke onset. CX3CL1 was correlated to measures of inflammation and its effect on outcome assessed.

Results—At 1 day after stroke, CX3CL1 was lower in patients with severe strokes. At 180 days after stroke, CX3CL1 concentrations were lower in patients with poor outcome. The association of CX3CL1 and outcome at 180 days was independent of initial stroke severity. Plasma CX3CL1 at 180 days was inversely associated with systemic markers of inflammation, including white blood cell counts and high-sensitivity C-reactive protein.

Conclusions—In contrast to our original hypothesis, lower concentrations of CX3CL1 are associated with worse stroke outcome. In light of recent studies suggesting an immunomodulatory and neuroprotective role for CX3CL1 in a variety of neurodegenerative diseases, a therapeutic role for CX3CL1 in stroke recovery should be considered. **(*Stroke*. 2012; 43:2300-2306.)**

Key Words: CX3CL1 ■ fractalkine ■ inflammation ■ outcome ■ stroke

Fractalkine, or CX3CL1, is a unique chemokine that exists in both a membrane bound form and a soluble form. CX3CL1 is expressed constitutively in neurons and its expression is inducible in vascular endothelial cells.[1] The CX3CL1 receptor (CX3CR1) is expressed by monocytes, lymphocytes, natural killer cells, macrophages, and microglia.[2,3] In its membrane bound form, CX3CL1 serves as an adhesion molecule for these cells; in its soluble form, it serves as a potent chemoattractant for them.[1–3] In the central nervous system, the CX3CL1/CX3CR1 interaction regulates the communication among neurons, glia, and microglia; is important in the response to injury; and may contribute to neurogenesis.[4–8] There are a number of publications suggesting that the CX3CL1/CX3CR1 pathway is important in the pathogenesis of neurodegenerative diseases like Alzheimer's and Parkinson's disease, but the findings are quite disparate, variably implicating CX3CL1/CX3CR1signaling as neuroprotective or neurotoxic.[9–12]

The potential contribution of CX3CL1 to ischemic brain injury has been explored in animal models of stroke. These studies show that CX3CL1 expression is upregulated in intact neurons within the penumbra, whereas both CX3CL1 and CX3CR1 expression are upregulated in the infarcted brain, the former in neurons and the latter in microglia.[13] Mice deficient in CX3CL1 have smaller infarct volumes and improved survival after middle cerebral artery occlusion.[14] Similarly, CX3CR1 knockout mice have smaller infarcts and better functional outcome as well as less inflammatory infiltrate and decreased expression of proinflammatory cytokines in the ischemic brain.[15]

In humans, cerebrospinal fluid concentrations of CX3CL1 are increased in a wide range of traumatic and inflammatory neurological diseases.[16–19] In addition, circulating CX3CL1 is elevated in patients with multiple sclerosis and neuropsychiatric lupus.[16,18] To our knowledge, soluble CX3CL1 has not been assessed in the plasma of patients with ischemic stroke. Based on the experimental data, we hypothesized that patients with more severe strokes would have higher concentrations of plasma CX3CL1, more evidence of inflammation, and worse stroke outcome. The plasma concentrations of the traditional

