

# Immuno-hematologic Characteristics of Infection-Associated Cerebral Infarction

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**We evaluated 50 consecutive patients with acute ischemic stroke to assess the prevalence of systemic infection preceding the neurological event. We analyzed the immuno-hematologic characteristics of patients with and without signs and/or symptoms of a preceding infectious process. Patients were examined  $\leq 7$  days after cerebral infarction and evaluated for fibrinogen, anticardiolipin antibodies, fibrin D-dimer (a fragment of cross-linked fibrin), plasminogen activator inhibitor-1, and protein S. Of the 50 patients, 17 had symptoms of infection beginning  $\leq 1$  month before the stroke (11 had upper respiratory tract infections, three urinary tract infections, two subacute bacterial endocarditis, and one pneumonia). Compared with patients without infection, patients with infection had significant increases in fibrin D-dimer concentration ( $5.3 \pm 1.1$  versus  $4.7 \pm 0.9$  log-transformed ng/ml,  $p < 0.05$ ) and cardiolipin immunoreactivity, IgG isotype ( $1.8 \pm 1.3$  versus  $1.1 \pm 0.9$  log-transformed phospholipid units,  $p < 0.04$ ), and, when studied  $\leq 2$  days after the stroke, increased fibrinogen levels ( $459 \pm 126$  versus  $360 \pm 94$  mg/dl,  $p < 0.05$ ). In conclusion, infection-associated cerebral infarction is common and is associated with substantial immuno-hematologic abnormalities. (*Stroke* 1991;22:1004–1009)**

**S**ystemic infection appears to be a risk factor for ischemic stroke, particularly in younger individuals.<sup>1–5</sup> We prospectively assessed the prevalence of recent infection in an adult stroke population. Our objectives were to determine the frequency of symptoms of an infectious process before the ischemic event and to investigate potential mechanisms by which infections might act as a stroke risk factor. Cerebral infarction is known to be associated with both substantial coagulation abnormalities and anticardiolipin antibodies (ACA).<sup>6–9</sup> We tested the hypothesis that patients who have cerebral infarction preceded by infection also have distinct immuno-hematologic characteristics.

## Subjects and Methods

We prospectively evaluated 50 consecutive patients admitted to Los Angeles County–University of Southern California Medical Center with a clinical diagnosis of stroke, available for investigation  $\leq 7$

days after the event, and with a cranial computed tomogram or magnetic resonance image showing a lesion compatible with cerebral infarction. Patients were evaluated over the 7 months between August 1989 and March 1990. This study was performed in accordance with guidelines of the institutional research committee. We excluded from the study patients who developed infection following the stroke, patients with established autoimmune disorders, recent ( $< 1$  month) myocardial infarction, deep vein thrombosis, hepatorenal failure, pregnancy, or malignancy. All patients received a complete history, physical, and neurological examination, the latter including the Toronto Stroke Scale.<sup>10</sup> Patients were characterized as having the stroke risk factors hypertension, diabetes, and cigarette smoking based on standard criteria.<sup>1</sup>

Patients were considered to have infection preceding the stroke if they had a positive history of fever or chills accompanied by one or more of the following: otalgia (otitis externa or media); cough with purulent sputum (upper respiratory tract infection or pneumonia if chest roentgenogram showed parenchymal consolidation); nausea, vomiting, and/or diarrhea (gastroenteritis); urinary frequency, dysuria, and/or positive urine culture (lower urinary tract infection); back pain with pyuria, bacteriuria, or positive urine culture (pyelonephritis); or penile or vaginal discharge (indicative of venereal disease). A close relative was questioned in cases of altered consciousness

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or aphasia. Infection was also considered present if physical examination along with laboratory studies performed on admission demonstrated the presence of sepsis, otitis, upper respiratory tract infection, pneumonia, bacterial endocarditis, renal or urinary tract infection, skin or soft tissue infection, gingivitis or dental abscess, septic arthritis, or osteomyelitis. Patients were characterized as having infection on a prospective basis, without knowledge of coagulation and immunologic assays.

