Occurrence of amyotrophic lateral sclerosis among Gulf War veterans

To the Editor: I recently read an article¹ by authors affiliated with the United States Department of Veterans' Affairs and the United Kingdom Ministry of Defense. It provides data relevant to the first report of an excess of amyotrophic lateral sclerosis (ALS) cases in the deployed population.² The relevant text¹ is as follows:

The findings of the ALS study have had to be qualified by two considerations:

(i) the results could have been influenced by ascertainment bias because they were based on just seven additional cases of ALS among Gulf War veterans in a study of 2.5 million participants; and

(ii) the mortality rate of Gulf War veterans due to ALS has not yet been found to be elevated.³

I had not previously read or heard the statement that the entire claim of excess incidence of ALS in deployed veterans hinged on seven additional cases of ALS. This information was not shared with the readers of *Neurology*.

In addition, since publication of the first report,² the original authors have confirmed that there was underascertainment in the nondeployed First Gulf War population.⁴ Compared to 67 cases reported in the original article, the range of point estimates derived using three capture-recapture methods was 70 to 81 cases. However, when the authors used the Washington state incidence estimates to derive an upper bound for the number of cases expected in the nondeployed population, it was as high as 90 or 95. The higher numbers are not reflected in the abstract of the article,⁴ and were not used by the authors in recalculating their estimates of the ALS incidence ratio of deployed and nondeployed veterans. They used the lower estimates.

Thus, the authors' claim of excess cases in the deployed population continues to hinge on accepting as valid a lower-than-expected number in the nondeployed population (relative to a well-ascertained US population), and is supported by methods that sidestep the implications of what appears to be at most a very small absolute number of excess cases.

This additional information appeared belatedly in publications most readers of *Neurology* may not have read.^{1,4} Furthermore, it is not readily retrievable because it is not reflected in the abstracts of those publications. It supports my original critique.⁵

Carmel Armon, *Springfield, MA*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We welcome this opportunity to again respond to the two major points of contention regarding our finding of a twofold increase in risk of ALS among 1991 Gulf War veterans.² These include underascertainment of cases among the nondeployed military personnel (i.e., the control group) and failure to use a general population as the control group.

We are aware that there may have been underascertainment of cases among the nondeployed military personnel who were on active duty during the 1991 Gulf War. Therefore, as Dr. Armon

points out, we assessed the presence and magnitude of case underascertainment using capture-recapture methodology.⁴ Details of the analysis can be found in that report.

Only when the number of cases among the nondeployed is projected to be 103 or greater (vs the 67 cases actually identified) does the 95% confidence limit on the rate ratio become statistically nonsignificant. We contend that this number of cases is unlikely as the rate of ALS in this group would exceed that of a general population, the report of military service being a risk factor for ALS notwithstanding.⁶

Regarding the use of a general population as the control group, military service is an occupation and the first principles of occupational epidemiology indicate that the most appropriate comparison group for a study of ALS among deployed military personnel is another group of military personnel. This is because entry into military service involves a selective process. A general population has not undergone this selective process and does not qualify as an appropriate comparison group. Moreover, as far as we can determine, we have the largest series of ALS cases who are under 55 years of age. Our rates are likely to be the most stable rates available for this age range, making our rate estimates more reliable than those from general populations.

Finally, the lack of an elevated risk of death from this rare disease among Gulf War veterans is a likely consequence of insufficient follow-up time; the most recent mortality study involves only 7 years of follow-up.⁷

We are gratified that while we academicians haggle about methodologic nuances to a degree befitting Talmudic scholars, former VA Secretary Anthony Principi acted on our findings by changing VA policy to make Gulf War veterans with ALS eligible for VA benefits.

Ronnie D. Horner, John R. Feussner, Edward J. Kasarskis, Steven C. Grambow, *Cincinnati, OH*

Disclosure: The authors report no conflicts of interest.

