Increased glutamate in CSF and plasma of patients with HIV dementia

To the Editor: The potential for glutamate levels in CSF as a useful indicator of excitotoxicity in the progression of HIV-1-associated dementia complex was recently reexamined by Ferrarese et al.¹ With a larger number of patients than the original work,² they again reported a positive correlation. Although we strongly advocate that dysregulation of glutamate dynamics in brain parenchyma may be an important component of retrovirus-induced neurodegeneration,³ our assessment of CSF found no correlation between glutamate concentration and either HIV infection or dementia.⁴ Ferrarese et al.¹ suggested that our data may be biased by the putative degradative activity of glutaminases in CSF while frozen at -70°C .^{1,5} On the contrary, we directly addressed these concerns and found them to be without foundation.⁴ No correlation between the CSF storage times and the glutamate concentration for all individuals was evident (figure 1). In addition, no differences in glutamate levels were observed in serial measurements of individual CSF samples frozen for a period of 1 day to more than 2 years. Most importantly, we reported that the method suggested by Ferrarese et al.¹ to inactivate enzymes in CSF samples, exposure to 4 mmol/L perchloric acid,⁵ results in a nearly instantaneous hydrolysis of glutamate.⁴ Despite this in-

formation, CSF samples in the study by Ferrarese et al.¹ were again treated in this manner (although the formula for perchloric acid was incorrectly given as monobasic phosphate).¹ Consistent with an unintended hydrolysis of glutamate by this process, CSF glutamate values from subjects in the Ferrarese cohorts were 8.5- to 2-fold lower (in regards to control and HIV) than those observed in our study ($3.3\ \mu\text{M}$).⁴ The artifacts introduced by perchloric acid exposure may not affect all samples uniformly. The apparent differences in glutamate observed by Ferrarese et al.¹ may be derived from hydrolysis of additional factors, for instance, present only in the CSF of patients with HIV-1-associated dementia complex. Clearly, it would be incorrect to conclude that glutamate in the CSF from these individuals was related to levels in the brain parenchyma.

Michael Graham Espey, PhD, Anthony S. Basile, PhD, *Bethesda, MD*; Robert K. Heaton, PhD, Ronald J. Ellis, MD, PhD, *San Diego, CA*

Reply from the Authors: We appreciate the interest of Espey et al. in our works on CSF glutamate levels in patients with HIV^{1,2} and in our original method of glutamate determination in biological fluids.⁵ They agree that the discrepancies observed between our results^{1,4} could be explained by methodologic differences, as we immediately inactivated CSF samples with perchloric acid followed by neutralization with K_2CO_3 , whereas they stored untreated samples. However, they propose that our method could lead to hydrolysis of CSF glutamate, which may not affect all samples uniformly. This is unlikely for several reasons. Acid-

Figure 1. Effect of perchloric acid on glutamate. Glutamate ($5\ \mu\text{M}$) was exposed to perchlorate as indicated, immediately (within approximately 1 second) followed by neutralization with 100 mM potassium carbonate (final pH 10). Shown are representative chromatograph overlays of fluorescence from o-phthalaldehyde derivatized samples following elution from a C_{18} reverse phase column with a 0.1 M sodium phosphate buffer containing 30% methanol (pH 5.22). The Ferrarese method (4 mM perchlorate treatment) causes a $>50\%$ decrease in glutamate concentration due to an instantaneous hydrolysis reaction.

Figure 2. (A) Elution profile of a 100 pmol untreated glutamate solution. (B) Elution profile of the same solution after exposure to perchloric acid 0.4 M, followed by immediate inactivation with K_2CO_3 0.7 M. Samples were eluted through a reverse phase HPLC column by a multistep gradient of two solvents (solvent A, 0.1 M sodium acetate buffer, pH 7.2; solvent B, methanol and tetrahydrofuran 97:3 vol:vol, pH 8). Fluorimetric detection was performed with excitation and emission wavelengths of 254 and 418 nm. Glutamate peak could be clearly identified at retention time of 12 minutes, at a pH of 7.3.

treated CSF displays large increases in glutamate levels, likely linked to hydrolysis of glutamine, which is normally 100-fold higher than glutamate. For this concern, we immediately neutralized samples with equimolar K_2CO_3 (final pH 7). CSF,⁵ plasma,¹ and glutamate solutions (figure 2) treated in this way present stable amino acid levels.

