Letters to the Editor

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Bone Mineral Density and Stroke Risk
To the Editor:

In their recent article, Jorgensen et al 1 examined the relationship between bone mineral density (BMD) and stroke. They reported that female, but not male, stroke patients had lower BMD than population controls. Like the few other previous reports, it was based on fewer than 85 total cases. We attempted to replicate their findings by analyzing data from a population-based study. We looked at stroke prevalence and BMD, using data from the cross-sectional Third National Health and Nutrition Examination Survey (NHANES III). 2 NHANES III collected data from a nationally representative sample of the civilian noninstitutionalized US population from 1988 to 1994. Analyses were limited to 6298 non-Hispanic white, non-Hispanic black, and Mexican-American men and women whose BMD levels were measured and who were aged 45 years and older at the time of the NHANES III examination, because relatively few strokes occur at younger ages. BMD was measured by trained examiners in mobile examination centers. Total proximal femoral BMD was measured by dual-energy x-ray absorptiometry (Hologic QDR-1000; Hologic, Inc). 3 Stroke prevalence was based on self-report. The few other previous reports, it was based on fewer than 85 total cases.

Baseline age, race-ethnicity, smoking status, alcohol consumption, and physical activity level were obtained by interview, and body mass index was calculated from measured height and weight. History of heart attack, congestive heart failure, and diabetes were based on self-reported doctors’ diagnoses. Hypertension was determined from blood pressure measurement at examination (systolic $\geq$140 or diastolic $\geq$90) or history of recent blood pressure medication.

Age- and Race-Ethnicity-Adjusted and Risk-Adjusted ORs for Stroke Among Women and Men by Total Proximal Femoral BMD Quartiles, NHANES III

<table>
<thead>
<tr>
<th>BMD Quartile</th>
<th>Age- and Race-Ethnicity-Adjusted OR (95% CI)</th>
<th>Risk-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56 799</td>
<td>1.88 (0.73–4.80)</td>
</tr>
<tr>
<td>2</td>
<td>43 805</td>
<td>2.22 (0.86–5.72)</td>
</tr>
<tr>
<td>3</td>
<td>36 803</td>
<td>2.21 (0.85–5.76)</td>
</tr>
<tr>
<td>4</td>
<td>18 815</td>
<td>1.00</td>
</tr>
<tr>
<td>P for linear trend</td>
<td>0.367</td>
<td>0.250</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63 769</td>
<td>1.18 (0.49–2.83)</td>
</tr>
<tr>
<td>2</td>
<td>42 768</td>
<td>0.74 (0.31–1.79)</td>
</tr>
<tr>
<td>3</td>
<td>40 768</td>
<td>0.73 (0.31–1.74)</td>
</tr>
<tr>
<td>4</td>
<td>25 770</td>
<td>1.00</td>
</tr>
<tr>
<td>P for linear trend</td>
<td>0.483</td>
<td>0.625</td>
</tr>
</tbody>
</table>

BMD range for women: $0.701–0.813$, $0.814–0.935$, $0.936$. BMD range for men: $0.851–0.936$, $0.957–1.057$, $1.058$. *Adjusted for age at interview, race-ethnicity, body mass index, history of heart attack, history of congestive heart failure, history of diabetes, hypertension, alcohol consumption, smoking status, and physical activity.

No statistically significant differences in age-adjusted mean BMD for women with reported stroke or no stroke were found (0.809 g/cm$^2$ vs 0.802 g/cm$^2$, $P=0.596$). Results were similar for men (0.935 g/cm$^2$ vs 0.947 g/cm$^2$, $P=0.358$). Weighted multivariate logistic regression analyses with SUDAAN were performed. The number of prevalent cases of stroke by gender and BMD quartile are shown in the Table. In women, odds ratios for stroke were elevated in the first 3 quartiles after adjusting for age and race-ethnicity and multiple stroke risk factors, but confidence intervals were wide. Compared with women in the fourth BMD quartile (reference group), stroke risk was highest in the third BMD quartile, with a multivariate-adjusted OR of 2.59 (95% CI 1.00 to 6.73). The interaction of age and BMD was significant for women ($P=0.031$).