Twenty-milliliter blood samples from each patient were anticoagulated with ethylenediaminetetraacetic acid (EDTA) or buffered sodium citrate. Citrated plasma along with serum for ACA assay were divided into aliquots of approximately 500  $\mu$ l and frozen at  $-80^{\circ}\text{C}$  until assayed. Hematocrit and white blood cell count and differential were measured using a conventional automated technique (F+4, Coulter Corp., Hialeah, Fla.). The fibrinogen concentration was measured in plasma anticoagulated with EDTA based on the turbidimetric rate of formation of fibrin polymer (Du Pont Pharmaceuticals, Wilmington, Del.). Fibrin D-dimer and plasminogen activator inhibitor-1 antigen (PAI-1) concentrations were measured in duplicate by enzyme immunoassay (American Diagnostica Inc., Greenwich, Conn.) of citrated plasma according to the manufacturer's instructions. The free protein S antigen was quantified by electroimmunodiffusion (American Diagnostica) of citrated plasma according to the manufacturer's instructions and expressed as a percentage of that in control plasma. The ACA concentrations were measured by an enzyme-linked immunosorbent assay method,<sup>11</sup> and the results were expressed in phospholipid units. The test was standardized using four ACA-positive serum samples with known IgG phospholipid unit and IgM phospholipid unit contents. Five normal serum samples, as well as five ACA-positive serum samples, were run as secondary standards in each assay. Serum samples containing more than 15 IgG phospholipid units or 6 IgM phospholipid units were considered "positive."

Unpaired Student's *t* tests, the  $\chi^2$  test, and Fisher's exact test were used for statistical analysis. Log-transformed data were used for statistical analysis when the latter best approximated a normal distribution. Results are given in text as mean  $\pm$  standard deviation (SD).

### Results

The interval from stroke to evaluation (including venipuncture) was  $2.9 \pm 1.7$  (range 1–7) days. There were 29 men and 21 women with an age of  $58.8 \pm 13.1$  (range 30–88) years. Of the 50 patients, 17 (34%) had signs and/or symptoms of infection beginning  $\leq 1$  month before the stroke (Table 1). Ten patients had symptoms of infection at the time of stroke, but these symptoms had begun prior to the neurological event in all cases. There were 11 upper respiratory tract infections, three urinary tract infections, two cases of subacute bacterial endocarditis, and one of pneumonia. There was a trend for a predominance of males among the patients with prior infection (76%) com-

TABLE 1. Clinical Data for 17 Patients With Infection-Associated Cerebral Infarction

Pt/Sex/Age (yr)	Signs/symptoms
6/M/39	Chills, cough, purulent sputum
8/F/68	Fever, sore throat
9/M/41	Fever, new heart murmur, splenomegaly, valve vegetations
10/M/59	Fever, productive cough, otitis externa
14/M/63	Fever, urgency, dysuria
16/F/74	Fever, cough, sputum
17/M/82	Chills, urgency, dysuria
18/M/45	Fever, new heart murmur, valve vegetations
19/M/76	Fever, cough, sputum, parenchymal consolidation on chest roentgenogram
25/M/54	Chills, cough, sputum
28/F/44	Fever, cough, sputum
30/M/77	Fever, cough, sputum
34/M/55	Fever, cough, sputum
41/M/53	Fever, cough, sputum, diarrhea
43/F/63	Fever, urgency, dysuria, abnormal urinalysis
45/M/77	Chills, ear pain, cough, diarrhea, urgency, dysuria
46/M/65	Chills, cough, sputum, pleuritic pain

pared with those without infection (48%, Table 2), but this difference did not achieve statistical significance, perhaps due to the small sample size. Cortical infarcts were more common in the group with prior infection (59%) than in the group without infection (36%), but again, the difference was not significant. There were no significant differences between males and females for any of the hematologic or immunologic variables (data not shown). Patients with prior myocardial infarction, congestive heart failure, and atrial fibrillation numbered three, two, and zero for those with infection and five, one, and two for those without infection, respectively (nonsignificant differences). Two patients were intravenous drug abusers, one with and one without infection; one patient with infection used intranasal cocaine. No patients were receiving anticoagulants at the time of assay; one patient with and one patient without prior infection were receiving aspirin.

Compared with patients without infection, those with infection-associated stroke had an increased fibrin D-dimer concentration, increased cardiolipin immunoreactivity (both IgG and IgM isotypes), and were more likely to be "positive" for ACA (Table 2, Figure 1). In addition, we compared the two groups as to whether the patients had values above the mean + 2 SD for the entire cohort of 50 patients for fibrinogen ( $>633$  mg/dl), fibrin D-dimer ( $>6.92$  log-transformed ng/ml), PAI-1 ( $>37$  ng/ml), or ACA ( $>3.56$  log-transformed phospholipid units [IgG isotype] or  $>3.98$  phospholipid units [IgM isotype]) or values below the mean  $-2$  SD for the entire cohort of 50 patients for protein S ( $<19.9\%$  of control). Seven patients with a prior infection (one with elevated fibrinogen, one with elevated fibrin D-dimer, two with elevated PAI-1, and

