

**Editors' Note:** Is brain natriuretic peptide a good predictor of outcome in neurologic diseases? Duello et al. and Montaner et al. agree that, in order to find a statistically significant relationship between brain natriuretic peptide and mortality in patients with stroke or subarachnoid hemorrhage, a very large number of patients is needed. Does widespread Bacille Calmette-Guérin vaccination at birth explain the low incidence of multiple sclerosis in the Indian subcontinent? Sethi and Ristori et al. discuss.

—Chafic Karam, MD, and Robert C. Griggs, MD

#### B-TYPE NATRIURETIC PEPTIDES AND MORTALITY AFTER STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

**Katherine M. Duello, Jay P. Nagel, Joseph L. Blackshear, William D. Freeman, Jacksonville, FL:**

We read with interest the article by Garcia-Berrococo et al.<sup>1</sup> The correlation of B-type natriuretic peptides (BNP) elevation with stroke mortality is noteworthy because it has been demonstrated that BNP values in normal subjects are dependent upon age and sex.<sup>2</sup> However, the authors reported after normalization of age, sex, and stroke severity, the upper quartile of BNP values still predicted nearly double the odds of death. Increased mortality has been reported with cardiac biomarker elevation after aneurysmal subarachnoid hemorrhage.<sup>3</sup> The plausible physiologic hypothesis for both stroke types might be that severe stress (e.g., neurocardiogenic injury) leads to death. At our institution, we compared BNP of 135 subarachnoid hemorrhage (SAH) patients and dichotomized for normal and abnormal values based on age- and sex-adjusted values. We did not find any correlation between BNP and mortality (odds ratio = 1.93, *p* value = 0.3, confidence interval 0.64–5.8). The authors pooled a large sample of patients (>2,000), which may account for this outcome difference. Perhaps BNP (and proNT BNP) could be considered markers of overall illness and thus mortality due to unknown factors, or underlying cardiac dysfunction, which later causes death. For example, the authors mentioned that BNP was more elevated in cardioembolic stroke subtypes.

**Author Response: Joan Montaner, Teresa Garcia-Berrococo, Barcelona, Spain:** Duello et al. showed a lack of relationship between BNP and mortality in a cohort of 135 SAH patients when correcting for age and sex. They also inquired about methodologic aspects that are relevant for our stroke mortality study and for any studies on outcome biomarkers (i.e., sample size and confounding factors correction). We agree that the large sample size in our study was vital for reaching statistical significance and similarly occurred for other large studies on natriuretic peptides that have shown that BNP is also related to mortality in SAH.<sup>4</sup>

We also agree that natriuretic peptides may reflect overall illness and are associated with mortality in different diseases and settings regardless of history of cardiovascular disorders (e.g., major surgery, sepsis, chronic obstructive pulmonary disease, or chronic kidney disease). Probably the most critical methodologic aspect of biomarkers concerns their real predictive added value on top of other conventional outcome-related variables. Similar to our results, in a population of community-dwelling elderly, BNP was a determinant of long-term mortality but its incremental value is probably too modest.<sup>5</sup> We share this conclusion and believe that BNP is not good enough for predicting outcome in neurologic diseases and do not recommend its routine use unless included in panels with other markers with cost-benefit studies supporting its validity.

Finally, Duello et al. also raised the issue of higher levels of BNP among cardioembolic strokes. That is a different but interesting aspect irrespective of outcome since that might help neurologists to differentiate stroke etiologies.<sup>6</sup>

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1. Garcia-Berrococo T, Giralt D, Bustamante A, et al. B-type natriuretic peptides and mortality after stroke: a systematic review and meta-analysis. *Neurology* 2013;81:1976–1985.
2. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–982.
3. Yarlagadda S, Rajendran P, Miss JC, et al. Cardiovascular predictors of in-patient mortality after subarachnoid hemorrhage. *Neurocrit Care* 2006;5:102–107.