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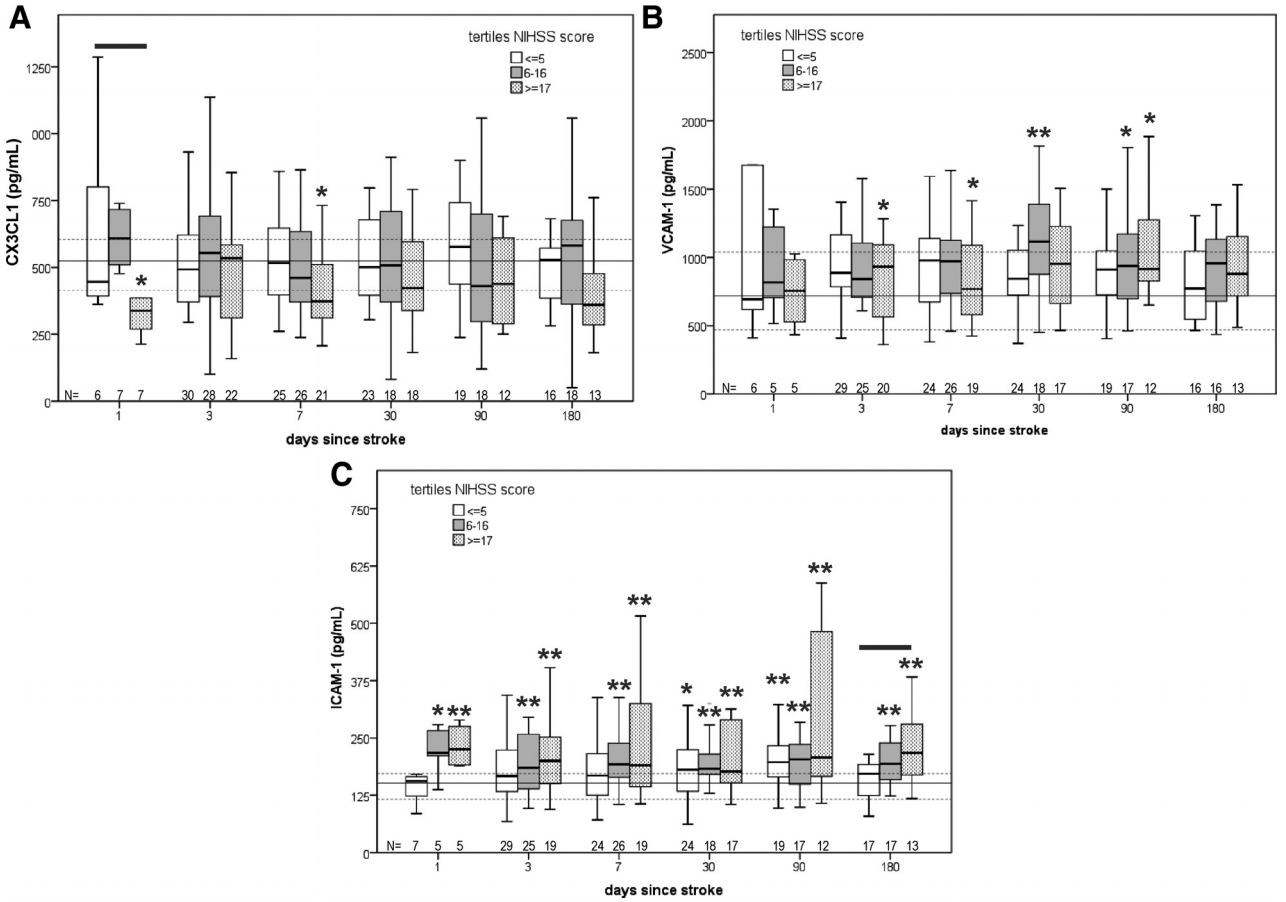

Figure 1. Concentrations of circulating CX3CL1 (**A**), VCAM-1 (**B**), and ICAM-1 (**C**) over the course of 180 days after stroke. The solid horizontal line represents the median value of the control population and the dashed lines the interquartile range. The solid line above the boxes indicates that the values among patients with different tertiles of stroke severity differ from each other at $P<0.05$ (Kruskal-Wallis H test); *The tertile of stroke severity differs from control subjects at $P<0.05$ and **the tertile of stroke severity differs from controls at $P<0.01$ (Mann-Whitney *U* test). CX3CL1 indicates fractalkine; VCAM, vascular cell adhesion molecule; ICAM, intracellular adhesion molecule.

leukocyte adhesion molecules vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 were also assessed because both are known to be elevated in plasma after ischemic stroke.[20–23]

Materials and Methods

Research Subjects

The patients in this study were part of a longitudinal study of immune responses after ischemic stroke. Patients were admitted to Harborview Medical Center from September 2005 through May 2009 and had to be at least 18 years and enrolled within 72 hours of symptom onset. Individuals with ongoing therapy for malignancy, known history of HIV, hepatitis B or C, history of brain tumor, anemia (hematocrit <35 on admission), and those taking immunomodulatory drugs were excluded. Blood was drawn as soon as possible after stroke onset and at 72 hours, 7 days, 90 days, and 180 days after stroke onset. Blood was also obtained from 40 volunteers to determine normative data for CX3CL1, VCAM-1, and ICAM-1 concentrations. The study was approved by the Institutional Review Board; all patients or their surrogates as well as control subjects provided informed consent.

