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Prothrombotic Gene Variations in Ischemic Stroke: No Differences between Large and Small Vessel Disease?

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Even if a relationship between hereditary thrombophilia and risk for ischemic stroke is probable, both the relevant prevalence of thrombophilias [1] and the question of the influence of specific subtypes of prothrombotic factors on the arterial thrombosis risk, whether due to large or small vessel disease, are controversial. Whereas the role of thrombophilic factors in venous thrombosis is well established [2], the results of previous, mostly small studies of arterial ischemic stroke are heterogeneous. These studies often lead to more uncertainty rather than a solution to this unanswered question. Therefore, the study conducted by Pruissen et al. [3] comparing genotype frequencies for 22 prothrombotic variants in a large sample size of patients with large and small vessel disease is of vital interest. Their findings indicate that previous claims about subtype associations should be interpreted with caution, as many genetic variants may not be specific to one subtype. The strengths of the study include its large sample size, the high genotyping call rates and the use of a sophisticated statistical method to account for multiple testing. It should be noted that the 'negative' results of the study do not detract from its significance; on the contrary, the study is highly valuable basic genetic analytic work.

The study results reflect a simple truth from daily clinical practice: it is rarely reasonable to search for prothrombotic factors in patients with ischemic stroke independently of large vessel, small vessel or cryptogenic origin. The results would rarely alter further therapeutic strategies in patient care. As described by the Virchow triad, thrombogenesis is a multifactorial process due to blood flow disturbance, failure of vessel integrity and/or hypercoagulability. In addition, both small and large vessel etiologies often overlap in one patient. Lastly, a reliable subtype classification of stroke etiologies is still missing. Accordingly, the guide-

lines for the diagnostic and therapeutic workup of patients in whom ischemic stroke due to thrombophilia is suspected are controversial. This should by no means imply a defeatist attitude towards the issue, but rather call for better understanding via further studies in specified subtypes of venous or of small or large artery disease.

Today only in small specified subgroups of mostly young stroke patients might the role of prothrombotic genetic variants be of relevance. As shown recently by the same group, specified variants of prothrombotic factor XIII subunits may be associated with a much higher risk for ischemic stroke in young women [4]. Due to a lack of therapeutic consequences, only a screening for antiphospholipid antibodies, but not for other prothrombotic factors, may be of relevance in patients with a suspected coagulopathy, whether due to a hereditary or an acquired thrombophilia [5]. This bears in mind the unjustifiable costs for broad routine thrombophilia screening in ischemic stroke patients.

The Leiden-Utrecht group has an outstanding reputation in the field of genetics and epidemiology of stroke and of prothrombotic gene variations and one can only encourage them to continue their work.

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