4. van der Bilt IA, Hasan D, Vandertop WP, et al. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis. *Neurology* 2009;72:635–642.
5. Beleigoli AM, Boersma E, Diniz Mde F, Vidigal PG, Lima-Costa MF, Ribeiro AL. C-reactive protein and B-type natriuretic peptide yield either a non-significant or a modest incremental value to traditional risk factors in predicting long-term overall mortality in older adults. *PLoS One* 2013;8:e75809.
6. Montaner J, Perea-Gainza M, Delgado P, et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. *Stroke* 2008;39:2280–2287.

### EFFECTS OF BACILLE CALMETTE-GUÉRIN AFTER THE FIRST DEMYELINATING EVENT IN THE CNS

**Nitin K. Sethi, New York:** Ristori et al.<sup>1</sup> reported the benefits of Bacille Calmette-Guérin (BCG) vaccination after clinically isolated syndrome (CIS). BCG vaccination may prevent progression to clinically definite multiple sclerosis in these patients. In countries like India where tuberculosis is endemic, BCG vaccination is administered to all children any time from birth to 15 days. If administered after 6 months, a Mantoux test is carried out, and if it is positive, the vaccine is withheld. Widespread BCG vaccination at birth may explain the low incidence of multiple sclerosis in the Indian subcontinent along with other hypotheses: distance from the equator, Epstein-Barr virus association vs causation, genetics, and hygiene. A well-designed study could clarify this vaccination hypothesis.

**Author Response: Giovanni Ristori, Silvia Romano, Giulia Coarelli, Maria Chiara Buscarinu, Marco Salvetti, Rome:** We thank Dr. Sethi for his comments on our article.<sup>1</sup> His hypothesis is plausible. Studies have been carried out regarding the association of early BCG vaccination and type 1 diabetes. Protective

effects of repetitive vaccinations have been shown in Turkey,<sup>2</sup> and an association between BCG vaccine and reduced production of GAD65 and IA-2 autoantibodies was demonstrated in Southern India.<sup>3</sup> It is unclear how early administration of the BCG vaccine may work over time and how it may affect autoimmunity prevalence in children and young adults. It is possible that early priming with BCG sensitizes this population to environmental nonpathogenic mycobacteria that exert long-term immunomodulatory effects, especially in developing countries. This may represent a sort of benign exposure to microbes that lacks or is deficient in the context of Westernization.<sup>4</sup> Another possibility is that BCG vaccination could provide protection from mycobacterial triggers and dysregulated immune response to mycobacterial antigens that have been associated with multiple sclerosis.<sup>5,6</sup>

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1. Ristori G, Romano S, Cannoni S, et al. Effects of Bacille Calmette-Guérin after the first demyelinating event in the CNS. *Neurology* 2014;82:41–48.
2. Karaci M, Aydin M. The effect of BCG vaccine from protection of type 1 diabetes mellitus. *J Contemp Med* 2012;2:1–8.
3. Sanjeevi CB, Ashok KD, Shtauvere-Brameus A. BCG vaccination and GAD65 and IA-2 autoantibodies in autoimmune diabetes in Southern India. *Ann NY Acad Sci* 2002; 958:293–296.
4. Rook GA. Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. *Proc Natl Acad Sci USA* 2013;110: 18360–18367.
5. Salvetti M, Ristori G, Buttinelli C, et al. The immune response to mycobacterial 70-kDa heat shock proteins frequently involves autoreactive T cells and is quantitatively dysregulated in multiple sclerosis. *J Neuroimmunol* 1996; 65:143–153.
6. Cossu D, Masala S, Frau J, Cocco E, Marrosu MG, Sechi LA. Anti *Mycobacterium avium* subsp. paratuberculosis heat shock protein 70 antibodies in the sera of Sardinian patients with multiple sclerosis. *J Neurol Sci* 2013;335: 131–133.

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## **B-type natriuretic peptides and mortality after stroke: A systematic review and meta-analysis**

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