Espey et al. found no correlation between time of storage at $-70^\circ C$ and glutamate levels in the CSF. These data are not surprising because no enzymatic activity can be present at that temperature. Instead, the crucial factor could be the time during which CSF samples are kept at room temperature before freezing and from sample thawing to high-performance liquid chromatography (HPLC) run. Because studies performed by our group showed this time is sufficient to cause a decrease in glutamate concentration of nearly 50%,⁵ lack of inactivation of enzymatic activity in the CSF might be a source of bias in the determination of glutamate levels.

For this reason, sample acidification with or without neutralization is now employed by several groups.⁶⁻⁸

Espey et al. found that when a glutamate solution is treated with perchloric acid and K_2CO_3 (their final pH is 10), the concentration of the amino acid decreases as a result of brief exposure to low pH. However, other authors suggested that alkaline condition may alter the stability of amino acid solutions.⁹

Moreover, in our HPLC conditions, glutamate is eluted after 12 minutes at pH 7.3, while in Espey et al.'s conditions, it is eluted after 30 minutes at pH 5.2. This pH is even lower than the one that is claimed to reduce glutamate by 50% within 1 second. The HPLC run itself might then explain the glutamate decrease observed by these authors. Because they used untreated samples in their original work in patients with HIV, both the time before freezing and the HPLC run in acid conditions may bias the results.

Head circumference and incident Alzheimer's disease: Modification by apolipoprotein E

To the Editor: Borenstein Graves et al. point to an intriguing association between small head circumference and a substantially elevated risk of AD in carriers of the *ApoE-E4* genotype.¹ They conclude that smaller head circumference leads to earlier age at onset of AD, and suggest that this distinctive relationship might reflect a smaller "brain reserve" in such individuals. Consequently, aging-associated neuronal repair mechanisms are more likely to be inadequate in individuals having a smaller head size, resulting in the observed faster AD disease progression.

We propose an alternative explanation for this observation—namely, that smaller head size might be associated with lower CNS availability of insulin or insulin-like growth factor-1 (IGF-1). Small head size at birth was recently found to be strongly associated with lower serum levels of insulin and IGF-1.² Individuals with a smaller head size at birth are likely to have smaller head circumference as adults,³ so the connection between smaller head size and lower brain insulin/IGF-1 levels seemingly persists through adulthood. Moreover, patients with AD were found to have lower CSF insulin compared with healthy adults, an association that was more pronounced in advanced AD.⁴ In addition, recent studies have demonstrated that IGF-1 effectively protected neurons against β -amyloid-induced neuronal cell death,⁵ the major cell-death mechanism believed to underlie AD neuropathology.

Together, these observations might point to a unique connection between reduced CNS insulin or IGF-1 availability and re-

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duced protection against aging-associated neurodegenerative processes culminating in AD, a connection that could be reflected by the newly observed relationship between smaller head size and increased AD risk.

David Gurwitz, PhD, Joab Chapman, MD, PhD, Abraham Weizman, MD, *Tel Aviv, Israel*

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Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes"

To the Editor: The recent article by Filippi et al.¹ has received a great deal of attention in the MS community but contains a number of inconsistencies which I hope the authors can clarify.

1. *Terminology:* The authors use the terms T1 black holes and T1 hypointense lesions interchangeably throughout the text. As

stated in the introductory paragraph of the article, these lesions are clearly distinct. The majority of new lesions appear hypointense at the time of enhancement; however, only a small fraction of these lesions evolve into the end stage lesion with axonal loss, which is termed a "black hole." Thus, in the Results section, when they selected 1251 new lesions that were hypointense at the time of enhancement, they incorrectly label these lesions as black holes despite the fact that many of these lesions recover.

2. *Missing scans:* The authors state that there were 170 of a total

Figure 1. Lesion evolution in placebo control and glatiramer acetate (GA)-treated patients. The proportion of new enhancing lesions that became isointense on T1-weighted images and did not evolve into T1 black holes is expressed as a function of time after enhancement. Data are derived from table 1.

of 9719 scans that were unavailable, and that missing scans represent 1.7% of the total. In this study, there were 119 patients taking glatiramer acetate and 120 patients taking placebo (total = 239) who were scanned once a month for 9 months (total = 2151 scans) and missing scans would account for 8% of the data. Perhaps they meant to say “scanning sequences” (e.g., T1, T1-Gd, T2), but missing even one of these sequences would eliminate the entire scan if they use all three sequences (as they describe in Materials and Methods) to determine enhancing lesions that correspond to a T2 lesion and appear hypointense on a T1-weighted scan.

