Letters to the Editor

THROMBOCYTOPENIA FOLLOWING STEROID THERAPY IN AN 83-YEAR-OLD WOMAN

To the Editor:

An 83-year-old woman was hospitalized for a brain tumor. Her medical history included hypertension and breast cancer surgically treated a few years before. She presented with neurological deficits including left hemiparesia, cognitive impairment, and changes in vigilance. A brain X-ray computed tomography revealed a right parietal tumor (55 × 48 mm) surrounded with edema. The most likely diagnoses were a metastatic lesion or a meningioma. Initial biological tests, chest X-ray, and abdominal ultrasound exploration were all normal. Tumor markers, including CA 15-3 and CEA, were negative. After multidisciplinary discussion, we did not consider the patient a candidate for neurosurgical intervention. We initiated symptomatic treatment for edema with synthetic ACTH (tetracosactid intramuscular injections, 0.5 mg twice daily) and changed the treatment 6 days later to prednisone when oral administration became possible. After a starting dose of 60 mg/day for 3 days, we reduced the dosage to 40 mg/day.

We observed mild thrombocytopenia, at 140,000 platelets/µl, first 10 days later, and it dropped to 75,000 platelets/µl over the next 4 days. Despite cessation of amlopine, platelet counts continued to decrease (59,000 platelets/µl). Except for neurological improvement, the clinical examination remained unchanged. We did not observe purpura or fever. Red blood cell counts were normal, although a slight neutrophilia was attributed to steroid therapy. Additional biological investigations revealed the presence of antinuclear antibodies without anti beta2 GP1 specificity and with no coagulation abnormalities. Antinuclear and antiplatelet antibodies were negative, and C-reactive protein, sedimentation rate, and serum protein electrophoresis were normal. Low serum albumin, at 25 g per liter, was suggestive of poor nutritional status. Epstein Barr Virus, Parvovirus B19, and human immunodeficiency virus serologies were all negative. However, IgM and IgG for cytomegalovirus (CMV) were positive by enzyme-linked immunosorbent assay. We did not perform a bone marrow biopsy, as we judged it too invasive, and it was against the patient’s desire.

The platelet count continued to drop to 31,000 platelets/µl, and we stopped oral prednisone, in the context of neurological improvement and doubts about its potential contribution to the thrombocytopenia. Subsequently, platelet counts increased progressively to reach the normal range (200,000 platelets/µl). The repeat IgM for CMV became negative whereas IgG remained positive. Cardiolipid antibodies were also negative.

In summary, we believe that transient thrombocytopenia was probably induced by a CMV infection or reactivation. The poor clinical condition in context of undernutrition, the fall of the platelet count during steroid use, followed by an increase after cessation of the immunosuppressive drug, and the results of serological tests, as well as the absence of reliable alternative hypothesis to explain the transient thrombocytopenia are in favor of CMV infection. However, we could not document proof of this infection and its relationship with thrombocytopenia, as we performed neither CMV cultures nor medullar analysis.

Lifetime prevalence of CMV infection is high in developed countries (40 to 80%). It usually results in latent infection in individuals with a normal immune function. Higher risk of reactivation, with increased morbidity and mortality, is well documented in immunosuppressed patients, but unusual in healthy subjects, even if some data reported clinical and laboratory findings in nonimmunocompromised adults (1). Immunological abnormalities, including antinuclear antibodies, as well as thrombocytopenia and other hematological disturbances, have been recognized in CMV infection or reactivation, even in nonimmunosuppressed patients (2,3,4,5). Elderly adults are often considered to have a reduced efficiency of immune system, especially those with a poor nutritional status or with coexisting illnesses, both of which increase immunity impairment (6,7). Despite these considerations, there is a paucity of papers about CMV re-infection in older people in the literature, in contrast with numerous herpes zoster publications about elderly people (8,9). Explanations could be the frequent misdiagnosis of such infection thought to affect well-defined immunocompromised patient groups first and the lack of specificity of clinical presentation and biological findings.

In conclusion, some elderly people become immunoincompetent. This can promote development of particular diseases, usually observed in other physiological or pathological contexts. The best effective prevention of these immune disorders remains the preservation of a good nutritional status. An approach to the management of malnutrition in elderly people has recently been published in the Journal of Gerontology: Medical Sciences (10).

