Dental and Other Aspects of a Possible Association Between Cerebrovascular Ischemia and Chronic Infection

To the editor:

I believe that the report of Grau and colleagues concerning acute cerebrovascular ischemia and infections has diagnostic, statistical, dental, and terminological aspects worthy of comment. This letter will address them sequentially.

All possible participants with two or more episodes of “cough with phlegm” during 3 or more months in each of 2 years were said to have “frequent or chronic bronchitis.” In addition, Table 2 tabulated people who had “two or more episodes in life so far.” That might not be too unusual in a middle-aged population. Even if major causes of cough such as tuberculosis or heart failure are ruled out, morning “cigarette cough” or postnasal drip syndrome, allergy, environmental irritants, vasomotor rhinitis, and sinusitis rather than true bronchitis quite possibly were present in some participants. Therefore, perhaps not all of the study’s productive coughers merited such classification.

Although multiple statistical methods were used, no probability value for significance was stated. This unusual omission is important because it was written that “…patients with cerebrovascular ischemia tended to have a worse dental status than the control group (P = .070 and P = .62, respectively).” By customary statistical criteria those differences, which are greater than .05, are not significant. Do the authors believe those larger probability values indicate meaningful differences? If not, their paper is largely based on that tendency rather than a significant association, despite use of the latter word in the title. This could well mislead the casual reader.

Regarding the dental aspects, the discussion states, “…periodontitis and periapical lesions but not caries contributed to differences between groups.” That conclusion, apparently based on Table 5, which indicates the difference in periapical lesions between the two groups to be more significant (P = .027) than the caries (NS) or the periodontitis (P = .047) scores, must be incorrect. That opinion is in error because periapical abscesses result from pulpul death secondary to bacterial pulps in carious, generally nonvital, teeth.5,6 By contrast, even teeth with severe periodontitis with deep pockets, resulting in their being loose, are usually vital. This is also the case in the much less common situation when advanced periodontal bone loss may cause them to appear to “float” when seen on radiographs.5,6 Consequently, the significant difference in periapical lesions between the patient and control groups indicates that the predominant type of dental infection in these patients is severe caries and not periodontitis.

The ability to distinguish the relative prevalence of caries and periodontitis in the subject populations has been made particularly difficult by the groupings in three of the five categories of dental abnormalities in Table 1.1 That table places “no teeth left in the maxilla or mandibula” (either jaw) and “no teeth left” (in both jaws) under the heading of caries. That attribution presumes that those multiple, absent teeth were extracted solely because of decay. However, in adults the most common cause of tooth loss is not caries but periodontal disease.6 Nonvital teeth had their own category in that Table 1. Yet, other than occasionally following trauma, tooth death reflects caries so deep that it caused pulpal necrosis, often requiring root canal therapy to avoid extraction.4,5 In that table such treatment was termed “radix filling.” Table 1 also lists the category “periapical lesions and bone pockets.” This combines apples and oranges. As previously stated, the former is almost always caused by caries, while periodontitis causes pocket formation. Unfortunately, by linking them the authors have made it impossible to separate those two disorders to detect any relation to chronic infection.

Therefore, I recommend that Grau et al reclassify their data as follows: The caries group should be concerned exclusively with deeply carious teeth, because more superficial caries cannot play any role in systemic disease. Teeth with small fillings radiologically and superficial caries clinically should be omitted from consideration, because it is only when cariogenic bacteria reach the dental pulp that blood and lymph channels can be invaded. Likewise, except for trauma, it is only in teeth with deep caries that periapical abscesses would develop. Therefore, the category “periapical lesions and bone pockets” must be split. The former must be included under caries and the latter under periodontitis. Likewise, the category “nonvital teeth” should be placed in the caries group. I believe that adoption of these recommendations would make a much clearer distinction between teeth involved by each of the two dental disorders. Few teeth would have both. In addition, it would be optimal to learn, if possible, why the missing teeth were extracted. Were they removed for deep caries, as indicated by a history of marked pain and the abscessed tooth being elevated slightly from its socket so that it felt “high” during occlusion, or for severe periodontal disease, as indicated by a history of dull, continuous pain and, particularly, of looseness? I believe that such reanalysis would more likely discern any possible association of one or both of those two major dental conditions with cerebrovascular ischemia.

By the way, several of the dental terms, although understandable, are incorrect or not commonly used in English. Decayed teeth are carious, not “cariotic.” The plural of pulp is pulps, not “pulpus.” The lower jaw is the mandible and the part of the tooth apical to the crown is its root, rather than the more Latinate “mandibula” and “radix,” respectively.7

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Response

We are pleased that the interest of Dr Lorber in our recent study gives us the opportunity to further discuss our methods and results.
Certainly, Dr Lorber’s suggestions require clarification and comment.