Age-specific analyses suggested an association mainly in women aged 45 to 64 years, but CIs were wide. Men, no association of BMD with stroke could be demonstrated in the multivariate model. For example, compared with men in the highest quartile, men in the lowest quartile had a multivariate-adjusted OR of 0.91 (95% CI 0.34 to 2.44). In a test for linear trend, BMD was not significantly related to stroke in women or men. When treated as a continuous variable in the multivariate analyses, BMD was not associated with stroke in women ($P=0.848$) or men ($P=0.819$). In summary, in a large national study, no significant association of BMD and stroke prevalence was found in men. A trend toward elevated risk in women with BMD <0.936 g/cm$^2$ with no dose-response relationship was found. Additional large-scale studies are needed to determine more precisely the nature (threshold vs dose response vs other) and magnitude of the BMD-stroke association, especially in women.

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Response
Mussolino and coworkers present some interesting results from NHANES III as a comment to our recent article in Stroke. 1 Similar to our findings, no association was found in men. In women, there were indications of a possible relationship between low bone mineral density and stroke risk, but no dose-response relationship was found in the analysis of NHANES data. The 2 studies differ, however, in several ways. The results from NHANES III are based on a much higher number of stroke cases (323 prevalent cases) than those in our study (63 incident cases). Because our cases were incident cases, there has not been any poststroke reduction in bone mineral density, whereas it is likely that many of the stroke patients included in the analysis from NHANES have experienced a reduction in bone mineral density due to the stroke, particularly in the paretic leg. 2 Only one of the stroke patients that met the inclusion criteria in our study declined to participate,
Letters to the Editor

Compelling Reasons to Screen Brain in HHT

To the Editor:

We read with great interest the article by Maher et al,1 in which the authors reviewed the medical records from hereditary hemorrhagic telangiectasia (HHT) patients seen at their institution over 20 years. However, we disagree with the authors’ final conclusion that HHT patients should not undergo routine screening for cerebrovascular malformations (CVMs) if asymptomatic. We advocate a single baseline MRI scan in all patients with HHT, as CVMs can cause devastating neurological complications.

The findings by Maher et al of a CVM prevalence rate of 12 of 321 (3.7%) in their patient group is rather low in comparison to those in other studies.2–3 The authors acknowledge this and attribute it to screening only symptomatic patients. We believe that neurological symptoms are not a good indicator of who should receive MRI screening, and, based on our experience, we have found that neurological symptoms are not necessarily present in individuals with CVMs.2–4 The consequences of a CVM-related hemorrhage could be devastating.

Other studies2–4 have described CVMs in HHT and have reported micro-arteriovenous malformations (AVMs), small AVMs, and macro-AVMs, as well as cerebral telangiectases and cavernomas. Fulbright et al,3 who used noncontrast and gadolinium-enhanced MRI, and Willemse et al,2 who used digital subtraction angiography (DSA), found a prevalence of CVMs of 22% and 12.2%, respectively. The difference in prevalence rates between these 2 studies may be due to increased detection of other CVMs, such as micro-AVMs and cerebral telangiectases found on contrast-enhanced MRI in the Fulbright et al study. However, in terms of AVMs (≥10 mm in diameter), which are predisposed to symptoms, both studies found a prevalence rate of 11% to 12%, respectively, in consecutive patients with HHT imaged by these techniques. In the retrospective analysis by Maher et al,1 only 46 of 322 patients underwent MRI imaging. If Maher et al had performed MR imaging in all their patients, we would have predicted that at least 32 of 321 (10%) of their patients, rather than the 12 who were symptomatic, would have had a CVM, which could potentially cause symptoms.2–4