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Relationship of vascular risk to the progression of Alzheimer disease

To the Editor: We read with interest the article by Regan et al. in which the authors discuss the role of vascular risk factors on disease progression in Alzheimer disease (AD).¹ There was no difference in rate of deterioration between people with and without vascular risk factors except in those who had a cerebrovascular accident. Thus, vascular risk factors may contribute to the expression of AD initially but are not part of the underlying etiologic process.¹

These findings correspond with our ongoing study carried out on a consecutive series of patients with AD² aimed at evaluating the genotype-phenotype effect of well-known vascular risk factors and their possible interactions. Among 230 patients with AD, 90

had been followed periodically through a 1-year follow-up. Each patient underwent a clinical and standardized neuropsychological assessment, including Mini-Mental State Examination (MMSE). Comorbidities (i.e., hypertension, history of cardiovascular events, and diabetes mellitus) were noted according to current clinical criteria.

Venous blood was collected for laboratory analyses and genotyping. Each patient was genotyped for apolipoprotein E (APOE) isoforms³ and methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C polymorphisms.⁴ In particular, the relationship between APOE genotype-cholesterol levels and MTHFR polymorphisms-homocysteine levels were considered.

Patients with AD were classified into two subgroups as presenting progressive cognitive decline through 1-year follow-up (pAD, MMSE 1-year minus MMSE baseline less than 0) or stable

cognitive functions (sAD, MMSE 1-year minus MMSE baseline greater than or equal to 0). pAD was present in 60% of patients (n = 54); sAD in 40% (n = 36). The two groups differed neither for APOE genotype distribution (APOE epsilon 4; pAD vs sAD, 46.3% vs 50.0%) nor for cholesterol levels (213.5 ± 45.8 vs 224.2 ± 40.0). In pAD and sAD, MTHFR C677T (TT, 25.9% vs 22.2%) and A1298C (AA, 48.1% vs 52.8%) polymorphism distributions as well as homocysteine levels (18.2 ± 12.5 vs 18.0 ± 7.5) were comparable.

Finally, no significant differences in comorbidities were present. We did not include patients with cerebrovascular accidents during the 1-year follow-up.

In agreement with the observation by Regan et al., these results show that vascular risk factors may play a different role in modulating disease onset or affecting progression. Further studies are needed on larger samples to establish genotype-phenotype effect of the different vascular risk factors on AD course.

B. Borroni, S. Archetti, M. Ferrari, B.M. Cesana, A. Padovani, *Brescia, Italy*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Borroni et al. for their interest and comments on our article.¹ We also read their findings that genotypes, certainly in the case of APOE, appear to have a significant effect on disease development⁵ and do not emerge as contributors to the course of the illness. This has been investigated before and certainly evidence does show a complex relationship between APOE and cognitive decline.⁶

These findings are similar to ours in that vascular risk factors do not contribute to disease advancement in AD.¹ Vascular risk factors augment the risk for the initiation of the disease, incontrovertibly amplifying it.⁷ This process could be secondary to the change in climate within the brain so as to allow the development of AD.

With the growing body of evidence that this is not due to atherosclerotic disease,⁸ these changes increasingly appear to be caused by an inflammatory response or oxidative stress, triggering the production of amyloid. External factors such as dietary supplements are now being examined and found to be beneficial.⁹

In the particular case of the Mediterranean diet, lack of deterioration was not associated with improved vascular markers¹⁰:

there was a conferred benefit independent of the vascular protection of the diet which may have been due to the antioxidant effect of the foods involved. Further research aimed at changing the internal environment of the brain to reduce the risk of AD is urgently needed.

Ciaran E. Regan, Cornelius Katona, Zuzana Walker, G. Livingston, *London, UK*

Disclosure: The authors report no conflicts of interest.

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Unexpected posthemorrhagic hydrocephalus in patients treated with rFVIIa

To the Editor: When a new drug is tried, it is important to identify adverse and serious adverse events. The data reported in the article by Subramaniam et al. require follow-up in the analyses of larger trials.¹ Their data are not comprehensive enough to allow for definite conclusions and the analysis of the data should also be considered.