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References
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C-REACTIVE PROTEIN, PHYSICAL DISABILITY, AND PROGNOSIS IN VERY OLD PATIENTS WITH ISCHEMIC STROKE

To the Editor:

Recently, much evidence showed that atherosclerosis could represent a chronic flogistic disorder and that its exacerbations could determine acute cardiovascular events, such as acute coronary syndromes (1). Many scientific reports regarding patients with ischemic heart disease have demonstrated that high values of markers of acute phase of inflammation, such as C-reactive protein (CRP), fibrinogen, and some interleukins, are related to the severity of the atherosclerotic process and its poor prognosis (2). The relationship between the acute phase of inflammation and prognosis in patients with ischemic stroke remains unclear, especially in very old patients.

The Framingham Study has demonstrated that healthy subjects with high values of CRP have developed a greater number of cerebrovascular accidents in the 20 years of observation compared with subjects with normal values of CRP (3). In the Third National Health and Nutrition Examination Survey, higher values of CRP were associated with self-reported past history of stroke (4). Di Napoli and colleagues have demonstrated that patients with ischemic stroke who have high values of CRP at hospital discharge are at higher risk of subsequent cerebrovascular events or death (5). In the prospective Leiden 85-Plus Study, a study relative to very old subjects, the researchers concluded that CRP is a nonspecific marker of fatal stroke because they observed that higher levels of CRP were associated with higher risk of death from stroke and from noncardiovascular causes (6).

In this letter, we report the preliminary data of our retrospective analysis on the influence of CRP, performed in the first 12 hours from hospital admission by nephelometric method (Dade/Behring Diagnostics, Marburg, Germany, sensitivity 0.0175 mg/dl, specificity 100%), on the prognosis of elderly patients aged 75 years old and older admitted to our acute geriatric ward for cerebrovascular attacks over a 4-year period (1997–2000). Out of a total number of 358 patients discharged with the diagnosis of transient ischemic attack (TIA) or stroke (435.0 and 436.0 codes of International Classification of Diseases, 9th Revision, Clinical Modification), we excluded from the analysis 70 patients with a previous diagnosis of cancers, chronic flogistic disorders, recent infectious diseases, or liver or renal failure, or with values of erythrocyte sedimentation rate higher than 20 mm/h. Our final study population was 288 patients, 185 women and 103 men, with mean age 82.92 ± 6.78 years. In all patients we performed brain computer tomography (BCT) in the first 72 hours from hospital admission. We followed 30-day mortality, length of hospital stay (LOS), physical disability at discharge or at the moment of death performed by the Modified Rankin Scale (7), 12-month mortality, and rehospitalization. The Modified Rankin Scale is a scale of six levels (from 0 to 5) based on clinical evaluation for quantifying progressive physical disability (see Appendix). For statistical analysis, we used the t test for the differences of the means of independent samples and the correlation index (r²) for the relation between CRP and prognostic parameters. Table 1 summarizes the characteristics of analyzed patients.

Mean values of CRP were significantly higher in patients with stroke compared with patients with transient ischemic attacks (5.85 vs 3.24 mg/dl, p < .05). Moreover,

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>288</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>185</td>
</tr>
<tr>
<td>Men</td>
<td>103</td>
</tr>
<tr>
<td>Mean age ± SD, years</td>
<td>82.92 ± 6.78</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>92</td>
</tr>
<tr>
<td>Stroke</td>
<td>196</td>
</tr>
<tr>
<td>30-days mortality, n (%)</td>
<td>31 (10.7%)</td>
</tr>
<tr>
<td>12-months mortality, n (%)</td>
<td>23 (8.9%)</td>
</tr>
<tr>
<td>Mean LOS ± SD, days</td>
<td>17.05 ± 10.04</td>
</tr>
<tr>
<td>12-months rehospitalization, n (%)</td>
<td>80 (31.1%)</td>
</tr>
</tbody>
</table>

Note: TIA = transient ischemic attack; LOS = length of hospitalization.

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CRP values were higher in patients with acute ischemic area documented by BCT compared with patients with chronic ischemic damage at BCT or negative BCT (6.16 vs 4.10 vs 2.74 mg/dl, respectively). Mean values of CRP were significantly higher in patients who died in the first 30 days from stroke compared to survivors (10.7 vs 4.36 mg/dl, p < .05).