Our definition of “chronic and frequent bronchitis” was not correctly cited. This diagnosis was based on cough with phlegm in as many as 3 months in each of the 2 preceding years or on two or more episodes with cough and phlegm in each of the 2 preceding years. We are aware of the fact that in a case-control study with a retrospective data collection, not all participants did have cough and phlegm due to bronchitis. However, we are convinced that this diagnosis is by far the most common one. Some of the conditions mentioned by Dr Lorber would result in a dry cough (e.g., allergy, environmental irritants) or in a productive cough primarily when the bronchial airways are additionally involved (e.g., sinusitis). Certainly, in addition to case-control studies such as ours there is a need for longitudinal studies to determine with more certainty the role of bronchitis as a stroke risk factor.

It is a commonly applied convention in science and medicine to take probability values of ≤.05 as significant. Obviously, we adopted these customary statistical criteria by stating that values of .070 and .062 were not significant (“NS,” Table 5) and by using the word “tended” in the text. The above probability values are the result of a univariate comparison of patients and control subjects; such analysis does not consider the possible impact of such potentially important confounders as social class, smoking, and diabetes mellitus on the results. Therefore, the important analysis is the age-adjusted multiple logistic regression analysis in which we included “poor dental status” by use of a predefined cut-off value in the “total dental index (TDI)” and four potential confounders. This analysis yielded a significant and independent association between acute cerebrovascular ischemia and poor dental status as defined. These data are included in the abstract, and there is nothing that could potentially mislead even a casual reader.

For grading the dental status, we used two indexes (TDI and Pantomography index [PI]) that have been previously developed and applied by others1,2 and slightly modified the TDI for our study. We are aware that a score summarizing and grading dental and periodontal disease represents a compromise which can be subjected to criticism. We agree with several statements by Dr Lorber regarding the descriptions of disease entities and their pathogenesis. However, we cannot agree with some conclusions drawn and the recommendations given. Similar to Dr Lorber’s statements, we had written that bacterial pulpitis is the source of periapical lesions, and we agree that caries is the most common origin of bacterial pulpitis. However, we do not think that superficial carious lesions (caries) and periapical lesions should be grouped together or that periapical lesions should simply be identified with caries because only “deep caries” reaching the pulp can lead to periapical infection and inflammation. Furthermore, omitting (superficial) caries from the analysis as suggested by Dr Lorber does not appear to be wise. Doing so would mean taking one of the interesting hypotheses (“only lesions with contact to blood or lymph channels are important as risk factors”) already as a basis of the study. It cannot a priori be taken as proved that, as stated by Dr Lorber, “superficial caries cannot play any role in systemic disease.”

Periapical lesions and vertical bone pockets are analyzed in a single subscore in the TDI. The common denominator of the two entities is that both are derived from inflammation of the alveolar bone and both can be adequately diagnosed by radiological methods only. Both show radiolucency on orthopantomography. It therefore appears reasonable to combine periapical lesions and bone pockets in one subscore. Patients had more severe findings in this subscore than did control subjects, and inflammation in both periapical lesions and bone pockets has contact with the systemic circulation.

We agree with Dr Lorber that in most cases nonvital teeth are a sequel of severe caries; however, we think that a subscore for nonvital teeth without (peri)apical finding is important particularly because such teeth without root canal therapy (“radix filling”) can represent an important inflammatory focus. However, nonvital teeth without periapical lesions were rare, and there was no difference between groups. We also agree that it would be interesting to know why the missing teeth were extracted. However, the questions proposed by Dr Lorber to distinguish tooth loss due to periodontal disease from that due to caries will probably not deliver reliable data in a case-control study with elderly people in whom tooth loss may have occurred years before.

The role of dental and periodontal infection as a possible risk factor for stroke and other vascular diseases requires further studies with larger numbers of subjects and various methodical approaches. For such studies, it is certainly worthwhile to develop alternative scoring systems that combine dental and periodontal diseases in a reliable manner.