3. **Lesion selection:** The authors identified 1722 enhancing lesions from months 1 to 6 of this study, of which 1251 (72.6%) were hypointense and were followed up. What selection criteria were used to choose these lesions? A quick review of the data in the Comi et al.² publication of the same trial suggests that there were approximately 4000 enhancing lesions that occurred in this time frame (3 enhancing lesions/patient × 239 patients × 6 months).
4. **Percent of patients represented in this study:** It is well documented that T1 holes do not occur in all patients. Some patients with relapsing-remitting MS (RRMS) have multiple enhancing lesions and never form T1 holes. The predisposition for T1 holes may have a genetic component and patients with secondary progressive MS tend to have more T1 holes than do patients with RRMS.³ Therefore, it is important to know the number of patients in the placebo and glatiramer acetate groups who were followed up in this study and whether these subgroups were matched for Expanded Disability Status Scale score and disease duration.³ It is unlikely that the entire population is represented.
5. **Table:** There are a number of mathematical errors.
 - a. In month 5, the total number of black holes in all patients (n = 253) exceeds that in the placebo (n = 150) + GA (n = 100) group. Similar results are shown for month 7.
 - b. For months 2, 3, 5, 7, and 8, when one back-calculates the number of new lesions (column 2) from the number and percentages listed in the columns 4 and 5 (labeled placebo and GA), the total number of new lesions (column 2) does not add up to the sum of the enhancing lesions in the two groups (e.g., in month 5, there were 1084 enhancing lesions

total [column 2], but I calculate 614 enhancing lesions in the placebo group + 454 enhancing lesions in the glatiramer acetate group, for a total of 1068 lesions; we’re missing 16 lesions).

- c. The authors state that they followed up 1251 lesions that were hypointense at the time of enhancement, but in month 3 there are 1543 enhancing lesions. How is this explained?
6. **T1 hole volume vs T1 hole number:** In the original publication of this trial by Comi et al.² there was no significant difference in T1 lesion volume between placebo and glatiramer acetate groups at the end of the 9-month study. In the current article,¹ there are fewer T1 holes in the glatiramer acetate-treated patients. How do the authors explain these data? Are there fewer T1 holes in the glatiramer acetate group, which have a larger volume?
7. **Re-enhancing T1 holes:** The authors state that the proportion of re-enhancing T1 holes was significantly higher in the placebo group (8.5%) than in the glatiramer acetate-treated group (5.0%) ($p < 0.002$). To what extent do re-enhancing holes contribute to the data, and why are re-enhancing holes even considered? Re-enhancing holes are a priori T1 holes, not hypointense lesions that have any capacity to recover.
8. **Mechanism of action of glatiramer acetate:** The authors state that glatiramer acetate reduces tissue damage and promotes the recovery of T1 hypointense lesions. However, if one plots out the data presented in table 1 in the original article,¹ the recovery curves between the placebo group and the glatiramer acetate-treated group are identical until months 7 through 8, when the placebo group unexpectedly deviates downward (figure 1). If glatiramer acetate promotes lesion recovery, one would expect to see two entirely different curves from the time of enhancement. Could this deviation in the placebo group be explained by re-enhancing T1 holes? And could the effect of glatiramer acetate be to prevent this re-enhancement at months 7 through 8, when glatiramer acetate reduces the total number of enhancing lesions?

Nancy D. Richert, MD, PhD, *Bethesda, MD*

Reply from the Authors: We appreciate the opportunity provided by Dr. Richert’s letter to clarify a few issues that may have arisen out of a casual reading of our article¹ and the constraints applied on its length by the review process. It also allows us to correct a few numeric errors in the manuscript that may have served to detract from our important observations on the evolution of individual MS lesions.

1. **Terminology:** This is in part a semantic issue. Some have used T1 hypointense lesions and black holes interchangeably—we agree with Dr. Richert’s implication that black holes is a designation that should be reserved for those hypointense T1 lesions that are long-standing and irreversible. However, we also recognized that before our study there was limited serial data on which to base a consensus definition of when to apply this term. For the purposes of our study, we defined black holes “as those lesions with signal intensity between that of the gray matter and the CSF on T1-weighted scans,” a definition that clearly includes both potentially reversible and permanent T1 hypointense lesions. We also noted in the introduction that many newly developed lesions are T1 hypointense at the time of their initial formation but only a proportion of them persist over time, and that those that are most persistent are the ones associated with the greatest degree of tissue destruction. Clearly, the proportion of the newly formed T1 hypointense lesions that persisted over time in our study is well delineated in the table, and can be better appreciated in figure 2. At what point in time these lesions should be considered as irreversible black holes is conjectural, but their late evolution in the placebo-treated group in the absence of re-enhancement is a novel finding of both considerable interest and concern.
2. **Missing scans:** Dr. Richert is correct; we wrongly reported the total number of scans. The third sentence of the results section should read: “The anticipated number of scans for the current analysis was 2390; only 122 of these (5.1%) were not available.” Although this oversight does not change the article’s message, we apologize to the readership for this mistake.
3. **Lesion selection:** Which lesions were selected for analysis in the current study is clearly presented in Materials and Methods.

