The follow-up of patients of sixty-five years of age and younger with acute ischemic stroke and transient ischemic attacks, and elevated D-dimer levels in plasma

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Abstract

D-dimer levels in plasma, a degradation product of fibrin, have been shown to correlate with the severity of ischemic stroke. In order to investigate the outcome of patients with elevated D-dimer we have carried out a follow-up study of patients of 65 years of age and younger with acute ischemic stroke or transient ischemic attacks (TIA) admitted to our stroke unit from 1991 to 1992. Twenty-two of the 57 patients who had elevated D-dimer levels in the plasma. High levels were associated with cardioembolic stroke. On follow-up after a mean of 12 years, 15 patients had died and six patients had suffered another stroke or TIA (three of whom were dead). Ten patients had suffered other cardiovascular events and seven of them were dead. We concluded that high levels of D-dimer in acute ischemic stroke patients on admission were associated with cardioembolic stroke and might have prognostic value for the development of further cardiovascular events. Advanced age was found to be an independent risk factor.

Introduction

Hematologic abnormalities appeared to be the main cause of ischemic stroke in approximately one percent of all cases, and derangement of the coagulation process in young people with stroke has been estimated to be about four percent.¹ The most studied factors in the coagulation process are anticardiolipin antibodies (ACA), which have been recognized as markers for an increased risk of thrombosis, and cerebral ischemia.² Previously we have shown an association between protein S deficiency and elevated ACA.¹ D-dimer levels in plasma, a degradation product of fibrin, have been shown to correlate with severity of ischemic stroke³ and clinical progression.⁴ We prospectively investigated all acute stroke patients of 65 years of age and younger admitted to our stroke unit between 1991 and 1992 for traditional risk factors and D-dimer. In order to study the outcome and long-term follow-up a questionnaire concerning cerebro- or cardioischemic events was sent to all patients during spring 2004 (n=42). Patients not responding to the written questionnaire were contacted by phone. In addition, the medical records from the departments of Neurology and Internal Medicine were checked for all patients.

Materials and Methods

Patients

With the approval for this study by the ethics committee of Linköping University Hospital, 502 patients, who were admitted to our stroke unit for suspected acute stroke during 1991 to 1992, were investigated for the presence of ACA.¹ Three hundred and ninety-four of the 502 patients of all age groups had ischemic stroke or transient ischemic attacks (TIA). In 66 patients of 65 years of age or younger ACA, protein C and S, free protein S, and ATIII were analysed.³ In 57 of these 66 patients (36 men and 21 women, mean age 51.4 yr, range 24-64 yr), D-dimer was measured as well. Blood samples were taken within 24 hours of admission in the patients. All patients underwent computed tomography of the brain to establish diagnosis. Strokes were classified on the basis of the presence of risk factors, the mode of onset, clinical findings, and the nature and location of the occluded vessel according to Berger et al.⁷ (cardioembolic: n=11, atherothrombotic: n=11, lacunar: n=19, TIA: n=11, unknown: n=5). In addition, previous stroke, myocardial infarction, and peripheral thrombosis were noted. Symptoms and laboratory signs of infection were recorded. Platelet count, activated partial thromboplastin time (APTT), sedimentation rate (SR), C-reactive protein (CRP), and white blood cell count were measured in all patients. Risk factors were scrutinized in each patient. Carotid Doppler was performed in 49 patients. Triglycerides and cholesterol were examined in 50 patients.

Figure 1. D-dimer levels in relation to stroke subtypes.
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plasma concentrations of D-dimer have been reported to be an indicator of recurrent embolization in patients suffering from cardioembolic stroke. A trend toward an increased risk of recurrent cardio- and cerebrovascular events on follow-up after a mean of 12 years in patients with elevated D-dimer levels was noted (eight of 22 patients compared to seven of 35 with normal D-dimer levels); however, the difference was not statistically significant ($p=0.17$). Patients with high D-dimer, fibrinogen, and CRP have been associated with an increased risk of recurrent cardiovascular events, which was found in our patients with elevated D-dimer levels (10 had suffered cardio-vascular events on follow-up).

In a review, Lowe (2005) discussed the potential clinical utility of D-dimer testing in the prediction of cardiovascular risk and prophylactic anticoagulation. In addition, D-dimer levels have been shown to predict clinical progression in ischemic stroke. There are further reports showing no relationship between D-dimer levels and recurrent ischemic stroke. Woodward et al. however, found that fibrinogen and CRP were risk factors for recurrent ischemic stroke. The severity of the recurrent events in our patients is evident because five of the eight patients died. D-dimer levels were found to be related linearly to stroke severity in 76 consecutive ischemic stroke patients. Moreover, D-dimer is reported to be a good predictor for identifying patients at high risk for stroke progression, supporting our observation of a severe course for many of the patients with elevated D-dimer levels. Patients with atrial fibrillation and elevated D-dimer levels are reported to be more prone to develop thromboembolic events. This conclusion is disputed by others. In our patients with elevated D-dimer levels, none of them had atrial fibrillation. However, high-grade carotid stenosis (≥75%) or carotid occlusion was found in five of our patients with elevated D-dimer levels. We concluded that high levels of D-dimer in patients with acute ischemic stroke are associated with cardioembolic stroke and may have a pathogenetic importance for development of further cardio- or cerebrovascular events. Advanced age seems to be an important independent risk factor for further cerebro- or cardiovascular events. Because there were relatively few patients in our study, its prognostic role remains somewhat uncertain and, as suggested by Squizzato et al. further larger studies are warranted.

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