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Serum Ferritin Concentrations Are Not Modified in the Acute Phase of Ischemic Stroke

To the Editor:

Three major molecular events in brain damage from cerebrovascular occlusion are at present the focus of interest: calcium overload, excessive acidosis, and enhanced production of free radicals. Free radicals are generated in increased amounts under ischemic conditions and react with and damage proteins, nucleic acids, and membrane lipids, disrupting cellular integrity.1 This oxygen radical activity is especially intense during reperfusion after sustained ischemia. The generation of radical hydroxyl, the most toxic and reactive of free radicals, is catalyzed by ferrous iron released from intracellular stores during ischemia; thus, the sensitivity of neurons to oxidative stress depends on the availability of iron in the ischemic focus.2,3 Iron is released from large transport proteins, particularly from ferritin, which accounts for one third to three quarters of brain iron.4 In the absence of inflammation, cancer, and infectious diseases, the serum concentration of ferritin is thought to be directly proportional to tissue iron stores and can be used to assess their size.5

Despite the theoretical importance of iron in oxidative brain injury, very little direct evidence exists to implicate iron in stroke. In experimental models, iron depletion or chelation

reduces ischemia-reperfusion–induced edema and metabolic failure.6,7 We found in 67 patients with acute ischemic stroke that high serum ferritin levels within the first 48 hours after stroke onset were associated with a poor prognosis, independent of the stress response.8 Using the same protocol, we have recently reproduced these results in a different and larger series of 103 patients (A. Dávalos, personal communication, European Stroke Conference, Amsterdam, the Netherlands, 1997). Median serum ferritin concentrations were 383 µg/L (quartiles, 158 and 442) in 40 patients with poor outcome and 218 µg/L (quartiles, 129 and 345) in 63 with good outcome (P=.004). Because ferritin concentrations in both studies were measured only once, usually several hours after stroke onset, an early increase due to the acute-phase response was not completely ruled out. The aim of this study was to demonstrate that serum ferritin concentrations were not modified during the acute phase (5 days) of ischemic stroke and that they were not related to stress and inflammatory reactions.

We studied prospectively a group of 34 consecutive patients (mean age 69±8 years; 14 males and 20 females) with an acute ischemic stroke of <8 hours in duration. Blood samples were collected at admission (mean time from stroke onset, 4.9±1.4 hours); at 12, 24, and 48 hours; and at day 5 from the onset of symptoms. Laboratory parameters measured for the purpose of this study were serum ferritin, cortisol, and C-reactive protein. In addition, leucocyte count and plasma fibrinogen were determined in the first blood sample. Diabetes was recorded in 9 patients, hypertension in 16, atrial fibrillation in 12, and ischemic heart disease in 2. The type of stroke was large-artery atherothrombotic infarct in 12 patients, cardioembolic in 11, lacunar in 6, and of unknown origin in 5. The mean Canadian Stroke Scale score at admission was 5.5±2.7. One patient died on the second day of hospitalization, and 6 patients had infectious or inflammatory diseases during the 5-day study period.

Comparisons for paired measures (Wilcoxon rank test) showed no statistical differences between the concentrations of ferritin at admission and those obtained at each time interval during the first 48 hours, whereas cortisol values decreased significantly and C-reactive protein showed a moderate increase after the first 24 hours from stroke onset (Figure). In those patients with infectious or inflammatory diseases, ferritin concentrations were stable during the early acute phase but increased significantly after 24 hours from stroke onset, as did C-reactive protein. Ferritin values did not correlate with leucocyte count and fibrinogen concentrations at inclusion (Spearman coefficients of .083 and .19, respectively; P=NS). The correlations between ferritin values and cortisol and C-reactive protein values of each sample obtained during the study period were not significant (coefficients, <.025; P=NS). Our results confirm that serum ferritin concentrations are not associated with the stress reaction and the acute phase response. The nonsignificant rise in serum ferritin during the first 2 days after stroke is of insufficient magnitude to explain the large difference in ferritin levels between the patients with good prognoses and those with bad prognoses reported by our group.8 These findings suggest that serum ferritin can provide a reliable index of iron stores in acute stroke patients without infectious or inflammatory diseases. Therefore, the association between increased concentrations of ferritin and poor outcome found in our previous investigations could be attributed to a potentially increased availability of iron in the ischemic area. A later increase of ferritin in some patients after the second day was consistent with stroke comorbidity. However, serum ferritin may be primarily an indicator of other vascular risk factors themselves related to stroke prognosis. Iron overload may elevate the risk of atherosclerotic diseases by promoting the oxidation of LDL cholesterol.9 High serum ferritin concentrations in the early acute phase of stroke could also result from inflammatory changes or infections preceding cerebral ischemia that have been recognized as risk factors for stroke and transient ischemic attack.10 Nevertheless, in this study the lack of association of serum ferritin on admission with other analytical parameters such as leucocyte count, fibrinogen, and C-reactive protein, which have been all related to previous chronic inflammation in patients with ischemic vascular diseases,11 makes this mechanism improbable. Serum ferritin determination should be included in future investigations on prognostic factors in acute ischemic stroke.

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