Multiple sclerosis frequency in Israel's diverse populations

To the Editor: In their recent article on the multiple sclerosis (MS) prevalence in Israel, Alter et al reported a gradient from the Native Israeli and the Europe/America-born population over the immigrants from North Africa/Asia and Christian Arabs, to the native Moslem Arabs, Druze, and Bedouins.[1]

The authors exclude genetic factors and the low UV/low vitamin D hypothesis as causally relevant. However, they focus on a socioeconomic gradient between the European/American and African/Asian lifestyle and mention a larger family size in the latter may favor early infection and protection from MS. Although their reasoning appears plausible, the authors do not further discuss environmental factors such as diet,[2] which is fundamentally different between European/American and North African Jews.

In ecologic[2] and case-control[3] studies, the hypothesis was raised that the ingestion during childhood of smoked and nitrate/nitrite-cured meat products is a risk factor for MS in a multifactorial context. In the culinary literature, the predilection of Jews from Eastern Europe, and later from Western and Central Europe and North America, for smoked meat varieties was emphasized.[4] Dishes like smoked brisket, smoked goose, smoked frankfurters and Vienna sausages, and a variety of smoked fishes give an impression of that attitude. In contrast, diet in North African Jews is similar to the general food pattern in North Africa and the Middle East, with a much higher weight on vegetables. Drying in the hot sun prevails for meat preservation,[5] whereas smoking is virtually unknown. Christian Arabs in Israel consume pork[6] but the type of preservation has to be shown.

Details such as temperature and duration of the smoking process and interaction with intestinal abnormalities during childhood infections should be studied in future epidemiologic investigations. The study among Orthodox Jews with large families proposed by the authors might be able to disentangle a possible role of infections and these dietary features in MS.

Klaus Lauer, *Griesheim, Germany*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We thank Dr. Lauer for his comments and assure him that we recognize the likelihood that the array of possible geoclimatic, sociocultural, and genetic factors that may influence MS susceptibility is large. Far from our excluding genetic factors, as he suggested, we mention that one of our colleagues is collecting genetic information from patients with MS of diverse ethnic origin in Israel and controls (A. Miller).

We cited reports implicating both actinic exposure and vitamin D in the etiology of MS. We did not mention smoked and nitrate/nitrite-cured meat products and smoked fish. We appreciate his calling attention to other plausible causative agents in an already complex array of possibilities.

To shorten the article, we actually deleted several pages of still other possible factors that might play a role in MS etiology. We also appreciated Dr. Lauer's citation of references to cookbooks of Jewish cuisine that readers of *Neurology* may enjoy.

Milton Alter, Esther Kahana, Nelly Zilber, Ariel Miller,
Wynnewood, PA

Disclosure: The article to which this letter refers was supported by grant RG3647-A-8, the National Multiple Sclerosis Society of USA. The authors report no conflicts of interest.

References

1. Alter M, Kahana E, Zilber N, for the Israeli MS Study Group. Multiple sclerosis frequency in Israel's diverse populations. Neurology 2006;66:1061–1066.
2. Lauer K. Diet and multiple sclerosis. Neurology 1997;49 (suppl 2):55–61
3. Geilenkeuser M, Griesenbeck K, Firnhaber W, Lauer K. The intake of defined meat products in multiple sclerosis (MS): a case-control study. J Neurol 2002;249 (suppl 1):204. Abstract.
4. Rose E. The new complete international Jewish cookbook. London: Robson Books, 1992.
5. Goldstein J. Saffron shores. Jewish cooking of the southern Mediterranean. San Francisco, CA: Chronicle Books, 2002.
6. Nathan J. The foods of Israel today. New York: Alfred A. Knopf, 2001.

Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population

To the Editor: We read the article by Kubo et al.[1] with interest and have questions pertinent to the study. How many patients died and had an autopsy in every cohort? How many patients classified as lacunar had on autopsy a suggestive brain lesion? Is it possible that an autopsic finding of lacunar stroke could have been a silent stroke instead of a lacunar stroke effectively responsible for patients' symptomatology? According to the TOAST classification criteria of lacunar strokes with absence of lesion on brain imaging, how did Kubo et al. classify a patient with a previous lacunar syndrome and negative autopsic evidence? Furthermore, was white matter hyperintensity on brain imaging or autopsy considered in the process of stroke subtype diagnosis? What is the agreement between clinical and autopsic definition of stroke subtypes in every cohort? How many patients had previously known diabetes, how many new diagnosed diabetes, and how many IGT or IFT?