Clinical Data

Clinical and demographic data were collected on all patients; information about therapeutic interventions for the treatment of stroke was collected. Stroke severity was determined by the National Institutes of Health Stroke Scale (NIHSS) score and outcome by the modified Rankin Scale, Glasgow Outcome Scale–extended (GOSE), and the Stroke Impact Scale (SIS).[24–26] In-hospital infection was defined as clinical symptoms of an infection (fever and/or pyuria for urinary tract infection and fever and/or productive cough and radiographic evidence of consolidation for pneumonia) and positive culture data (for both productive cough and radiographic evidence of consolidation for pneumonia and urinary tract infection). Total infarct volume on initial diffusion-weighted MRI imaging was calculated by the ABC/2 method.[27]

Laboratory Studies

White blood cell counts were determined by the clinical hematology laboratory. The concentration of high-sensitivity C-reactive protein was determined by the hospital laboratory using standard methods. Additional plasma was immediately frozen at −80°C; the concentrations of ICAM-1, VCAM-1, and CX3CL1 were determined by enzyme-linked immunoassay (R&D Systems). The sensitivity of the assays was 0.096 ng/mL, 0.6 ng/mL and 0.018 ng/mL, respectively. Interleukin-6 was measured using a cytometric bead-based system (Fluorokine MAP; R&D Systems); the lower limit of detection was 1.1 pg/mL.

Statistics

Descriptive data are presented as median and interquartile range for continuous variables; group comparisons were performed using the Kruskal-Wallis H test and the Mann-Whitney *U* test as appropriate.

Table 1. Neurological Outcomes at 180 D

Outcome Measure				mRS			GOSE		SIS
Median (IQR)				2 (1–3)			6 (5–8)		94 (69–100)
Correlations	Unadjusted	Adjusted for Initial NIHSS	Adjusted for Initial Infarct Volume	Unadjusted	Adjusted for Initial NIHSS	Adjusted for Initial Infarct Volume	Unadjusted	Adjusted	Adjusted for Initial Infarct Volume
CX3CL1	−0.397, P=0.005	−0.348, P=0.016	−0.415, P=0.004	0.421, P=0.005	0.171, NS	0.278, P=0.062	0.421, P=0.005	0.337, P=0.029	0.374, P=0.015
VCAM-1	−0.023, NS	−0.095, NS	−0.071, NS	0.115, NS	0.219, P=0.149	0.213, P=0.160	0.115, NS	−0.164, NS	−0.185, NS
ICAM-1	0.125, NS	−0.135, NS	0.024, NS	−0.316, P=0.032	0.170, NS	0.030, NS	−0.316, P=0.032	−0.131, NS	−0.251, P=0.097
Poor outcome		>3			<5			<70	

IQR indicates interquartile range; mRS, modified Rankin Scale; GOSE, Glasgow Outcome Score–extended; SIS, Stroke Impact Scale; NIHSS, National Institutes of Health Stroke Scale; CX3CL1, fractalkine; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; NS, not significant (P≥0.200).

Correlations between circulating concentrations of CX3CL1, VCAM-1, and ICAM-1 at 180 d and neurologic outcome at this time point are also presented using Pearson *r*. Data are normalized and analyses are both unadjusted and adjusted for initial stroke severity (using the NIHSS score or initial infarct volume). Poor outcome is arbitrarily defined as an outcome worse than 75% of the entire cohort.

