Risk of Ischemic Cerebrovascular Disease in \( \alpha_1 \)-Antitrypsin Deficiency

To the Editor:

The study by Dahl et al.\(^1\) raises important issues with regard to the potential relationship between \( \alpha_1 \)-antitrypsin deficiency and vascular disease, particularly ischemic cerebrovascular disease (ICVD). We wish to comment on this point.

Given that \( \approx50\% \) of all cerebral ischemic events are the thromboembolic complications of an atheroma and that such a mechanism is highly probable when carotid artery stenosis \( \geq 50\% \) is present,\(^2\) we can estimate that stroke was due to atherothromboembolism in \( \approx203 \) out of 406 patients with ischemic stroke (432 stroke cases minus 26 presumed cases of intracerebral hemorrhage) in the community-based sample of the study and in all of the 699 subjects in the hospital-based sample, considering the selection criteria. This means that stroke cases due to large-vessel atherosclerotic disease are probably overrepresented in the entire series (203+699=902 subjects out of 1105=81.6\%) with a consequent underrepresentation of those caused by different mechanisms.

This is relevant when interpreting the results of the study. The possibility that \( \alpha_1 \)-antitrypsin deficiency may protect against cerebral ischemia due to atherothromboembolism is biologically plausible. However, given the heterogeneity of biological mechanisms predisposing to stroke, the effect of such deficiency in subtypes of stroke the pathogenesis of which is different from that of large-vessel atherothromboembolism remains to be tested. Hence, the authors’ conclusion, “...MZ heterozygosity is associated with reduced risk of ICVD...” may be somewhat misleading. A clear definition of the pathogenic subtypes is important in epidemiological studies examining the role of candidate polymorphisms in a complex phenotype such as ischemic stroke.\(^3\) Sparse reports have pointed out that \( \alpha_1 \)-antitrypsin deficiency may represent a risk factor for specific non-atherosclerotic arterial disorders causing cerebral ischemia, such as spontaneous dissection of the cervical arteries.\(^4,5\)

This hypothesis has never been explored in a case-control study. Unfortunately, the study of Dahl et al.\(^3\) though extremely valuable as a result of its large size and case-control design, affords no answers to this question, because stroke patients have not been divided into pathogenic subgroups.

Finally, the authors’ decision to combine incident cases of stroke (recruited in the setting of a population-based study) with stroke survivors (recruited in the setting of an outpatient clinic) in the same sample may introduce a selection bias and further weaken the results of the study.

We believe that these factors (ie, stratification by pathogenic subtypes and recruitment setting) should be carefully monitored in future epidemiological studies aimed at examining the complex interaction between \( \alpha_1 \)-antitrypsin deficiency and ICVD.

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Response

We appreciate the constructive comments offered by Drs Pezzini, Vignolo, and Padovani. Our study found that severe ZZ and intermediate MZ \( \alpha_1 \)-antitrypsin deficiencies were associated with reduced blood pressure.\(^1\) Furthermore, MZ heterozygosity was associated with reduced risk of ischemic cerebrovascular disease (ICVD) and ischemic heart disease, and with increased age.

We agree that stratification by pathogenic ICVD subtypes is warranted, because an effect of \( \alpha_1 \)-antitrypsin deficiency could vary by different subtypes.\(^2\) However, stratification by subtypes reduces the statistical power and increases the chance of spurious findings. Furthermore, because increasing blood pressure is strongly associated with stroke risk, probably involving all of the main pathological types of stroke,\(^3\) the reduced blood pressure in intermediate \( \alpha_1 \)-antitrypsin deficiency that was observed in our study may rather affect all of the major types of ICVD than a single subtype of ICVD. Although atherothromboembolism-type cerebral ischemic events could be overrepresented in our study, the reduced risk of ICVD associated with intermediate \( \alpha_1 \)-antitrypsin deficiency may therefore apply to all of the major subtypes of ICVD.

Previous reports suggest \( \alpha_1 \)-antitrypsin deficiency as a potential risk factor for arterial aneurysms.\(^4,5\) The mechanism behind this association could be weakening of the arterial wall due to destruction of elastic lamellae beyond that causing reduced blood pressure. Among Copenhagen City Heart Study controls, 3 (0.6\%) MZ heterozygotes and no SZ and ZZ individuals had been hospitalized from arterial aneurysms (International Classification of Diseases, 8th revision, 441 to 442; 10th revision, I71 to I72), compared with 87 (1.0\%) of MS/MM individuals (\( \chi^2; P=0.85 \)).

We also agree that cases ideally should have identical recruitment settings; nevertheless, we combined ICVD cases recruited in two different settings to achieve maximal statistical power. When the two groups of cases were analyzed separately, the odds ratios for ICVD in ZZ versus MS/MM individuals were 0.63 (0.36 to 1.1) and 0.78 (0.49 to 1.2) after adjustment for age and gender.

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