In this study, lacunar subtype was the most prevalent subtype, which contradicts other reports that included a Western population.[2,3] The authors explain this finding with possible race and lifestyle-related factors but we believe the epidemiologic weight of lacunar stroke in Western studies could be underestimated. We appreciate that Kubo et al. used autopsy findings to classify the ischemic stroke subtype which clarifies the subtypes definition. In our opinion, the higher prevalence of lacunar subtype in this study could not only be related to geographic or racial peculiarity of the Japanese population but also simply due to the higher accuracy of diagnostic subtype definition by imaging and autopsy.

In an observational study conducted in Palermo, we[4] observed a higher prevalence, compared to other studies, of lacunar strokes between 303 patients with ischemic stroke even if this finding could be probably related to the high prevalence of diabetics in our population. Megherbi et al.[5] showed a higher prevalence of lacunar strokes in diabetics. Kubo et al. reported in each cohort a percentage of hypertension comparable to other studies but the prevalence of glucose metabolism disorders generically grouped by the authors by the term "glucose intolerance" appears lower in comparison with previous reports.[2,3]

Finally, could lacunar stroke represent an underestimated Western subtype of stroke?

A. Tuttolomondo, A. Pinto, D. Di Raimondo, P. Fernandez, G. Licata, *Palermo, Italy*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We appreciate the interest of Dr. Tuttolomondo et al. in our recent work analyzing secular trend in the incidence of ischemic stroke subtypes using three study cohorts.[1]

In our study, morphologic examination by autopsy was performed on 109 subjects (89.3% of subjects with ischemic stroke) in the first cohort, 87 subjects (70.2%) in the second cohort, and 51 subjects (37.2%) in the third cohort. The remaining 32 subjects with ischemic stroke (25.8%) in the second cohort and all 137 subjects with ischemic stroke in the third cohort underwent examination with brain imaging.

Of 212 subjects who developed lacunar infarction in three cohorts, 122 (57.5%) were morphologically examined by autopsy and the remaining 79 (37.3%) by brain imaging. Since we considered morphologic findings significant and the existence of pathologic

lesions corresponding to neurologic findings essential for the diagnosis of ischemic stroke, all subjects with lacunar infarction under autopsy examination had significant pathologic findings.[6] Thus silent strokes did not count as lacunar infarctions.

Moreover, we did not use white matter hyperintensity on brain imaging or leukoaraiosis on autopsy as a diagnostic tool of lacunar infarction. We classified most cases of ischemic stroke into subtypes retrospectively by searching preferentially pathologic lesions corresponding to neurologic findings, and thus we did not estimate the concordance rate between clinical diagnosis and autopsy findings.

A 75 g oral glucose tolerance test was performed in almost all study subjects of the third cohort but was not in those of the first and second cohort.[7] Among the 137 subjects with ischemic stroke in the third cohort, 22 had previously known diabetes, 9 had newly diagnosed diabetes, and 21 had impaired glucose tolerance or impaired fasting glucose.

In our Japanese population, lacunar infarction was the most common subtype of ischemic stroke, contrary to the previous reports of Western populations.[2,3] This discrepancy cannot be explained by the differences in the frequencies of major risk factors, such as hypertension and diabetes, between the populations. The differences in race and lifestyle-related factors including diet might contribute to this discrepancy.

Further study and consideration are needed to clarify the issue raised by Dr. Tuttolomondo et al. regarding the underestimation of epidemiologic weight of lacunar infarction in Western studies.

Michiaki Kubo, Toshiharu Ninomiya, Yumihiro Tanizaki, Yutaka Kiyohara, *Fukuoka, Japan*

Disclosure: The authors report no conflicts of interest.

References

1. Kubo M, Kiyohara Y, Ninomiya T, et al. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. Neurology 2006;66:1539–1544.
2. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 1999;30:2513–2516.
3. Woo D, Gebel J, Miller R, et al. Incidence rates of first-ever ischemic stroke subtypes among blacks: a population study. Stroke 1999;30:2517–2522.
4. Pinto A, Tuttolomondo A, Di Raimondo D, Fernandez P, Licata G. Cerebrovascular risk factors and clinical classification of strokes. Semin Vasc Med 2004;4:287–303.
5. Megherbi SE, Milan C, Minier D, et al. European BIOMED Study of Stroke Care Group Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke 2003;34:688–694.
6. Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2626–2622.
7. Kubo M, Kiyohara Y, Kato I, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke 2003;34:2349–2354.