For correlations, parametric data were log-transformed and the data presented as the Pearson correlation coefficient. Logistic regression was used to test the association between admission clinical and laboratory measures and poor outcome (GOSE <5) at 180 days, both unadjusted and adjusted for stroke severity as measured by the highest NIHSS in the first 72 hours or the total infarct volume on MRI. The OR is used as the measure of association. Significance was set at $P<0.05$. No formal adjustment is made to probability values to account for the fact that many predictor variables are tested; results should therefore be interpreted cautiously in light of the multiple comparisons performed.

Results

A total of 114 patients were enrolled in the parent study; plasma CX3CL1 concentrations were available for 85 of these 114 patients. The median age of these 85 patients was 56 years (range, 46–67 years), the median NIHSS score was 10 (range, 4–18), the median infarct volume was 10.7 mL (range, 1.3–68.5 mL), and 33 (39%) were women. The highest plasma CX3CL1 by 72 hours in these 85 patients was 514 ng/mL (range, 367–650 ng/mL). In keeping with our prior publications on the larger patient population from the parent study, we categorized patients into tertiles based on stroke severity.[28,29] Important clinical and demographic data from these tertiles are presented in online-only Data Supplement Table I. Patients with more severe strokes were more likely to evidence systemic inflammation than patients with less severe strokes. Changes in plasma CX3CL1, VCAM-1, and ICAM-1 over time are depicted in Figure 1. Patients with the most severe strokes (NIHSS score ≥17) have lower plasma CX3CL1at 24 hours after stroke onset when compared with patients with less severe strokes. In comparison to the control population (N=40), patients with more severe strokes had lower concentrations of plasma CX3CL1 at Days 1 and 7 (Figure 1A), whereas the concentrations of circulating VCAM-1 (Figure 1B) and ICAM-1 (Figure 1C) were higher among patients with severe stroke at multiple time points after stroke.

The distribution of clinical outcomes at 180 days is presented in the upper portion of Table 1. Higher circulating concentrations of CX3CL1 at this time point are associated with better clinical outcome (higher scores on the GOSE and SIS and lower scores on the modified Rankin Scale). The correlation between outcome (modified Rankin Scale and SIS) and CX3CL1 persists even after controlling for initial

