Editors' Note: In reference to "Recurrent stroke on imaging and presumed paradoxical embolism: A cross-sectional analysis" by Dr. Kitsios et al., Dr. Uchino brings up the possibility of "index event bias" (IEB), which is seen in studies that select patients based on the occurrence of an index event and often leads to paradoxical observations. The authors respond as to why IEB is unlikely a strong factor in this case. Dr. Lattanzi describes a progressive myelopathy that does not meet the criteria for any of the currently defined idiopathic inflammatory demyelinating disorders. Authors Schmalstieg et al. agree that current classifications are incomplete.

Megan Alcauskas, MD, and Robert C. Griggs, MD

RECURRENT STROKE ON IMAGING AND PRESUMED PARADOXICAL EMBOLISM: A CROSS-SECTIONAL ANALYSIS

Ken Uchino, Cleveland: Kitsios et al.¹ did not find an association between imaging indicators of paradoxical embolism and presence of percutaneous patent foramen ovale (PFO) closure. The study may have selected the wrong outcome. Radiographic evidence of prior stroke is a reasonable surrogate for recurrent stroke. However, patients with conditions predisposing them to paradoxical embolism should not necessarily be associated with higher stroke recurrence compared to patients with cryptogenic stroke without suggestion of paradoxical embolism. The authors' hypothesis could have been that stroke recurrence is more strongly associated with not having clinical conditions triggering paradoxical embolism.

It would be helpful to know the risk factor profiles of the patients in the study registry. Silent brain infarctions have been consistently associated with age and hypertension.² Stroke recurrence may be more strongly associated with age and traditional risk factors than a presumed mechanism of paradoxical embolism. Traditional risk factors might also be less prevalent among those with presumed paradoxical mechanism compared to those without. It is possible that "index event bias" (IEB) led to the paradoxical

observation that some risk factors associated with a first event are "protective" of recurrent events.³ It has also been shown that PFO is not a risk factor for stroke recurrence in cryptogenic stroke patients.⁴

Author Response: David E. Thaler, Georgios D. Kitsios, Boston: We thank Dr. Uchino for his interest in our article¹ and concur that evidence of prior stroke on imaging ("precurrence") is an acceptable surrogate for recurrent stroke. We concede that the menace of IEB³ may threaten our conclusion that provoked paradoxical embolization is no more likely to recur than when unprovoked. However, for a strong impact of IEB, one would expect—as Dr. Uchino suggests—that conventional vascular risk factors would be distributed unequally in the 2 groups: more prevalent in those with unprovoked embolism. This was not seen in our cohort (unpublished data). However, age was associated with precurrence but we adjusted for its confounding effect in multivariate models. Drs. Kent and Thaler⁴ did recognize PFO as a risk factor for recurrence in cryptogenic stroke patients. PFO compensates for the shortfall in other risk factors in those without PFO but the risk of recurrent paradoxical embolism is lower than other cryptogenic mechanisms. We emphasize that factors that increase confidence in the diagnosis of PFO-related stroke may be different from those that predict recurrence. Multivariate models using both of these dimensions may clarify who may benefit from PFO-targeted treatments.⁵

Copyright © 2012 by AAN Enterprises, Inc.

1. Kitsios GD, Lasker A, Singh J, Thaler DE. Recurrent stroke on imaging and presumed paradoxical embolism: a cross-sectional analysis. *Neurology* 2012;78:993–997.
2. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol* 2007;6:611–619.
3. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA* 2011; 305:822–823.
4. Kent DM, Thaler DE. Is patent foramen ovale a modifiable risk factor for stroke recurrence? *Stroke* 2010;41(10 suppl): S26–S30.
5. Kent DM, Thaler DE, RoPE Study Investigators. The Risk of Paradoxical Embolism (RoPE) Study: developing risk models for application to ongoing randomized trials of per-

