

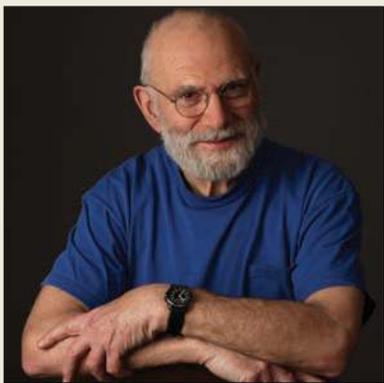
NEUROLOGY TODAY®

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INSIDE 9/17/15

REMEMBERING OLIVER SACKS: In his own words. **14**

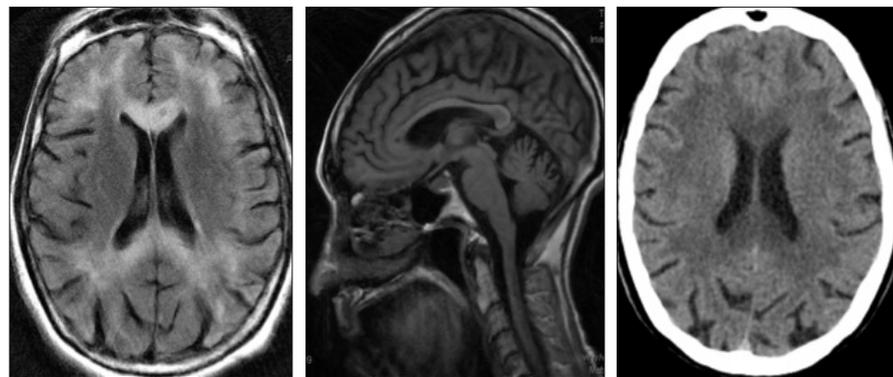


DAVID A. HAFLE: On his pathway to unraveling MS genetics. **22**

EPILEPSY: The first 3D-printed pill aims to help therapy compliance. . . **26**

New This Month: Can You Solve the *Neurology Today*—NeuroBowl Case Challenge?

BY BIRENKUMAR PATEL, MD



Neurology Today is launching a new “brain teaser” feature this month with the NeuroBowl Case Challenge. Every month, we’ll introduce a challenging case from the annals of the AAN Annual Meeting’s NeuroBowl competition. We’ll provide a brief description of the presenting symptoms and ask you, our readers, to submit your diagnosis.

FIRST CASE

A 52-year-old woman who was an alcoholic developed progressively worsening delirium over four days. On exam, she was delirious and made nonsensical statements. Her speech was fluent, but dysarthric. Otherwise, her physical

exam was normal. Her mean corpuscular volume was elevated in the low 100s, and she was HIV- and syphilis-negative. Her alcohol and toxicology tests were negative, and CSF was unremarkable. See her neuroimaging below:

What is her diagnosis? Email your responses to NeurologyToday@wolterskluwer.com. Use “NT-NeuroBowl Case Challenge” in the subject line and include your name, title, and contact information.

Stay tuned for the correct diagnosis in the next issue of *Neurology Today*, along with an analysis of all the responses we have received. •

Dr. Patel is a neurology resident at the Medical College of Georgia.

FOR DMD, DIFFERENT GLUCOCORTICOID REGIMENS=DIFFERENT OUTCOMES

BY JAMIE TALAN

Two standard glucocorticoid regimens — prednisone/prednisolone and deflazacort — may differ in their ability to delay loss of ambulation and in their side effect profile, according to results from a natural history study of Duchenne muscular dystrophy (DMD).

The findings, published ahead of print in the Aug. 26 online edition of *Neurology*, show a significant difference in the drugs’ abilities to delay use of a wheelchair. The patients on steroids fared better in ambulation than those who had not received steroids, but the boys and young men on deflazacort had an extra two years of independent walking compared with those on prednisone.

The nature of observational studies makes interpretation difficult because the scientists are following patients who are on more than a dozen different regimens and doses, the study authors told *Neurology Today*. But the findings underscore the importance of a double-blind randomized controlled clinical trial comparing equivalent doses of the two drugs, which is now underway.

Continued on page 10



PUBLISHED BY:



A New Genetic Study Associates Low Vitamin D and Risk for Multiple Sclerosis

BY SUSAN FITZGERALD

A new genetics study strengthens evidence from earlier observational studies that vitamin D deficiency is associated with an elevated risk of multiple sclerosis (MS).