Figure 2. Percentages of new lesions persisting as T1 hypointense lesions over the follow-up period in placebo (black line) and glatiramer acetate-treated (gray line) patients.

These were lesions that arose from a previously normal white matter region and were both new on T2-weighted scans and enhancing on the corresponding postcontrast T1-weighted images. They could only be selected from sessions in which at least 3 months of follow-up imaging was available, and the lesions could not undergo re-enhancement. This lesion population is obviously a defined subgroup of the total enhancing lesions found on study as reported by Comi et al.²

4. *Percent of patients represented in this study:* All patients of the original trial cohort² contributed to the current analysis. Dr. Richert raises the interesting issue that persistent T1 hypointense lesions or late-evolving black holes may occur more commonly in a subgroup of patients genetically predisposed to more destructive lesions—a suggestion worthy of additional research. Because we were aware that there might be a patient predisposition to form black holes, as described in our article,¹ we performed the analysis twice, with and without correction for intrapatient lesion correlation. The two analyses yielded similar results. Future pharmacogenomic studies might better approach this issue.
5. *Table:* The original table contained two minor mistakes: for glatiramer acetate-treated patients, the number of black holes should have been 103 instead of 100 for month 5, and 46 instead of 44 for month 7. We cannot explain the origin of these two mistakes (the percentages in brackets in the published table were related to the correct numbers). However, the discrepancy does not affect the analysis. With these corrections, it is indeed possible to back-calculate the numbers of lesions reported for all patients in column 2 of the original table (all percentages were rounded). As regards Dr. Richert's point 5c, we did not state that we "followed 1251 lesions, which were hypointense at the time of enhancement," but that 1251 of the 1722 new lesions were classified as T1 hypointense at the time of their appearance. Column 2 of the original table reports the number of newly developed, nonenhancing lesions available for the analysis 1 to 8 months after their appearance. These figures must differ from that at baseline, as a given lesion could not enter the analysis if its enhancement persisted, if it re-enhanced, or if a scan time point was missing. This explains why the new lesion numbers in column 2 are higher for months

2 through 4 than for the other months (on month 1 after their appearance, many lesions were still enhancing, while lesions having only a 3-month follow-up did not have further monthly scans).

6. *T1 black holes volume vs T1 black holes number:* This study¹ and that by Comi et al.² are based on two completely different analyses. In this study, we evaluated the proportion of individual new lesions evolving into black holes; in that by Comi et al.,² we measured the overall volume of T1 hypointense lesions. In the entire cohort reported by Comi et al.,² there was a 65% relative reduction in the accumulation of mean T1 hypointense lesion volume from baseline to month 9 for the glatiramer acetate-treated compared to the placebo-treated patients that did not reach significance ($p = 0.14$).
7. *Re-enhancing lesions:* We did not report the number of re-enhancing T1 holes (as stated by Dr. Richert), but the number of identified new lesions that re-enhanced during the follow-up. By definition of what constituted a new lesion in the current study, re-enhancing lesions did not at all contribute to the main analysis of the study, i.e., proportion of new lesions evolving into black holes. This was also clearly indicated in the footnote to the original table.
8. *Mechanisms of action of GA:* Based on the significant reduction of the proportion of new lesions evolving into black holes, we stated that glatiramer acetate "exerts a beneficial effect on the events leading to irreversible tissue disruption once lesions are formed." As indicated above, any difference in black holes accrual between glatiramer acetate- and placebo-treated patients cannot be attributed to re-enhancement. A plot of the proportion of newly enhanced lesions that remain as T1 hypointense lesions over time is shown in figure 2. The two curves may start to diverge after month 5; the differences become significant at months 7 and 8. Although not proven by our data, we believe that this behavior is compatible with the concept that glatiramer acetate may promote lesion recovery or retard late tissue destruction. Indeed, it would be very surprising to see an immediate effect of any drug on lesion recovery, and it would have been even more surprising for a drug like glatiramer acetate, which takes a few months to exert its effects, at least as monitored by MRI enhancement.² Dr. Richert incorrectly states that at month 7 through 8, "the placebo group unexpectedly deviates." Actually, the placebo group curve starts to deviate from month 6, while the glatiramer acetate-treated group curve steadily goes downwards (figure 2).