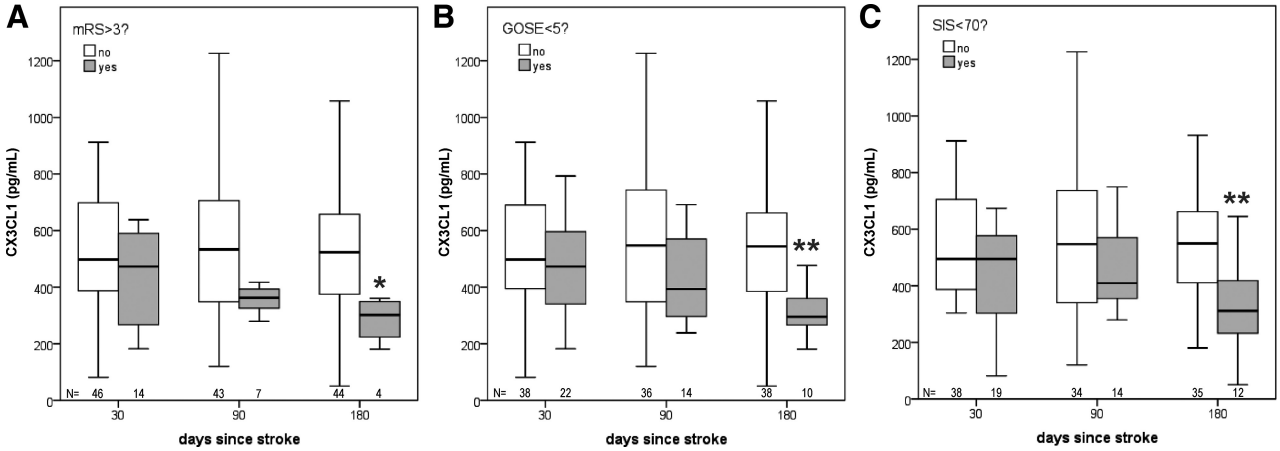

Figure 2. Concentrations of CX3CL1 over the course of 180 days after stroke onset in patients with poor outcome compared with those without poor outcome (based on mRS [**A**], GOSE [**B**], and SIS [**C**]). *$P<0.05$ and **$P<0.01$ unadjusted for initial stroke severity (Mann-Whitney *U* test). (After controlling for initial stroke severity using the NIHSS score, the probability value for CX3CL1 and mRS=0.155, GOSE=0.046, and SIS=0.022; controlling for initial stroke severity using infarct volume, the probability value for CX3CL1 and mRS=0.132, GOSE=0.015, and SIS=0.014.) CX3CL1 indicates fractalkine; mRS, modified Rankin Scale; GOSE, Glasgow Outcome Scale–extended; SIS, Stroke Impact Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Predictors of Poor Outcome (GOSE <5) at 180 D After Stroke

At 180 D	OR (95% CI) Unadjusted	*P* Value	OR (95% CI) Adjusted for NIHSS	*P* Value	OR (95% CI) Adjusted for Infarct Volume	*P* Value
Baseline demographics (n=99)						
Age per 10 y	1.684 (1.085–2.614)	0.020	4.304 (1.528–12.12)	0.006	2.489 (1.269–4.884)	0.008
White	1.286 (0.126–13.085)	NS	0.450 (0.031–6.598)	NS	3.800 (0.082–175.8)	NS
Male	0.903 (0.326–2.496)	NS	1.219 (0.255–5.837)	NS	0.889 (0.243–3.252)	NS
HTN	1.111 (0.409–3.021)	NS	1.046 (0.224–4.893)	NS	1.588 (0.433–1.301)	NS
DM	2.778 (0.964–8.006)	0.059	1.673 (0.319–8.784)	NS	3.470 (0.907–13.27)	0.069
CAD	1.714 (0.587–5.006)	NS	2.290 (0.384–13.65)	NS	3.522 (0.875–14.17)	0.076
AF	0.868 (0.207–3.636)	NS	1.344 (0.122–14.82)	NS	1.172 (0.188–7.317)	NS
Smoker	2.471 (0.891–6.850)	0.082	1.837 (0.381–8.861)	NS	2.433 (0.664–8.916)	0.180
Old stroke on imaging*	2.050 (0.655–6.414)	NS	60.50 (2.120–1726)	0.016	4.361 (0.992–19.16)	0.051
Temperature per °C	3.920 (1.560–9.855)	0.004	1.423 (0.459–4.408)	NS	2.126 (0.805–5.619)	0.128
Initial stroke characteristics and treatment (n=99, except for infarct volume, where n=97)						
NIHSS per point	1.364 (1.188–1.567)	<0.001	. . .	. . .	1.043 (0.956–1.138)	NS
Infarct volume per 10 mL*	1.182 (1.079–1.295)	<0.001	1.043 (0.956–1.138)	NS	. . .	. . .
IV tPA	1.267 (0.427–3.754)	NS	1.240 (0.249–6.188)	NS	1.496 (0.367–6.089)	NS
Endovascular therapy	3.630 (0.739–17.824)	0.112	1.681 (0.177–15.948)	NS	1.874 (0.243–14.451)	NS
Hemicraniectomy	11.333 (1.187–108.2)	0.035	1.479 (0.099–21.99)	NS	0.015 (0.000–1.028)	0.052
Initial laboratory values (highest value by 72 h; n≥65 for all variables)						
WBCs per thousand/mL	1.176 (1.034–1.337)	0.014	0.890 (0.718–1.103)	NS	1.078 (0.916–1.269)	NS
PMNs per thousand/mL	1.438 (1.139–1.815)	0.002	1.162 (0.809–1.668)	NS	1.321 (1.017–1.716)	0.037
Lymphs per thousand/mL	0.699 (0.261–1.869)	NS	0.986 (0.247–3.944)	NS	0.505 (0.119–2.152)	NS
Monos per thousand/mL	15.760 (2.023–122.7)	0.008	2.736 (0.081–92.20)	NS	8.691 (0.617–122.4)	0.109
hsCRP per 10 mg/L	1.236 (1.082–1.411)	0.002	1.339 (1.158–1.548)	NS	1.161 (1.016–1.328)	0.029
IL-6 per pg/mL	1.067 (1.010–1.126)	0.020	1.038 (0.951–1.133)	NS	1.061 (1.007–1.119)	0.026
Glucose per 10/dL	1.090 (1.001–1.189)	0.049	1.069 (0.925–1.235)	NS	1.085 (0.979–1.202)	0.119
CX3CL1 per 100 pg/mL	0.894 (0.272–1.100)	NS	1.037 (0.814–1.322)	NS	1.011 (0.814–1.257)	NS
VCAM-1 per 100 pg/mL	0.820 (0.681–0.987)	0.036	0.830 (0.585–1.178)	NS	0.905 (0.733–1.118)	NS
ICAM-1 per 100 pg/mL	1.034 (0.625–1.711)	NS	0.723 (0.343–1.524)	NS	0.998 (0.521–1.912)	NS
Medical complications (n=99)						
Any infection	9.200 (2.785–30.39)	<0.001	3.277 (0.553–19.42)	0.191	9.840 (2.149–45.04)	0.003
Stroke etiology (n=99)						
Lacunar	NC	. . .	NC	. . .	NC	. . .
Cardioembolic	1.096 (0.331–3.635)	NS	1.298 (0.187–9.025)	NS	1.320 (0.281–6.208)	NS
Large-vessel atherosclerosis	5.371 (1.513–19.06)	0.009	4.539 (0.641–32.16)	0.130	6.090 (1.280–28.97)	0.023
Other	0.606 (0.191–1.919)	NS	0.406 (0.073–2.258)	NS	0.487 (0.112–2.116)	NS
Unknown	0.603 (0.174–2.094)	NS	0.587 (0.087–3.949)	NS	0.454 (1.081–1.300)	NS