The study of Maher et al did not include the clinical characteristics of their patient population or a detailed pedigree analysis of the family members. Patients did fill out a questionnaire that included family history questions, but the findings were not reported in the article. The authors included only living patients and therefore likely failed to report deaths due to CVMs in family members, thus reducing the actual prevalence of CVMs in their group (survivor bias). A subset of HHT families may be more prone to harboring CVMs, and there is some evidence to suggest that families with a high prevalence of pulmonary AVMs (PAVMs) may have an increased likelihood of also having a CVM.5 The increased prevalence rate of CVMs in the other studies previously discussed2–3 may be related to this finding, as both centers have a strong referral bias for PAVMs. In the future, genotype-phenotype analyses will advance our understanding of the relationship of PAVMs and CAVMs.

There are still many unanswered questions with regard to CVMs and screening in HHT. The current gold standard for CVM screening is 4-vessel angiogram, but it remains too costly and invasive to be a standard screening technique. To better understand the relationship between CVMs and HHT, we need to combine data from multiple centers using our current available screening techniques, such as noncontrast and contrast-enhanced MRI, to determine the actual prevalence of CVMs in HHT and to characterize the morphology of HHT-related CVMs. Studies such as that by Matsubara et al4 have characterized CVMs in HHT in a small group of patients, but pooled center data will further expand this knowledge and also permit to characterize prospectively the risk of micro-, small, and macro-AVMs in a large, unselected group of HHT patients.

The findings of Maher et al1 support those of Willemse et al,2 who found that HHT-related CVMs have a lower risk of hemorrhage than sporadic CVMs, but these findings alone are not persuasive enough to suggest that routine screening in HHT patients should not be practiced. In light of this, we feel strongly that all HHT patients should undergo baseline MRI screening, as neurological complications can be devastating. The risk of neurological events in HHT patients outweighs the costs generated by prospective screening. Family members of families who have had a serious neurological event should be given priority for screening. Pooled center data will also permit setting up guidelines for treatment of specific aspects of HHT-related CVMs, such as their multiplicity and size. The goal of MRI screening in HHT is to prevent life-threatening complications from CVMs.

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Response

We appreciate the interest of Mandzia et al in our study. 1 We agree it is likely that the prevalence rate of CVMs in our report (3.7%) would be higher if we screened each patient with arteriography or MRI/MR angiography (MRA). It is not clear, however, that the increased yield would lead to better clinical outcomes. As Mandzia et al acknowledge, the natural history of CVMs in HHT is not well described. We reported a low occurrence of intracranial hemorrhage in this population (2.1%). This low risk of hemorrhage is supported by the data of Fulbright et al as well as that of Willemse et al. 2,3 Furthermore, in our series, patients had generally good functional outcomes following hemorrhage.

Mandzia et al correctly state that a subset of HHT families may be more likely to harbor CVMs. As we stated in our discussion, we agree that there may be such a subset of patients at increased risk, and one should consider more aggressive screening in these families.