Terminating artificial nutrition and hydration in persistent vegetative state patients: Current and proposed state laws

To the Editor: Larriviere and Bonnie carried out a well-designed survey of US state laws regarding withdrawals of artificial hydration and nutrition (AHN) in persistent vegetative state (PVS). This survey shows the diverse legal approaches in the United States.[1,2] Some statutes refer to PVS as a terminal condition. I consider that PVS cannot be classified as a terminal state. It is well established that with appropriate nursing care and with ANH, patients with PVS can live for years.[3]

For example, a patient with incurable lung cancer will die even with appropriate nursing care, ANH, and with the most advanced medical care. In several states, PVS is not defined, but statutes refer to the concept of unconsciousness, permanent unconsciousness, and so on.[1] These terms could introduce some misunderstandings. Consciousness has two physiologic components. The first is arousal that mainly depends on the function of the ascending reticular activating system and awareness. The second is the content of consciousness that represents the sum of the cognitive, affective, and other higher brain functions depending on complex brain functions related to cerebrum and limbic levels.

It has been also argued that brainstem diencephalic and cortical structures interact to generate both components of consciousness. In coma, both consciousness components are impaired, and hence comatose patients can be classified as being unconscious. On the contrary, PVS cases reflect the only circumstance in which an apparent dissociation of both components of consciousness occurs: arousal is preserved and awareness is apparently lacking.[4] I used the term apparently because the subjective dimension of consciousness is impossible to test.[5]

I have chaired several discussions and meetings about the Schiavo case in Cuba. Although most scholars agree regarding the rights of Terry's spouse as her legal guardian, that unfriendly debate between her husband and her parents is considered ghastly. The right of lawful surrogates to request ending of life-sustaining therapies in specified conditions, presenting patients' preferences, "whether in the form of written advance directives or explicit oral statements,"[2] is legally and ethically settled. In my country, it is rare that a young person writes a living will about his or her wishes of declining ANH. This fact complicates this legal practice, because the degree of confidence that the surrogate is defending the patient's true desires is extremely low. I agree that neurologists have a fundamental role to educate their patients to express in advance directives about their surrogates and their wishes for stopping specific treatments.[2]

Calixto Machado, *Havana, Cuba*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We agree with Dr. Machado's point that there is a need for neurologists to educate patients and their families about end of life planning and to help promote the use of advance directives. We also agree with Dr Machado's general observation that the terminology used in end-of-life decision-making statutes sometime diverges from the definitions used in clinical medicine.

For example, Dr. Machado correctly notes that patients with PVS can live for years in this state with the proper medical support, including AHN, and that this condition therefore does not fit a traditional medical notion of terminal condition—a condition in which death will occur regardless of the application of life-sustaining procedures. Several of the state statutes define terminal condition in this manner.[1] The problem is that the statutes that use the scientifically preferable definition have done so in order to curtail family prerogatives to withdraw treatment from patients with PVS.

As this example shows, legislative drafting is a purposive enterprise. By defining a terminal condition to include cases in which AHN are needed to sustain life (thereby incorporating PVS), legislators have provided the patients, their families, and the medical community with an extrajudicial mechanism for decision-making in these cases.

In our opinion, these decisions should be made by patients' families and their doctors unless there are legitimate disputes about the diagnosis or the patient's wishes. Defining terminal condition in this somewhat unusual way strikes us as a practical way of accomplishing a desirable legislative purpose.

Similarly, we agree with Dr. Machado that consciousness and unconsciousness are terms that can give rise to confusion. However, the statutory use of these terms generally mirrors our current clinical understanding by defining unconsciousness as a condition in which ". . . awareness of self and environment are absent. . . "[1] The ambiguities exist only because medicine has yet to find a way to assess for the presence of awareness by anything other than indirect measures. This is another instance in which the legislatures have defined a clinical term (unconsciousness, including PVS) to accomplish a desirable legislative purpose of

enabling families to terminate treatment based on their understanding of the patient's values and preferences. The law will not stand still, however.

The challenge neurologists will be facing in the future is to help legislators, courts, and families understand the similarities and differences between PVS and minimally conscious states. As medicine's understanding of impaired consciousness advances, so too will that of the law.

Dan G. Larriviere, Richard J. Bonnie, *Charlottesville, VA*

Disclosure: The authors report no conflicts of interest.

References

1. Larriviere D, Bonnie RJ. Terminating artificial nutrition and hydration in persistent vegetative state patients: current and proposed state laws. Neurology 2006;66:1624–1628.
2. Bernat JL, Beresford HR. The controversy over artificial hydration and nutrition. Neurology 2006;66:1618–1619.
3. Giacino JT, Kalmar K. Diagnostic and prognostic guidelines for the vegetative and minimally conscious states. Neuropsychol Rehabil 2005;15: 166–174.
4. Machado C. Is the concept of brain death secure? In: Zeman A, Enamorado A, eds. Ethical Dilemmas in Neurology. London: W.B. Saunders Company; 2000:193–212.
5. Machado C. Cerebral processing in the minimally conscious state. Neurology 2005; 65:973–974; author reply 973–974.