The authors report only nine cases. They also estimated the expected risk of hydrocephalus based on the modified Graeb criteria and compared it to the observed rate.² Furthermore, the original criteria were not validated, the population in the study was heterogeneous, and the prevalence of intraventricular hemorrhage (IVH) was 30% and hydrocephalus 41%.³

The modified criteria were derived from a population that seemed more homogeneous (i.e., everybody had IVH); the prevalence of hydrocephalus was not reported and the score was not validated. Sensitivity and specificity were calculated but the absolute true and false positive and negative results were not provided.² With less than 10% expected probability and 55% observed rate of hydrocephalus, the authors concluded that rFactor VIIa might have contributed to its development.

The probability of hydrocephalus using likelihood ratios can be easily estimated.⁴ If there was a low pretest probability (prevalence) of hydrocephalus of 10% and the modified Graeb scores were assessed in the patients of Subramaniam et al., then the risk for hydrocephalus is 1 to 2%. However, if there was a prevalence of hydrocephalus of 50%, then the risk of developing it is 16 to 35%. The original Graeb criteria perform even better with a probability of hydrocephalus of 56 to 72%.

Third, the authors never mention that IVH alone is a risk

factor for hydrocephalus; all of their patients with IVH developed it.^{3,5} It would be fairer to compare the observed rate with the rate of hydrocephalus in patients with IVH who were not treated with the drug. Finally, the authors hypothesized that rFactor VIIa impaired clot resolution but provided no evidence to document the presence of the rFactor VIIa in CSF.¹

Safety is just as important as efficacy. These findings need follow-up but conclusions based on faulty or limited data and assumptions based on invalidated scales can be misleading.

Salvador Cruz-Flores, *St. Louis, MO*

Disclosure: Dr. Cruz-Flores has received a grant award from NovoNordisk for participating in the Phase III trial of Factor VIIa in intracerebral hemorrhage.

Reply from the Authors: We thank Dr. Cruz-Flores for his comments. They are well taken but the point of our brief report was to raise the possibility of an untoward adverse event that has not been previously documented. He is correct that we did not measure CSF levels of FVIIa. Obtaining acute CSF samples outside the operating room would have been dangerous. Our article is speculative by design. We await data from the current FAST trial, a phase 3 randomized trial of factor VIIa for acute ICH, to either affirm or refute our hypothesis.

Michael D. Hill, MD, Suresh Subramaniam, MD, *Calgary, Canada*

Disclosure: The authors report no conflicts of interest.

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Helicobacter pylori eradication and L-dopa absorption in patients with PD and motor fluctuations

To the Editor: Pierantozzi et al.¹ did not consider that the *Helicobacter pylori* infections might have been the result of a systemic metabolic abnormality that was the primary cause of the Parkinson disease (PD) and gut dysfunction as in peptic ulceration.²

H pylori requires a microaerophilic environment and optimally a much higher pCO₂ than that found in the lumen of the gut of healthy subjects in which to thrive in vitro. A common cause of an abnormally elevated gastric intraluminal pCO₂ in ambulatory patients is chronic mesenteric ischemia but this may only be present during metabolic stress because of metabolic compensation.³ A chronically reduced intramucosal pH, often associated with an elevated pCO₂, might be the product not only of mesenteric artery disease but also of mitochondrial toxins including translocating gut endotoxin and the cytokines it releases.

An abnormally low intramucosal pH appears to be an indication of a decline in Daniel Atkinson energy charge⁴; this is thought to be the final common pathway in the evolution of chronic gastrointestinal dysfunction, acute mucosal injury, translocation, and indeed all organ dysfunctions. Gut dysfunction may be necessary for *H pylori* infection and for any dysfunction or injury that might be induced by *H pylori*.

While the gut mucosa is considered the canary of the body in the face of acute reductive stress in the critically ill, the brain would seem to be the canary of the body of acute and chronic reductive stress in ambulatory patients. Synaptic vesicles in the brain that concentrate and store catecholamines, including dopamine, also concentrate and store ATP.⁵ It is possible that PD might be a local product of regional or systemic cause of a decline in energy charge including the translocation of endotoxin and the cytokines it releases.