Vitamin D is strongly suspected of being one of multiple risk factors for MS based on epidemiological studies, but it has been difficult to prove that the correlation is causal. This latest study focused on four genetic variants associated with vitamin D synthesis or metabolism to make a case that vitamin D insufficiency is likely directly linked to an increased risk for MS.

Continued on page 18



Vitamin D, MS Risk

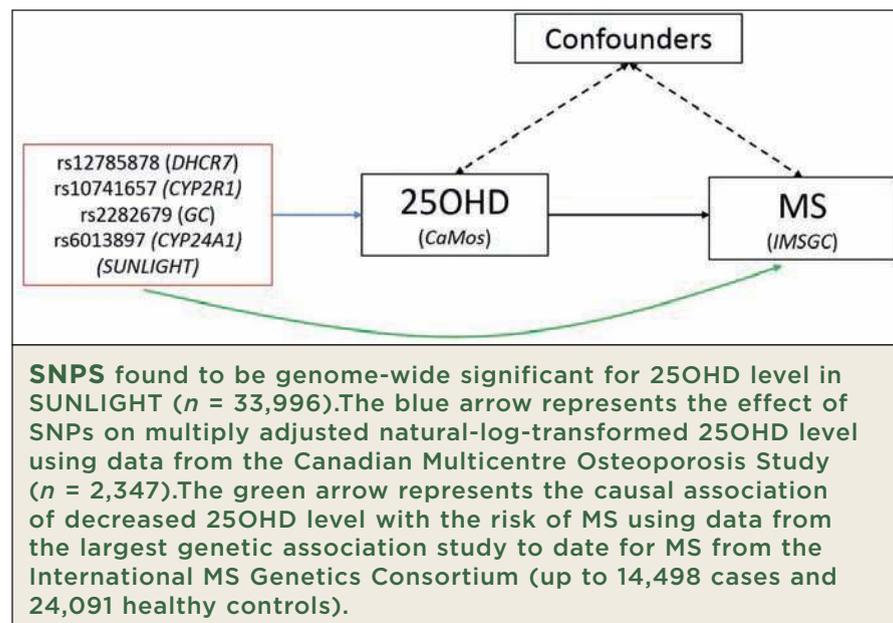
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ARTICLE IN BRIEF

An analysis of several genome-wide association studies offers additional evidence to support the association between low circulating levels of vitamin D and an increased risk of multiple sclerosis.

“The identification of vitamin D as a causal susceptibility factor for MS may have important public health implications since vitamin D insufficiency is common and vitamin D supplementation is both relatively safe and cost-effective,” the researchers wrote in the Aug. 25 online edition of *PLoS Medicine*. “These findings provide rationale for further investigating the potential therapeutic benefits of vitamin D supplementation in preventing the onset and progression of MS.”

Brent Richards, MD, an associate professor of medicine at McGill University and senior author of the paper, told *Neurology Today* that the findings “only speak to prevention. They cannot speak to treatment.”



“What we can say is that individuals at risk for multiple sclerosis, such as those with a family history, should be sure they have adequate vitamin D levels,” he said.

STUDY METHODOLOGY

The new study used a research method called Mendelian randomization, which uses genetic associations to test the effects of biomarkers on the risk of

disease, to evaluate whether genetically lowered vitamin D levels influenced MS risk. The multi-step study focused on four single nucleotide polymorphisms (SNPs) that had been previously associated with 25-hydroxyvitamin D (25OHD) levels in the so-called SUNLIGHT study (Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits), a genome-wide association study comprising nearly 34,000 participants. All four SNPs lay

in, or near, genes strongly implicated in separate mechanisms influencing vitamin D levels, the study authors noted.

Using another database, the Canadian Multicentre Osteoporosis Study, the researchers calculated the degree to which each of the four genetic variants affected vitamin D levels. They then used those calculations to determine whether there was an association between genetically reduced vitamin D levels and susceptibility to MS among participants in the International Multiple Sclerosis Genetics Consortium study, a genome-wide association study involving about 14,500 people with MS and 24,000 healthy controls.

“Using summary data for MS and 25OHD levels from large European populations, our study demonstrates that a genetic decrease in natural-log transformed 25OHD by 1 SD [standard deviation] was associated with a two-fold increase in risk of MS, providing strong evidence in support of a causal role of vitamin D in MS susceptibility,” the researchers concluded.

STUDY LIMITATIONS

An editorial summary by the *PLoS Medicine* editors noted that, in practical terms, *Continued on page 19*

Bookshelf

Continued from page 17

him a California state championship. He later regrets this activity, coming to see it as a youthful indiscretion as he finds himself obliged to deal with the predictable, and painful, orthopedic complications.