GOSE indicates Glasgow Outcome Scale–extended; NIHSS, National Institutes of Health Stroke Scale; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; AF, atrial fibrillation; IV tPA, intravenous tissue-type plasminogen activator; WBCs, white blood cell; PMNs, polymorphonuclear cells; lymphs, lymphocytes; monos, monocytes; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; CX3CL1, fractalkine; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; NS, not significant ($P \geq 0.200$); NC, not calculable.

*There were 2 patients who did not have an admission MRI; information regarding infarct volume and old strokes was therefore not available.

stroke severity. There was no relationship between VCAM-1 at 180 days and stroke outcome and the relationship between ICAM-1 and outcome was explained by initial stroke severity.

For the purpose of further analyses, poor outcome was considered to be an outcome worse than 75% of the entire cohort (values lower than the lower interquartile range for the SIS and GOSE and values higher than the upper interquartile

Table 3. Correlations Among Plasma CX3CL1, Initial Stroke Severity (as Determined by NIHSS Score and Infarct Volume), and Inflammatory Markers at Various Time Points After Stroke

			WBCs		PMNs	
Day From Stroke	NIHSS	Infarct Volume	Adjusted for NIHSS	Adjusted for Infarct Volume	Adjusted for NIHSS	Adjusted for Infarct Volume
1	−0.343, P=0.150	−0.283, NS	−0.230, NS	−0.292, NS	−0.121, NS	−0.210, NS
3	−0.122, NS	−0.140, NS	−0.114, NS	−0.106, NS	−0.017, NS	−0.028, NS
7	−0.196, P=0.009	−0.261, P=0.029	−0.056, NS	−0.065, NS	0.023, NS	−0.050, NS
30	−0.147, NS	−0.119, NS	−0.174, P=0.191	−0.184, P=0.170	−0.150, NS	−0.162, NS
90	−0.232, P=0.109	−0.091, NS	−0.250, P=0.094	−0.270, P=0.073	−0.251, P=0.100	−0.283, P=0.066
180	−0.209, P=0.158	−0.095, NS	−0.423, P=0.003	−0.467, P=0.001	−0.483, P=0.001	−0.517, P<0.001

CX3CL1 indicates fractalkine; NIHSS, National Institutes of Health Stroke Scale; WBCs, white blood cells; PMNs, polymorphonuclear cells; lymphs, lymphocytes; monos, monocytes; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; NS, not significant (P≥0.200).