In conclusion, we agree with Mandzia et al that there are still many unanswered questions regarding screening for CVMs in HHT. Given the safety of performing a head MRI/MRA, a study evaluating the impact of these noninvasive techniques on clinical outcomes is needed. We agree that pooled data analyses of HHT patients from multiple centers will provide useful information regarding the incidence, radiographic characteristics, and natural history of CVMs in HHT. Given the risk of arteriovenous malformations associated with hemorrhagic telangiectasia, a 3D axis scatterplot that shows the relationship between 3 variables with a statistical software package (Statistica, StatSoft, Inc). The backdrop of the 3D axis scatterplot is not a base plane and grid as with the standard 3D scatterplot, but a horizontal plane drawn at the middle of the range of the vertical (z) variable with a single pivoting axis through its center. The variables were assigned to the axes such that the variable that is most likely to discriminate between the patterns of relations among the other 2 was specified as z (the vertical axis) and was assigned to the consciousness/orientation domain. Then, by interactively rotating the display, the levels of consciousness/orientation at which the pattern of relationship between x (sensorimotor functions) and y (speech/verbal communication) changes were identified. Points above the horizontal plane reflect the most critically ill patients with severely altered consciousness; those below were less impaired in consciousness/orientation. The 3D axis scatterplot shown in the Figure revealed the relationships between the 3 domains:
each point in the plot represents 1 case on admission (filled circles) and at discharge (open circles). Both panels revealed that the strength of the relationship between the domains increased at discharge compared with admission. This could be used to evaluate the effectiveness of therapeutic interventions and comparison of various treatment protocols and procedures. For example, to examine the effect of treatment in this study cohort, the main outcome variable was set at the lower range of the 95% confidence interval of the admission scores in each domain. This range includes all cases with scores less than the lower range of the 95% CI of the admission scores in each domain. In other words, this range of scores defined the beneficial effect of interventions, or “best treatment effect.” The latter must appear distinct by any stroke scale and may provide a measure of the responsiveness common for all stroke scales rather than the use of decrements (in some scales, increments) in points from...
baseline scores used until now. For the NIHSS, the 95% CIs for consciousness/orientation, sensorimotor functions, and speech/verbal communication were 0.62 to 2.94, 8.5 to 12.5, and 0.99 to 2.56, respectively. There were 14 points (cases) within the range of best treatment effect, of which 11 cases were patients at discharge and 3 at admission. In other words, 11 cases were true treatment effect or true positives, while 3 cases were false-positives. The “cluster zone of best treatment effect” for the NIHSS can be seen in the circled area in panel A. For the mNIHSS, the 95% CIs for consciousness/orientation, sensorimotor functions, and speech/verbal communication were 0.52 to 2.26, 5.6 to 8.94, and 0.49 to 1.51, respectively. There were 11 points (cases), of which 10 were patients at discharge and 1 a case of mild partial stroke at admission. The cluster zone of best treatment effect for the mNIHSS could be seen in the circled area in panel B. Therefore, the predictive value can be calculated by assessing the proportion of the total of positive cases that are truly treatment related. The predictive value of the NIHSS was 11/14, or 78.6%. This means that the likelihood that a patient detected as having a best treatment effect by the NIHSS was a true positive effect of treatment was 78.6%. Similarly, the predictive value of the mNIHSS was 10/11, or 91%. This means that the likelihood that a patient detected as having a best treatment effect by the mNIHSS was a true positive effect of treatment was 91% in this cohort population of patients.

The NIHSS predicted that 11 cases (11/18, or 61.1%) benefited significantly from the treatment at discharge. However, 1 patient included in this cluster zone lies at the border of the cluster and thus had significant motor impairment. Conversely, mNIHSS predicted that only 10 cases (10/18, or 55.5%) benefited significantly from the treatment at discharge, with minimal impairment in all domains. This may suggest that the NIHSS may overestimate a putative drug effect, mainly due to its wide 95% confidence range, thus confirming the findings by Lyden et al.¹ that mNIHSS, because of its narrower confidence range, has improved power to detect treatment effect. Both the responsiveness and the predictive validity of the mNIHSS compared with the NIHSS were improved. It is obvious that the greater the proportion of cases in the cluster zone of the mNIHSS to the overall study cohort the more effective was the treatment regimen under investigation. The latter may provide a visually demonstrable index of drug efficacy in stroke clinical trials.

A few pitfalls of the present approach were the use of data from the NIHSS rather than prospective data collected directly from the mNIHSS. This may imply bias, as discussed by Lyden et al.¹ The other pitfall is rather a technical problem: the overlap of multiple data points may create a potentially time-consuming effort when a large number of cases are analyzed. Software improvements of the 3D scatterplot module in the statistical package that could automatically track and separate overlapping points by a user-selected tolerance limit are required to enable the widespread use of this approach in major stroke clinical trials. In conclusion, the NIHSS and mNIHSS were shown as constructs with several dimensions. However, the mNIHSS has improved responsiveness. The mNIHSS is a welcome improvement, and if used in combination with the 3D vector component analysis may provide ready detection of drug efficacy in future stroke clinical trials.

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