TABLE 2. Epidemiological, Clinical, and Immunohematologic Characteristics for Patients With and Without Prior Infection

Characteristic	Prior infection (n=17)	No infection (n=33)
Age (mean±SD yr)	60.9±13.7	57.8±12.9
Sex (males/females)	13/4	16/17
Previous stroke or transient ischemic attack	6 (35%)	9 (27%)
Hypertension	9 (53%)	17 (52%)
Diabetes	3 (18%)	13 (39%)
Cigarette smoking	5 (29%)	14 (42%)
Toronto Stroke Scale on admission (mean±SD score)	30.0±22.5	33.5±28.2
Cortical/deep infarcts	10/7	12/21
Hematocrit (mean±SD%)	38.3±6.0	40.2±4.6
Leukocyte count (mean±SD 10 <sup>3</sup> /ml)	9.4±2.6	9.3±3.5
"Positive" ACA	6 (35%)*	2 (6%)
ACA titer, IgG isotype (mean±SD log-transformed phospholipid units)	1.8±1.3†	1.1±0.9
ACA titer, IgM isotype (mean±SD phospholipid units)	2.0±1.9†	1.2±0.6
Fibrin D-dimer (mean±SD log-transformed ng/ml)	5.3±1.1†	4.7±0.9
Fibrinogen level (mean±SD mg/dl)	439±120	391±107
Plasminogen activator inhibitor-1 (mean±SD ng/ml)	21.5±10.9	18.5±7.5
Free protein S (mean±SD % of control)	76.4±30.6	81.2±29.8

ACA, anticardiolipin antibodies.

\*†*p*<0.025 and 0.05, respectively, different from patients without prior infection.

three with elevated ACA values) and one patient without infection (elevated fibrinogen value) had one of these findings (*p*<0.002).

Approximately half the patients (24 of 50) were studied ≤48 hours after the stroke. Among these patients, eight had a prior infection. Compared with the 16 patients without infection, these eight patients had a significantly higher level of cardiolipin immunoreactivity, IgG isotype (1.93±1.07 versus 0.93±0.90 log-transformed phospholipid units, *p*<0.025), a higher fibrin D-dimer concentration (5.6±0.7 versus 4.6±0.8 log-transformed ng/ml, *p*<0.01), and a higher fibrinogen concentration (459±126 versus 360±94 mg/dl, *p*<0.05, Figure 2). There were no significant differences in the stroke risk factor distribution between the groups studied within 48 hours.

### Discussion

Syrjanen et al<sup>1</sup> reported a significantly higher incidence of infection in ischemic stroke patients aged <50 years old than in controls. This study along with previous reports<sup>2-5</sup> support the contention that preceding infection is a risk factor for stroke. The mechanism underlying this phenomenon is not known. Hemostasis alterations are known to be present in both patients with stroke<sup>6,7</sup> and patients with infection, particularly sepsis and other severe infections.<sup>12,13</sup> This has led us and others<sup>1,4</sup> to postulate that altered coagulation may represent a link between infection and stroke, perhaps via cytokines (e.g., interleukin-1 and tumor necrosis factor) known to have procoagulant effects.<sup>14-17</sup> In our series of patients with cerebral infarction, 34% (17 of 50) had

evidence of infection, most commonly relatively mild respiratory infections, ≤1 month before the stroke. These findings are strikingly similar to those in the Scandinavian study of Syrjanen et al,<sup>1</sup> who found a preceding febrile infection in 35% of a group of young stroke patients. It is of note that the populations of the two studies are vastly different, with our stroke patients representing a non-age-selected group of inner-city residents.

The concentration of fibrin D-dimer, a product of cross-linked fibrin degradation, is useful as an index of thrombin activity.<sup>18</sup> The fibrin D-dimer concentration is increased in patients with deep vein thrombosis,<sup>19</sup> myocardial infarction,<sup>20</sup> and acute cerebral infarction.<sup>6,7</sup> As a group, stroke patients with infection had an increased level of fibrin D-dimer, indicating some procoagulant tendencies. To place these fibrin D-dimer levels into context, our patients with infection-associated stroke had levels roughly comparable to those of other recently reported stroke<sup>7</sup> and myocardial infarction<sup>13</sup> cohorts; these fibrin D-dimer levels were, however, substantially lower than those of a group of septic patients hospitalized in an intensive care unit.<sup>13</sup> It is uncertain whether patients without stroke and with the generally mild infections of the current study might have similar hemostatic findings.