Other gut bacteria, such as *E coli*, are present in the gut in larger numbers and may contain and release far more endotoxin than *H pylori* and would be eradicated or reduced in number by the antibiotics used to achieve *H pylori* eradication. The increase of L-dopa absorption observed in this study may have little or no relation to *H pylori* eradication.

Richard G. Fiddian-Green, *Rickmansworth, UK*

Disclosure: The author reports that Tonometric patents have been issued in his name.

Reply from the Authors: Dr. Fiddian-Green states that “*Helicobacter pylori* infection might have been the result of a systemic metabolic abnormality that was the primary cause of PD and gut dysfunction as in peptic ulceration.” We did not address this issue because the objective of our study focused on the reversible *H pylori*-induced interference with L-dopa intestinal absorption in infected patients with PD.

We think Dr. Fiddian-Green's assertion is unlikely. He believes that events such as chronic mesenteric ischemia or metabolic stress are necessary predisposing conditions for *H pylori* infection given the peculiar metabolic needs of the organism. This hypothesis is not supported by epidemiology and pathophysiology data on *H pylori* infection. Epidemiologic studies unequivocally show that

H pylori infection is acquired during childhood⁶ when the predisposing events hypothesized by Dr. Fiddian-Green (i.e., chronic mesenteric ischemia or metabolic stress) are highly improbable.

Concerning the high pCO₂ levels required for the organism's survival, there is compelling evidence that they are produced by the strong urease activity present on the organism's surface, which uses the urea of the gastric acid environment as substrate to produce ammonia and CO₂, thus creating the optimal conditions for *H pylori* survival in the gastric lumen.⁷

In addition, Dr. Fiddian-Green comments that *H pylori* infection itself may represent an innocent bystander and that the improvement of pharmacokinetic and clinical response to L-dopa that we found after eradication may be partially due to the efficacy of *H pylori* eradication therapy on organisms other than *H pylori*. This hypothesis cannot be excluded. Nevertheless, as we reported, the relationship between the *H pylori*-related gastritis/duodenitis relief and the significant clinical improvement observed in *H pylori*-eradicated patients with PD is certain.

We do consider the possibility that gastrointestinal motility alterations, as frequently found in L-dopa-treated patients with PD,⁸ may allow bacterial overgrowth even in the stomach.⁹ These bacteria, which are generally able to metabolize neutral amino acids,¹⁰ might in turn directly affect L-dopa intestinal absorption and their elimination due to anti-*H pylori* antibiotic treatment. Consequently, this could induce a better L-dopa adsorption, but this hypothesis needs to be further evaluated.

A. Pietroiusti, M. Pierantozzi, L. Brusa, S. Galati,
A. Stefani, G. Lunardi, E. Fedele, G. Sancesario,
A. Bergamaschi, A. Magrini, P. Stanzione, A. Galante,
Rome, Italy

Disclosure: The authors report no conflicts of interest.

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Autonomy and ars moriendi

To the Editor: In a personal history,¹ Dr. Steven Ringel argues both sides of two distressing cases. Both cases concern adults with decision-making capacity who have expressed a desire to live and

for whom life-extending measures—albeit scarce or costly ones—are available. Both patients cede decision making to others and, as a consequence, die.

In the main case, the argument attempts the familiar but impossible utilitarian task of weighing presumptions of quality

against projections of quantity of life. The outcome: a young woman with Friedreich ataxia and end-stage heart failure lets her “overwhelmed” and “exhausted” parents take her home, rather than undergoing a heart transplant.

In an ancillary case, which could be titled “For Love or Money,” a man with amyotrophic lateral sclerosis does not go on a ventilator because his wife, despite her deep love for her husband, holds him to his promise not to leave her destitute.