Data are presented as Pearson r. The correlation of CX3CL1 with inflammatory markers is adjusted for initial stroke severity using the NIHSS score or the infarct volume.

range for the modified Rankin Scale). Initial values (at 1 day, 3 days, or 7 days after stroke onset) of CX3CL1, VCAM-1, and ICAM-1 were not independently predictive of 180-day outcome (data not shown). Figure 2 depicts the changes in CX3CL1 over time based on outcomes at those time points. Even after controlling for initial stroke severity, at 180 days after stroke, the concentration of CX3CL1 is lower in those patients with poor outcome than in those with better outcomes; there is also a trend toward decreasing CX3CL1 values over the course of time in patients with poor outcome compared with those with better outcomes. The concentrations of VCAM-1 and ICAM-1 were similar in patients with poor outcome and in those with better outcomes (data not shown). The difference in plasma CX3CL1 between patients with poor outcome and those without was most robust for the GOSE and the SIS (Figure 2). Using the GOSE as the indicator of outcome, important differences between those with a poor outcome and those without are presented in Table 2; data are adjusted for initial stroke severity using either the initial NIHSS score or infarct volume. The most consistent independent predictor of outcome (apart from NIHSS score or infarct volume) was patient age.

Table 3 shows the correlation between CX3CL1 and initial stroke severity as well as between CX3CL1 and circulating leukocytes, high-sensitivity C-reactive protein, and interleukin-6 at various time points after stroke. There is a trend toward an inverse relationship between CX3CL1 and peripheral markers of inflammation at multiple time points after stroke, but the relationship is most marked at 180 days after stroke.

Discussion

In contrast to our original hypothesis, we found that patients with more severe strokes (NIHSS score ≥17) had decreased concentrations of plasma CX3CL1 in comparison to patients with less severe strokes and control subjects at 1 day after stroke onset. This relative decrease in CX3CL1 in comparison to control subjects appeared to persist to 180 days after stroke but was only significant at 7 days after stroke. Most striking was the finding that patients with poor neurological outcome at 180 days after stroke (defined by the modified Rankin Scale, GOSE, and SIS) had significantly lower plasma CX3CL1 than patients with better outcomes. Importantly, plasma concentrations of CX3CL1 early after stroke onset were not predictive of long-term outcome.

To our knowledge, this study is the first to address the role of CX3CL1 in patients with stroke. In vitro, neuronal injury leads to cleavage of CX3CL1 from its membrane-bound form.[30,31] Whether this cleaved CX3CL1 enters the circulation or remains within the local microenvironment is unknown. Published animal data provide information only about the expression of CX3CL1 in the brain after stroke.[13] In review of our own animal data, however, we find that the concentration of plasma CX3CL1 is lower in animals undergoing transient middle cerebral artery occlusion as compared with those undergoing a sham surgery (P=0.071) 1 month after the surgical procedure (unpublished data). Our clinical data are in keeping with this observation.

CX3CL1 acts as both an adhesion molecule and chemotactic agent for lymphocytes, monocytes, natural killer cells, and microglia, suggesting that it should help to mediate the inflammatory response. There are accumulating data, however, that suggest the situation is a bit more complex than initially appreciated. For instance, CX3CL1 can suppress microglial activation and decrease the release of proinflammatory cytokines.[8,11,32,33] In fact, the enhanced microglial activation in the brains of aged animals is associated with (and may be due to) decreased CX3CL1 expression in these older animals.[34,35] CX3CL1 also appears to modulate the response to systemic inflammatory stimuli because CX3CL1-deficient mice display enhanced "sickness" behavior after injection of lipopolysaccharide.[36] CX3CL1 may also protect neurons against excitotoxic injury.[37] Based on these observations, a recent study was undertaken to address the potential neuroprotective properties of CX3CL1 and found that intracerebroventricular administration of the chemokine improved outcome from stroke through an apparent inhibition of microglial activation.[38] To explore whether CX3CL1 affected the inflammatory response in our patient cohort, we evaluated systemic markers of inflammation, including the numbers of circulating white blood cells, plasma high-sensitivity C-reactive protein, and interleukin-6. Higher CX3CL1 was associated with a trend toward decreased white blood cells, polymorphonuclear