We analyzed the patients in three groups according to different length of stay (LOS): patients with LOS ≤ 12 days (102 patients), patients with LOS > 13 and < 18 days, and patients with LOS ≥ 19 days. Mean values of CRP were 2.86 mg/dl in patients with LOS ≤ 12 days, 5.54 mg/dl in patients with LOS > 13 and < 18 days and 6.01 mg/dl in patients with LOS ≥ 19 days.

One hundred eleven patients had a Rankin score ≤ 2, 63 patients had a score of 3, 52 patients had a score of 4, and 48 patients had a score of 5. Figure 1 shows the relation between CRP and disability. Note that disability increases with the increasing of CRP values (r² = .68). Of the 31 patients who did not survive in the first 30 days from acute ischemic event, 28 had Rankin scores > 3 (5 patients had Rankin scores of 4 and 23 patients had Rankin scores of 5). Mean LOS was > 19 days in patients with a Rankin score ≥ 3, whereas it was < 15 days in patients with a Rankin score ≤ 2 (p < .05). Twenty-three patients died after the first month from acute cerebrovascular event. We didn’t find significant differences in CRP values between this group of patients and the survivor patients (4.78 vs 4.96 mg/dl, p = NS). Eighty patients were rehospitalized in the next 11 months. We didn’t find significant differences between CRP values of rehospitalized patients with respect to those of patients who were not rehospitalized (3.01 mg/dl vs 3.28 mg/dl, p = NS). The mean causes of rehospitalization were: (i) TIA/stroke, 30; (ii) ischemic heart attack, 11; (iii) bone fractures, 11; heart failure, 10; (v) digestive bleeding, 4; and (vi) other causes, 14. Only for the patients rehospitalized for cerebrovascular causes did we find a significant difference in CRP values with respect to those patients who were not rehospitalized (5.18 vs 3.28 mg/dl, p < .05). Figure 2 shows the relation between disability, 12-month mortality, and rehospitalization. Both variables rise linearly with an increasing score on the Modified Rankin Scale (r² ~ 1).

Our study, with the limitations of retrospective studies, confirms that high values of CRP could represent a marker of poor prognosis in elderly patients with ischemic cerebrovascular attacks. High values of CRP seem to increase short-term mortality, LOS, physical disability, and long-term rehospitalization for cerebrovascular events. In particular, our study focused the attention on the relation between CRP and physical disability. We noticed a direct correlation between increasing values of CRP and increasing levels of Rankin scores in patients with ischemic stroke. Di Napoli and colleagues, utilizing the Barthel index (8), showed similar results in younger patients with stroke. Di Napoli and colleagues found the higher values of CRP to be associated with larger infaracts by BCT both at admission and at discharge (9). These observations give rise to the hypothesis that CRP represents not only a risk factor for cerebrovascular attacks but a marker of severity of local inflammation produced by ischemic damage of the brain and of the successive disability. This conclusion is confirmed in our study by higher levels of CRP and disability associated with longer LOS and higher short-term mortality. Moreover, higher values of CRP could represent also a marker of poor long-term prognosis, in particular regarding subsequent cerebrovascular events.

Disability post-stroke is a major medical and social problem in the elderly population. Only a portion of elderly patients with mild or moderate disability reaches independent functionality. One third of elderly patients affected by stroke remain disabled; one third of them go to a nursing home (10). Many social, demographic, and clinical factors are associated with high risk of disability in elderly patients with stroke (11,12). CRP at hospital admission could be added to other variables identifying the patients with high risk of disability. Future prospective studies should be undertaken to confirm our observation, if possible, utilizing high sensitivity methods for the dosage of CRP (13).

Frailty is an important problem in older persons (14,15). Newman and colleagues (16) have shown that infarct-like lesions in the brain are one of the important predictors of frailty. Both elevated levels of interleukin-6 and CRP have been associated with frailty (17,18). Loss of muscle mass with aging (sarcopenia) is associated with elevated levels of CRP (19). Our study further supports a role of chronic inflammation in the pathogenesis of frailty.

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**Figure 1.** C-Reactive Protein (CRP) and disability.

**Figure 2.** Disability and 12-month prognosis.
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REFERENCES

Appendix
Modified Rankin Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability, despite symptoms; able to perform all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to perform all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requires some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requires constant nursing care and attention</td>
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