Sacks' experiments with drug use also receive attention, and readers of his 2012 book *Hallucinations* will recall this unsettled period of his life. As in the previous book, the author unwaveringly discloses his serious problems with a variety of licit and illicit drugs, from the spell of which he happily escaped.

Also in this book, Sacks reveals his lifelong homosexuality, recounting that he was aware of his sexual orientation as a child but concealed his urges lest his mother be outraged. As an adult, he has had several homosexual relationships, and he describes some sexual encounters in graphic detail. Falling in love just after turning 75, Sacks writes tenderly of sharing his life with a younger writer, Billy, to whom the book is dedicated.

A number of noteworthy people have played a part in this interesting life. Sacks offers affectionate portraits of many well-known friends, including the poets Thom Gunn and W. H. Auden, the neuropsychologist A.R. Luria, and neuroscientists Gerald Edelman and

Francis Crick. Among the members of his impressive family are the Israeli diplomat Abba Eden and the Li'l Abner cartoonist Al Capp. He received the Commander of the Order of the British Empire award from Queen Elizabeth, pleased that his nervousness did not disrupt the decorum of the event.

The book is as much about Sacks' development as a writer as it is about his pursuit of neurologic knowledge. He sees each patient as an opportunity to explore his or her peculiar predicament, while at the same time developing a special kind of empathy based on examining how the specific neurologic dysfunction comes to be. The books that spring forth from his ceaselessly active pen are the tangible products from which any curious reader may benefit. Insightful passages on the processes of writing and publishing are also provided. Some books are relatively easy to write, some maddeningly difficult. Publishers have their own ideas about what should and should not be included. And of course critics have their expected range of opinions.

A theme that appears at several points is the indifference with which his books have usually been received by fellow neurologists. His writing has been very popular with general readers — and, in the case of *Awakenings*, led to a successful 1990 film with Robert DeNiro and

Robin Williams — but neurologists have been more circumspect. Perhaps his approach to complex and little understood neurologic disorders is seen as more literary than scientific. Yet Sacks is well aware of this potential pitfall. He relies, for example, on his friend and colleague Isabelle Rapin to keep him from “loose, exaggerated, or uncorroborated statements,” and help him avoid “many embarrassing blunders.” The result is a rare combination of neurologic expertise and expressive skill.

Indeed, writing is at the very core of his being. As an introspective and frugal boy, his only extravagance was books. He began keeping journals at 14, has maintained a voluminous correspondence, and writes over a thousand meticulous clinical notes a year. “It seems to me,” he tells us, “that I discover my thoughts through the act of writing, in the act of writing.” This process is powerful, nearly irresistible: “I get intoxicated, sometimes, by the rush of thoughts and am too impatient to put them in the right order.” On the last page of his book, he summarizes with the statement, “I am a storyteller, for better and for worse.”

Compelling as it is, *On the Move: A Life* becomes still more poignant in light of Sacks' own impending mortality, which he announced in a *New York Times* op-ed piece in February. Ever

desirous of explaining the medical situation with utter honesty, he recounted how the ocular melanoma he contracted nine years ago had recently metastasized to his liver. Now he is the patient, occupying the role he has so expansively chronicled in others for so long. Yet we will always have his books.

This wise and prolific author has done more than anyone to bring the wonders of neurology to a general audience. That his books adorn the dispassionate world of science with literary excellence should not diminish what he has accomplished; on the contrary, we are all better off for what he has done, and this autobiography tells us beautifully how he has done it. •

Dr. Filley is a professor of neurology and psychiatry and director of the Behavioral Neurology Section at the University of Colorado-Denver School of Medicine.

LINK UP TO MORE INFORMATION:

- *Neurology Today*: “Everything You Always Wanted to Know About Oliver Sacks,” <http://bit.ly/sacks-nt>
- Oliver Sacks: What Hallucination Reveals About Our Minds: A TED Lecture: <http://bit.ly/TED-Sacks>
- Books by Oliver Sacks: www.oliver-sacks.com/books-by-oliver-sacks/

Vitamin D, MS Risk

Continued from page 18

the findings suggest that increasing an individual's circulating 25OHD level by approximately 1.5-fold decreases the odds of developing MS by 50 percent.

But the editors also noted that because the study involved only people of European descent, it is not clear whether the findings apply to other ethnicities. They also pointed out the difficulty in separating out vitamin D as a risk factor for MS.