Table 3. Continued

Lymphs		Monos		hsCRP		IL-6	
Adjusted for NIHSS	Adjusted for Infarct Volume	Adjusted for NIHSS	Adjusted for Infarct Volume	Adjusted for NIHSS	Adjusted for Infarct Volume	Adjusted for NIHSS	Adjusted for Infarct Volume
−0.104, NS	−0.073, NS	0.045, NS	0.024, NS	−0.439, P=0.177	−0.508, P=0.110	0.085, NS	−0.034, NS
−0.157, P=0.197	−0.130, NS	−0.105, NS	−0.096, NS	−0.016, NS	−0.004, NS	0.002, NS	0.006, NS
−0.117, NS	−.093, NS	−0.209, 0.103	−0.239, P=0.066	−0.019, NS	0.015, NS	0.054, NS	0.066, NS
−0.116, NS	−0.118, NS	−0.349, P=0.007	−0.352, P=0.007	−0.097, NS	−0.118, NS	−0.128, NS	−0.128, NS
−0.118, NS	−0.133, NS	−0.152, NS	−0.165, NS	−0.101, NS	−0.146, NS	0.100, NS	0.101, NS
0.030, NS	0.041, NS	−0.271, 0.072	−0.302, P=0.044	−0.332, P=0.024	−0.384, P=0.008	−0.224, P=0.139	−0.254, P=0.092

cells, monocytes, and high-sensitivity C-reactive protein at multiple time points after stroke; these associations were significant at 180 days after stroke.

The potential role of CX3CL1 and its interactions with CXC3R in neurodegenerative diseases is actively being studied, although the data are somewhat contradictory.[9–12] In addition to its potential to modulate the inflammatory response in the brain, CX3CL1 appears to be important in neurogenesis.[8] Neuroprotective properties of CX3CL1 have been demonstrated both in vitro and in vivo.[11,39–41] Presuming that plasma CX3CL1 has access to brain, it is possible that a relative deficiency of CX3CL1 at later time points after stroke (ie, 180 days) hinders important recovery processes. It is interesting to note that patients with mild cognitive impairment have higher circulating CX3CL1 than patients with Alzheimer disease, and patients with mild/moderate Alzheimer disease have higher circulating CX3CL1 than patients with severe Alzheimer disease.[42]

There are several limitations to this study, including the relatively small number of patients for which CX3CL1 data were available (N=85) and the very small number with CX3CL1 measured at 24 hours. The wide variation in stroke severity and the quality of outcome measures, however, allow for a full description of the changes in CX3CL1 and its association with the clinical course after stroke. As already mentioned, circulating CX3CL1 was assessed given that direct access to the central nervous system compartment is not available in clinical studies; evaluation of the local expression of CX3CL1 may have yielded different results. Because CX3CL1 is expressed by both neurons and endothelial cells, we have no way of knowing whether increased plasma CX3CL1 in patients with good outcome reflects increases in neuronal CX3CL1, endothelial CX3CL1, or both.

In summary, our data suggest that decreased CX3CL1 may be associated with more systemic inflammation and worse long-term outcome from stroke. Based on these data as well as emerging experimental data that suggest a neuroprotective effect of exogenous CX3CL1 administration, further studies to address the potential neuroprotective properties of CX3CL1 in stroke are warranted. Perhaps most exciting is the possibility that CX3CL1 could in some way modulate stroke recovery given its potential role in neurogenesis and that differences in CX3CL1 were apparent at 180 days in patients with poor outcome compared with those with better outcome. Additional studies with this chemokine in experimental stroke to assess both its neuroprotective and neurorestorative roles are warranted.

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Disclosures

None.

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