SOLITARY SCLEROSIS: PROGRESSIVE MYELOPATHY FROM SOLITARY DEMYELINATING LESION

Simona Lattanzi, Ancona, Italy: We observed patients with characteristics similar to those described by Schmalstieg et al.¹ and we also referred to them as having a variant of multiple sclerosis (MS). However, we also encountered cases of progressive myelopathy in the setting of demyelination of spinal cord which, despite an extensive diagnostic workup and a follow-up period of at least 5 years, did not meet the diagnostic criteria for a defined nosologic entity nor were suggestive for MS variants. There are differences between these cases and those described by Schmalstieg et al.: higher age at onset of symptoms (median 59 years, range 50–72); absence of CSF findings characteristic of MS; single or multiple spinal lesions respectively in 4 and 6 cases; and positive response to immunosuppressive treatment. We hypothesized an idiopathic progressive myelopathy of inflammatory-demyelinating nature as an entity inside the spectrum of the noninfectious idiopathic inflammatory demyelinating disorders (IIDDs) but different from those currently known. Differential diagnosis of chronic progressive myelopathy presents a major diagnostic challenge because of the many conditions in the differential diagnosis.² IIDDs classification probably could not currently be considered completed and new nosologic entities or variants

Author Response: William F. Schmalstieg, Rochester, MN: Dr. Lattanzi discusses a group of patients with progressive myelopathy apparently related to inflammatory demyelinating disease of the spinal cord. As in our series, the patients she describes did not meet diagnostic criteria for MS. In our series of patients with a single radiologically stable lesion, 4 of 7 received some type of immunosuppressive or immunomodulatory therapy and there was no history of any convincing response to therapy as described by Dr. Lattanzi. However, it is possible that patients with more recently acquired or recently active lesions could respond differently to therapy. Longitudinal follow-up in cases carefully characterized beyond the imprecise label of “progressive MS” will hopefully better inform understanding and ability to prognosticate in these cases and determine which patients might respond to existing and future disease-modifying therapies. Given the incomplete understanding of the pathogenesis of CNS inflammatory demyelinating diseases, we agree that current diagnostic criteria are “incomplete.”

Copyright © 2012 by AAN Enterprises, Inc.

1. Schmalstieg WF, Keegan BM, Weinshenker BG. Solitary sclerosis: progressive myelopathy from solitary demyelinating lesion. *Neurology* 2012;78:540–544.
2. Canellas A, Rovira Gols A, Izquierdo Rio, et al. Idiopathic inflammatory-demyelinating diseases of the central nervous system. *Neuroradiology* 2007;49:393–409.

CORRECTION

Transcobalamin 2 variant associated with poststroke homocysteine modifies recurrent stroke risk

In the article “Transcobalamin 2 variant associated with poststroke homocysteine modifies recurrent stroke risk” by F.-C. Hsu et al. (*Neurology*® 2011;77:1543–1550), the panel labels in figure 1 are correct but there is an error in the curves. Panel A, the low dose arm, should have the curves from panel B, and panel B, the high dose arm, should have the curves from panel A. The editorial staff regrets the error.

CORRECTION

Cognitive effects of one season of head impacts in a cohort of collegiate contact sport athletes

In the article “Cognitive effects of one season of head impacts in a cohort of collegiate contact sport athletes” by T.W. McAllister et al. (*Neurology*® 2012;78:1777–1784), there is an error in the abstract. The percentage of athletes demonstrating lower than expected performance on the California Verbal Learning Test (CVLT) should read 22% rather than 24%; however, the correct percentage is reported in both the text and table 3. The authors regret the error.

Neurology[®]

Recurrent stroke on imaging and presumed paradoxical embolism: a cross-sectional analysis

Ken Uchino, David E. Thaler and Georgios D. Kitsios

Neurology 2012;79:392-393

DOI 10.1212/WNL.0b013e318263dc57

This information is current as of July 23, 2012

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/79/4/392.full>

References

This article cites 5 articles, 2 of which you can access for free at:
<http://n.neurology.org/content/79/4/392.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2012 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.