Ethicist Jeffrey Spike once told me humorously that when we are children our parents make our decisions, when we are adults our spouses do, and when we are old our children do. A competent adult does have the right to shift decision making to another person who is willing to accept the burden. Having watched in dismay as that process went awry, however, I vote for encouraging patients like Dr. Ringel’s to retain their right to say, “Let’s give it a try.”² I believe we should always do all we can to keep patients in charge of such choices.

At the same time, I respect Dr. Ringel’s clinical judgment. Some ethical questions are true dilemmas.

David Goldblatt, *Penn Yan, NY*

Disclosure: The author reports no conflict of interest.

Reply from the Author: I appreciate Dr. Goldblatt’s wise reminder of the unintended consequences of shifting decision making away from a patient. We all like to think of ourselves as independent human beings able to make our own decisions. Today’s medical technology, which allows us to extend life, and the almost daily discoveries of new cures for illness, certainly foster these feelings of autonomy. But increasingly, modern medical management of chronic medical conditions has created inadvertent dependency. For those with debilitating illnesses, families and caregivers have become essential components of the management team. Chronically ill patients often cannot survive without their help.

The President’s Council on Bioethics has been looking into the ramifications of mutual dependency in health care decision-making.³ Ironically, its recent report discourages an individual’s use of living wills and advance directives to control his or her own

treatments and death. Instead, it argues that it is more effective for someone with a chronic or terminal illness to acknowledge dependency by asking a loved one to assume power of attorney for medical decisions. David Brooks, a *New York Times* columnist, refers to this paradigm shift as a “declaration of dependence.”

Having advised patients and families who face progressive and often fatal neuromuscular disorders for many years, I can attest to the overwhelming demands on family members taking care of someone chronically ill and their feelings of inadequacy. Sometimes a family member who is not ready to let go of a loved one wants us to keep that person alive. For a lot of reasons, at times we comply, perhaps even because of our own fear of death. In other situations, as in the cases I portrayed, caregivers face the realities of their loved ones’ diseases and come to accept impending death before the person who is dying.

We regularly witness complexity and chaos in the lives of our patients and their families. As we struggle to help them, we must not substitute our judgment for all involved. But as the President’s Council of Bioethics reminds us, our modern technological brand of medicine forces us to reexamine the advice we offer to patients and their families as they make treatment choices that can sustain or end their lives. And in that reexamination, we need to accept that there are, unfortunately, limits to autonomy.

Steven P. Ringel, *Denver, CO*

Disclosure: The author reports no conflicts of interest.

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Corrections

Correspondence: Diagnostic evaluation of clinically normal subjects with chronic hyperCKemia

There was an error in the byline to the Correspondence by R.H. Walker et al. in response to “Diagnostic evaluation of clinically normal subjects with chronic hyperCKemia” (*Neurology* 2007;68:535–536). The byline of the Correspondence should read as follows:

Ruth H. Walker, MB, ChB, PhD, *Bronx, NY*; Hans H. Jung, *Zurich, Switzerland*; and Adrian Danek, MD, *Munich, Germany*

Correspondence: Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers

There were errors in the disclosures in the Correspondence regarding “Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers” (*Neurology* 2007;68:471). The disclosures should have read as follows:

To the Editor, by Christine M. Hulette and Kathleen Welsh-Bohmer: Supported by NIA P50 AG05128 and R01 AG07198 and Glaxo Smith-Kline.

Reply from the Authors, by M. Schnaider Beeri, M. Rapp, J.M. Silverman, J. Schmeidler, H.T. Grossman, J.T. Fallon, D.P. Purohit, D.P. Perl, A. Siddiqui, G. Lesser, C. Rosendorff, and V. Haroutunian: Supported by NIA K01 AG023515-01A2 (Dr. Beeri), P01 AG-02219 (Dr. Haroutunian), and P50 AG-05138 (Dr. Sano). The authors report no conflicts of interest.

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Correspondence: Diagnostic evaluation of clinically normal subjects with chronic hyperCKemia

Ruth H. Walker, Hans H. Jung and Adrian Danek

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