Ischemic Stroke Due to or Associated With Deficiency of Coagulation Inhibitors?

In their interesting article, Martinez et al state that their rate of ischemic stroke of unexplained origin in young adults (35%) “appears to be lower than that in other reports in this age group.” In fact, it is higher. Various authors in the last 10 years have reported the following figures for young people with strokes of undetermined cause: 4.2%, 7%, 9%, 10%, and 20.3%. Also, a figure of 9.8% has been reported in adults younger than 30 years of age. Recently, Carolei et al., using very strict criteria, considered that 15.3% of young adults in their series had strokes of unknown origin. They further defined a group of patients with strokes of undetermined cause (19.8%), in which there was “only one atherogenic risk factor and associated medical disease or probably nonembolic cardiac abnormalities alone.” The “unknown” and “undetermined” added up to 35.1%.

In Buenos Aires, we have found 14% of ischemic strokes to be of undetermined cause in a series of 100 young patients with cerebral infarction (data presented at the II South American Conference on Cerebrovascular Disease, World Federation of Neurology, Buenos Aires, 1992).

Martinez et al mention two reports in which the undetermined group is higher than theirs. In one of them, the authors recognize the high proportion of nonidentified causes and attribute this to the fact that “the group is a combination of community and tertiary patient referrals.” They also acknowledge that the frequency of cardioembolism may have been underestimated “because of local referral patterns.” The other report is a study from 1978, a time when several causes of ischemic stroke, let alone deficiency of coagulation inhibitors, were still unrecognized.

Thirty-three percent of the patients in the Martinez study underwent echocardiography. In other series, echocardiography was performed in 52%, 72.2%, 63%, 46%, 92.7%, and 97% of the patients. It is to be noticed that in these studies, the one with the lowest number of echocardiograms performed is also the one with the highest proportion of strokes of undetermined origin. In our series, echocardiography was done in 62% of the cases.

The lower use of echocardiography in the Martinez study may have accounted for underestimation of cardioembolic stroke. The authors do not state whether echocardiography was performed in the 10 patients in whom a deficiency of coagulation inhibitors was described. On angiography, partial or total arterial occlusions were found in 8 of the patients. These could have been embolic, especially the branch occlusions (4 patients). Apparently, no repeat angiography was performed to corroborate the findings.

The authors state that “support for causal role of the hemolysis disorder includes its persistence in subsequent months or identification of the abnormality in family members.” In 3 patients the inhibitor deficiency normalized at the 3-month follow-up. Cerebral ischemia may therefore have been due to other causes, especially in patient 3, who had heavy alcoholism, and patient 5, who took oral contraceptives and tested positive for antinuclear and anticoagulolin antibodies. All of these are recognized risk factors for stroke.

Coagulation inhibitor test results were normal in the patients’ family members, whereas low values have been observed in the relatives of heterozygous patients with the disorder. No qualitative or functional assays are reported, and relatives were studied in only 6 of the 10 cases. But even if the patients in this study were heterozygous and did have the deficit, the association could be fortuitous and the stroke due to other causes. For protein C deficiency in particular, the prevalence of heterozygosity is said to be as high as 1 in 200 asymptomatic individuals, most without thrombosis.

The precise role of coagulation inhibitors in stroke remains to be determined. Certainly, coagulation inhibitor deficiency may be an unrecognized cause of ischemic stroke. It may also be a consequence of it. Therefore, it is difficult to attribute strokes to this deficiency when cardiac sources of embolism may have gone undetected, relatives of some of the patients studied do not have the deficit, other patients’ family members are not tested, qualitative assays are not carried out, inhibitor values normalize in a follow-up test, and other risk factors and mechanisms may account for the ischemic event. In the patients studied in this letter, it would be more cautious to consider their strokes “associated with” rather than “due to” coagulation inhibitor deficiency.

Osvaldo Fustinoni, MD
Department of Neurology
J.A. Fernández Municipal Hospital
Buenos Aires, Argentina

References


Response

Dr Fustinoni has raised some criticisms to our study that can be summarized as follows: (1) the rate of 35% of strokes of unexplained origin in our series of 60 young adults; (2) the number of patients who underwent echocardiography; (3) the angiographic findings; and (4) the precise role of coagulation inhibitor deficiency in the ischemic stroke of some of our 10 reported cases. We want to point out the pitfalls Dr Fustinoni had in the interpretation of these selected parameters.

1. There is a considerable variation in the rate of stroke of unknown origin in young people among studies. Adams et al reported 7% of strokes to be of undetermined origin; Lisovski
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