Endotoxin and cytokines produce in vitro endothelial cell expression of tissue factor and downregulation of thrombomodulin and are typically associated with increased concentrations of PAI-1, the major plasma inhibitor of tissue plasminogen activator.<sup>14,16,21</sup> Another central element of the coagulation pathways is activated protein C, a potent anticoagu-

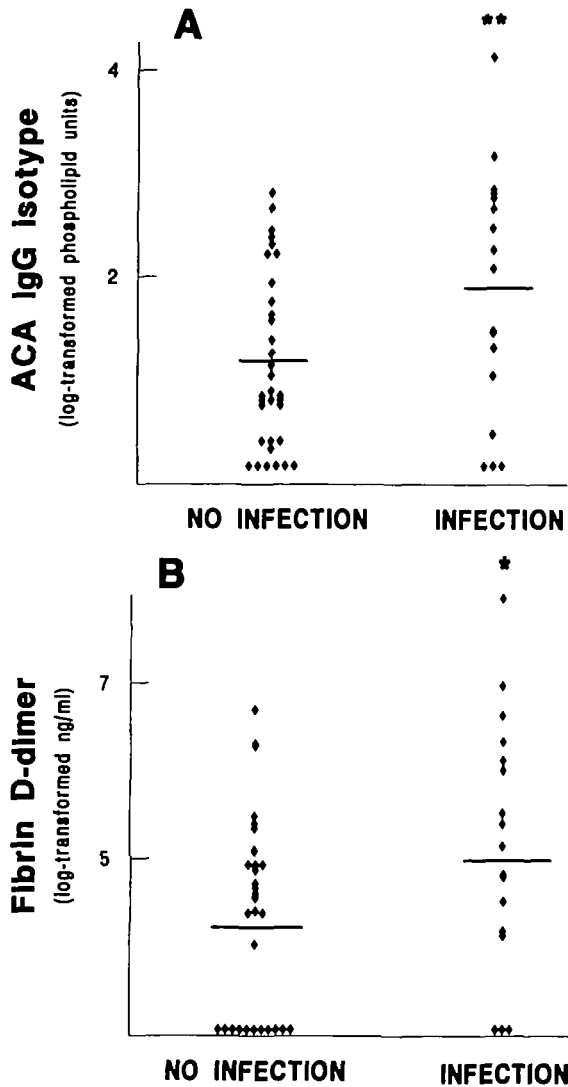


FIGURE 1. Scatterplots of (A) anticardiolipin antibodies (ACA), IgG isotype, and (B) fibrin D-dimer levels in patients with and without prior infection. Diamonds represent individual patients. Horizontal lines represent mean values for each group. \* $p < 0.05$  different from patients without prior infection; \*\* $p < 0.04$  different from patients without prior infection.