Circulating levels of vitamin D are determined "in part by exposure to sunlight, and MS is more common at higher latitudes, where exposure to sunlight is decreased," they wrote. People who get MS might share an unknown risk factor (confounding), or they may have lower vitamin D levels because they spend more time indoors (reverse causation), the editors noted.

"Although the Mendelian randomization approach used here largely avoids the possibility of confounding or reverse causation, the reliability of these findings may be limited by some of the assumptions made by the researchers during their analysis," they wrote.

EXPERTS COMMENT

MS experts who were not involved with the current study told *Neurology Today* that that it would be difficult to conduct a randomized controlled trial of vitamin D for MS prevention because it would have to involve a very large number of people over many years to get results that would be statistically meaningful. Right now the focus is primarily on determining if supplementation with the vitamin

can help slow disease progression or lengthen the time between relapses, they said.

But they agreed that the genetic study provided important new information on the association between vitamin D insufficiency and MS.

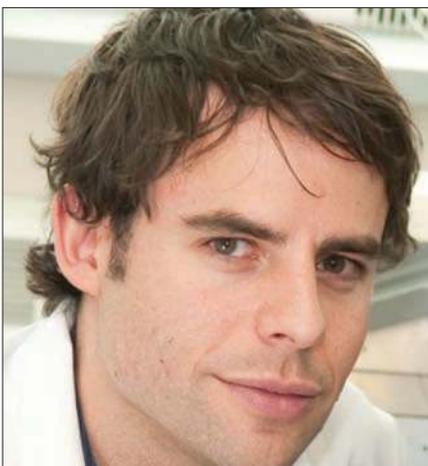
Alberto Ascherio, MD, PhD, a professor of nutrition and epidemiology at the Harvard T.H. Chan School of Public

There are 250 known genetic variants associated with MS, including ones related to vitamin D metabolism.

Health and a professor of medicine at Harvard Medical School, said the new study "is an important complement to

the work that we and others have done over the past 10 years.

Continued on page 20



DR. BRENT RICHARDS said the findings "only speak to prevention. They cannot speak to treatment. What we can say is that individuals at risk for multiple sclerosis, such as those with a family history, should be sure they have adequate vitamin D levels."

Vitamin D, MS Risk

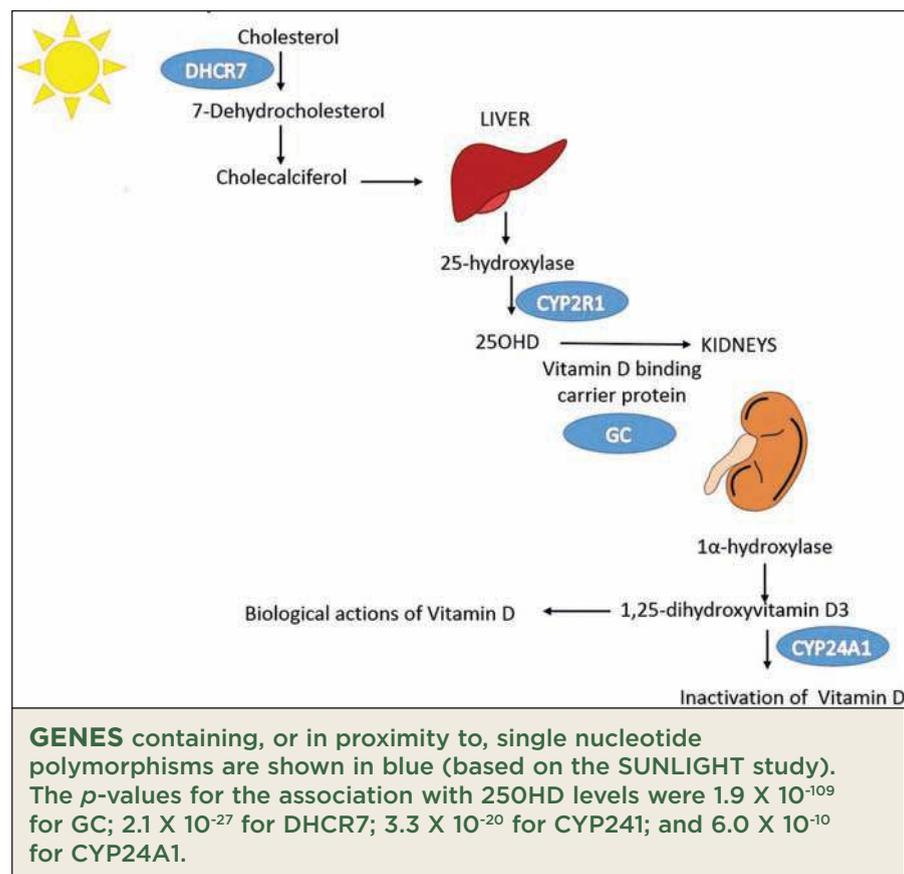
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“It provides strong evidence in favor of causality,” said Dr. Ascherio, who led the research team that in 2006 published a seminal study in the *Journal of the American Medical Association (JAMA)* that showed an association between higher vitamin D levels and decreased risk of MS. The study, which involved blood samples from healthy young adult US military personnel, found that men and women with the highest levels of vitamin D had a 60 percent lower risk of developing MS than their counterparts with the lowest levels.

