Editors' Note: Friedrich Thinnies proposes an interesting hypothesis for the association between skin cancer and reduced Alzheimer disease risk. Willey critiques the statistical methods in the study by Martínez-Sánchez et al. on statins and stroke severity. However, both parties agree that no definite conclusion can be made before a clinical trial on acute treatment of stroke patients with statins is completed. Martin discusses his experience with trigger factors in migraine and points out to Hougaard et al. that triggers have been studied in the past, contrary to the authors' claim.

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

NONMELANOMA SKIN CANCER IS ASSOCIATED WITH REDUCED ALZHEIMER DISEASE RISK

Friedrich P. Thinnies, Göttingen, Germany: I propose a biologically based hypothesis for the association between skin cancer and reduced Alzheimer disease (AD) risk.¹ Amyloid A β peptides, cut from the amyloid precursor protein of neurons, are assumed to induce brain-wide neuronal apoptosis via opening plasma lemma-standing type 1 voltage-dependent anion channels (VDAC). This process results in AD whenever critical brain regions are affected.^{2–4} Either reaction partner carries one or several GxxxG motifs. Furthermore, data indicate that amyloid A β peptides can be extruded from the brain by ABC transporters at the blood–brain barrier and cancerous transformations accompany changes in the expression level or the functionality of multidrug resistance modulators that then disturb chemotherapy.⁵ However, enhanced extrusion of apoptogenic amyloid A by raised ABC transporter activities of cancer survivors might diminish or even abolish intrabrain apoptotic effect. These findings, along with other data,⁵ may explain why cancer survivors have a lower risk of AD. Finally, the VDAC/amyloid interaction model of AD pathogenesis could explain the reverse relationship of AD and cancer.⁵

© 2013 American Academy of Neurology

1. White RS, Lipton RB, Hall CB, Steinerman JR. Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk. *Neurology* 2013;80:1966–1972.

2. Thinnies FP. Amyloid A-beta cut from APP by beta secretase BACE1 and gamma secretase induces apoptosis via opening type-1 porin/VDAC in cell membranes of hypometabolic cells-A basic model for the induction of apoptosis. *Mol Genet Metab* 2010;101:301–303.
3. Thinnies FP. Apoptogenic interactions of plasmalemmal type-1 VDAC and A-beta peptides via GxxxG motifs induce Alzheimer's disease: a basic model of apoptosis. *Wien Med Wochenschr* 2011;161:274–276.
4. Mattson MP, Begley JG, Mark RJ, Furukawa K. Abeta 25-35 induces rapid lysis of red blood cells: contrast with Abeta1-42 and examination of underlying mechanisms. *Brain Res* 1997;771:147–153.
5. Thinnies FP. New findings concerning vertebrate porin II on the relevance of glycine motifs of type-1 VDAC. *Mol Genet Metab* 2013;108:212–224.

TREATMENT WITH STATINS AND ISCHEMIC STROKE SEVERITY: DOES THE DOSE MATTER?

Joshua Willey, New York: Martínez-Sánchez et al. addressed the issue of nonrandomization of trial participants taking statins before stroke (confounding by indication), using propensity scores.¹ This statistical method may not fully account for prestroke imbalances, which may affect the probability that a patient would be prescribed a statin as an outpatient. For example, older patients with atrial fibrillation (AF) who are likely to have larger strokes may be less likely to be prescribed statins (table 1).¹ Comparing tables 1 and 2, what accounts for the difference in the proportion of patients with AF and those with cardioembolic strokes? What would occur if AF, or cardioembolic vs all others, was included in the models from table 3? In those models, all stroke subtypes are included but with such small numbers that a model fit may be problematic. Until a clinical trial is completed with high doses acutely administered, we caution against high doses being administered to all stroke types. The data support not withholding statins,² but at least one study raised the possibility of no benefit from statins in the acute setting with a trend to worse outcomes.³

Author Response: Patricia Martínez-Sánchez, Blanca Fuentes, Elena Díaz-Domínguez, Marta Martínez-Martínez, Exuperio Díez-Tejedor, Madrid: We thank Dr. Willey for his comments on our

Neurology[®]

Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk

Friedrich P. Thinnies

Neurology 2013;81;2056

DOI 10.1212/01.wnl.0000436924.94798.59

This information is current as of December 2, 2013

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/81/23/2056.1.full>

References

This article cites 5 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/81/23/2056.1.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 © 2013 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.