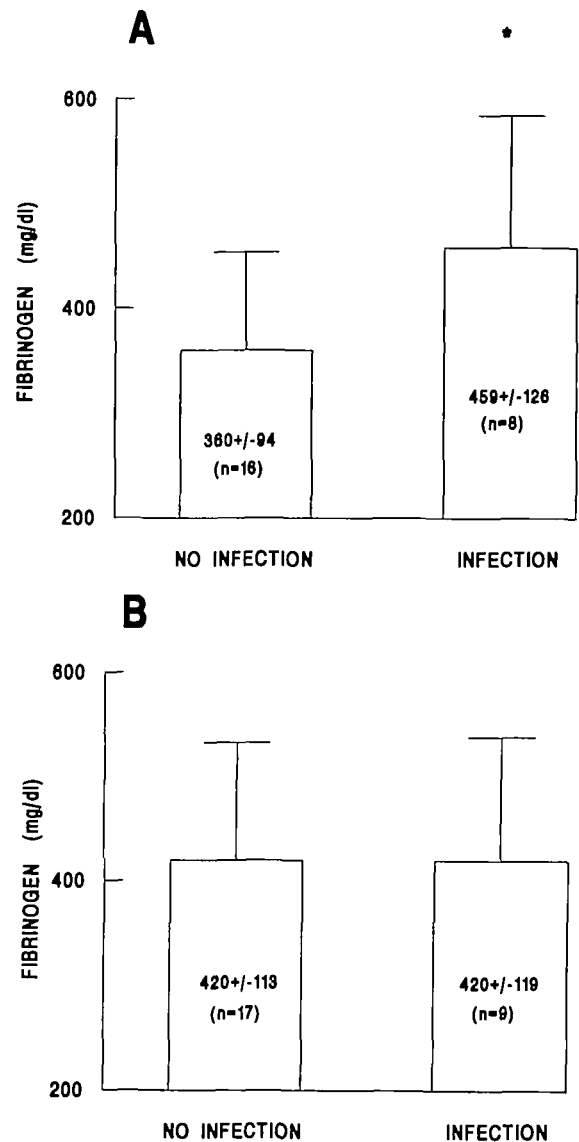


FIGURE 2. Bar graphs of mean  $\pm$  SD fibrinogen levels in patients with and without prior infection for (A) patients studied  $\leq 48$  hours after stroke and (B) patients studied 3–7 days after stroke. \* $p < 0.05$  different from patients without prior infection.

lant whose cofactor, protein S, is normally present in both the free and bound forms.<sup>22,23</sup> The amount of free protein S, the active form, has been reported to be decreased in patients with infections.<sup>22</sup> In our study, neither the PAI-1 nor the free protein S levels differed between the groups. However, patients with the highest PAI-1 levels tended to be those with prior infection.

The nature of the association between stroke and ACA is not known.<sup>8,9</sup> In our study, patients with a preceding infection had significantly greater cardiolipin immunoreactivity than patients without infection. This is compatible with earlier reports indicating an association between infection and ACA.<sup>24,25</sup> These antibodies, often associated with lupus anticoagulant, may have procoagulant properties including

the reduction of prostacyclin elaboration by endothelial cells.<sup>26,27</sup> The procoagulant effects of ACA may have contributed to the increased levels of fibrin D-dimer in some of our cerebral infarction patients. These findings also suggest that cardiolipin immunoreactivity may need to be interpreted cautiously in stroke patients with a recent infection.

An increased fibrinogen concentration is a risk factor for stroke in men<sup>28,29</sup> and accompanies the acute-phase reaction associated with both infection and cerebral infarction.<sup>30</sup> The rise of fibrinogen levels after acute stroke is known to begin 2–4 days after the ischemic event, and fibrinogen levels reach a maximum by 14 days.<sup>31</sup> In our study, patients with prior infection had significantly increased fibrinogen

levels when studied earlier, but not later, than 48 hours after the stroke (Figure 2). We interpret this finding in the following way: when studied early, acute-phase responses in stroke patients may be primarily related to events other than the stroke, (e.g., prior infection); beyond 48 hours, acute-phase responses from the stroke itself predominate, resulting in comparable fibrinogen levels for patients with and without infection. Increased fibrinogen levels may contribute to the pathogenesis of cerebral infarction by multiple mechanisms; there is an inverse relation between fibrinogen levels and cerebral blood flow,<sup>32</sup> middle cerebral artery blood velocity in the elderly,<sup>33</sup> cerebral vascular reactivity,<sup>34</sup> and, perhaps, fibrinolytic activity.<sup>35</sup> In addition, fibrinogen serves as the major intercellular link for platelet aggregation via the glycoprotein IIb-IIIa complex.<sup>36</sup>

Experimental studies have demonstrated a deleterious effect of hyperthermia, consisting of increased brain injury with moderate increases in brain temperature.<sup>37,38</sup> These findings represent an explanation for a potential association between infection and stroke severity. We did not find differences in the extent of the neurological deficit between patients with and without a prior infection. There was, however, a trend for a predominance of cortical infarcts over small deep infarcts in patients with a previous infection, a difference that did not reach statistical significance, perhaps due to the small sample size. In addition, white blood cells appear to play an important role in the pathogenesis of reperfusion injury in cerebral ischemia.<sup>39-41</sup> The potential association of a recent infection with a concomitant elevated leukocyte count in patients with stroke was not found in our study; patients with a prior infection had white blood cell counts similar to those of patients without infections.

In summary, cerebral infarction is commonly preceded by systemic infection. Compared with stroke patients without infection, patients with infection-associated cerebral infarction tend to have increased fibrin generation, increased cardiolipin immunoreactivity, and hyperfibrinogenemia. These findings indicate that immunohematologic assays of acute stroke patients should be interpreted in light of the patient's history of recent infection, however mild. It must be noted that we have not shown that these immunohematologic findings are specific for patients with recent infection accompanied by stroke. Nevertheless, our findings are consistent with a link between cerebral infarction, infection, and a procoagulant state.

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