Dr. Ascherio and colleagues published another study in 2014 in *JAMA Neurology* that showed that among patients with MS who were treated with interferon beta-1b, a lower level of vitamin D early in disease was a predictor for worse MS activity and disease progression.

Ellen M. Mowry, MD, FAAN, an associate professor of neurology and epidemiology at Johns Hopkins University, agreed with others that the findings of the genetic study provided good insights, but added that the final word is not in. “I think we should be cautious in the way we advise people about taking vitamin D. While observational data is encouraging, just like with any medication it deserves more study,” she said.

Dr. Mowry said it is possible that an acceptable vitamin D level for one



person may not be high enough for another person, and that a one-size-fits all approach to supplementation may not be ideal. She recently published a small study in the journal *Multiple Sclerosis* that found that when the same dose of vitamin D was given for 90 days to a group of MS patients with vitamin D deficiency, as well as healthy controls with a deficiency, the MS group ended up

having lower circulating levels of the vitamin.

She is now leading a multicenter study, funded by the National MS Society, that aims to randomize 172 MS patients to the standard adult dose of 600 international units (IU) or 5,000 IU of vitamin D daily. Over the two years of the study, researchers will measure clinical changes and quality of life factors and conduct MRI brain

scans to look at number of lesions, gray matter volume, and cortical thickness.

“If we do confirm that supplementing with vitamin D is helpful, we’ll also have to determine the best target range.”

David A. Hafler, MD, FAAN, the William S. and Lois Stiles Edgerly professor of neurology and immunobiology and chair of neurology at Yale School of Medicine, also praised the work of the study authors, adding: “I think the data on vitamin D is becoming more and more compelling.”

Dr. Hafler, who studies autoimmunity and inflammatory factors related to MS, said that genome mapping and a growing number of MS-related genetic studies have helped provide “a fuller picture of MS.” He said there are 250 known genetic variants associated with MS, including ones related to vitamin D metabolism. His Yale research lab has found, among other things, that high dietary intake of salt appears to be another risk factor for MS. Other environmental risk factors include smoking, obesity, and infection with Epstein-Barr virus.

“It’s not bad genes or bad environmental factors necessarily that put a person at risk for MS. It’s the combination of the genes and environment,” Dr. Hafler said. “To fully understand that interplay, there’s still more work that needs to be done.” •

EXPERTS: ON A GENETIC STUDY LINKING VITAMIN D AND MS RISK



DR. ELLEN M. MOWRY said that the findings of the genetic study provided good insights, but the final word is not in. “I think we should be cautious in the way we advise people about taking vitamin D. While observational data is encouraging, just like with any medication it deserves more study.”



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DR. ALBERTO ASCHERIO said the new study “is an important complement to the work that we and others have done over the past 10 years.”

LINK UP FOR MORE INFORMATION:

- Mokry LE, Ross S, Ahmad OS, et al. Vitamin D and risk of multiple sclerosis: A Mendelian randomization study. *PLoS Med* 2015;12(8):e1001866.
- Munger KL, Levin LI, Hollis BW, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; 296(23):2832-2838.
- Ascherio A, Munger KL, White R, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurol* 2014; 71(13):306-314.
- Bhargava P, Steele SU, Waubant E, et al. Multiple sclerosis patients have a diminished serologic response to vitamin D supplementation compared to healthy controls. *Mult Scler* 2015; Epub 2015 Aug. 18.
- Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol* 2010; 67:618-624.
- The International MS Consortium: http://eaglep.case.edu/imsgc_web/
- The Canadian Multicentre Osteoporosis Study: <http://camos.org>