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High-grade carotid stenosis detected before general surgery: Is endarterectomy indicated?

To the Editor: Evans and Wijicks¹ recently reported that internal carotid artery (ICA) stenosis carried a perioperative stroke risk of approximately 3.6% in a series of 284 unselected patients undergoing general anesthesia and noncardiac, noncarotid surgery. For prophylactic carotid endarterectomy to be recommendable in patients with known ICA stenosis, they suggested that the global perioperative risk of carotid endarterectomy plus the general surgical procedure would need to be significantly lower than 3.6%. Although this risk was higher than in unselected popula-

tion, they concluded that it was not sufficient to prompt prophylactic carotid endarterectomy. This conclusion is correctly based on the crude sum of the percentages emerging from the study, but could be misleading.

First, caution is needed in drawing conclusions for clinical management from small series, such as the one reported by Evans and Wijicks,¹ which included 10 cases observed over 10 years. Small numbers prevented any stratification of the risk according to ICA stenosis severity and had no significant power for meaningful analysis.

Second, we unfortunately have no information on the relationship between preoperative neurologic symptoms, degree of ICA

stenosis, and perioperative stroke in this series. Without this information, it is impossible to say whether carotid endarterectomy would be useful in a given patient.

Further, although 36% (102/284) of patients in this setting of unrelated surgery had preoperative neurologic symptoms, the authors' conclusions are drawn as if all perioperative neurologic events had occurred in asymptomatic patients.

However, if we exclude perioperative strokes ipsilateral to an occluded ICA and strokes occurring in patients with an apparently normal ICA, half of the perioperative strokes (5/10) occurred in patients with an anatomically severe ICA stenosis that would have benefited from carotid endarterectomy. Because there is compelling evidence of perioperative strokes being related to severe, previously asymptomatic ipsilateral ICA lesions, an important finding of the study by Evans and Wijicks¹ is that patients with severe ICA lesions represent a subgroup of patients at special risk for increased neurologic morbidity when undergoing unrelated surgery.

A positive correlation between stroke risk and increasing degrees of stenosis was also found in asymptomatic patients in the European Carotid Surgery Trial,² and a similar finding was reported by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Investigators³ in a subgroup analysis of asymptomatic stenoses contralateral to symptomatic lesions in patients enrolled in NASCET. So why not recommend considering prophylactic carotid endarterectomy in asymptomatic patients with severe ICA stenosis before any unrelated elective surgery?

Enzo Ballotta, MD, Padua, Italy

Reply from the Authors: We thank Dr. Ballotta for his comments. True, our study,¹ when compared with large trials, is small, observational, and retrospective. Nevertheless, it represents the first clear attempt to address this important clinical dilemma. A prospective study would be welcomed. But we do think our data shows there is no imperative for routine carotid endarterectomy in patients with asymptomatic carotid lesions detected before a planned general surgical procedure.

We should clarify that with regard to "preoperative symptoms," all of our patients, by selection, had asymptomatic carotid stenosis. Among other risk factors for perioperative stroke, we found

that patients with a previous history of TIA or stroke did not have a higher perioperative risk. Those previous ischemic events were, in all instances, either remote, unrelated to the demonstrated carotid artery stenosis, or both. In fact, in our practice a patient with recent symptoms referable to a high-grade carotid stenosis would have undergone an endarterectomy before any elective surgery. All such patients were excluded.

Our finding that in a group selected for the presence of stenosis one-half of the perioperative strokes occurred ipsilateral to a severe carotid stenosis is unsurprising. Because the perioperative stroke rate in that group was not significantly different from the overall group or any subgroup, it does not follow that endarterectomy in all of these patients would have been beneficial in terms of significantly reducing the combined perioperative stroke risk.

The fact that asymptomatic patients with greater than 60% stenoses have a modest reduction in ipsilateral stroke risk over 5 years does not imply that all subsequent ipsilateral perioperative strokes would be prevented or that the combined perioperative stroke risk would be lowered sufficiently to justify the routine performance of prophylactic endarterectomy. We simply do not know why perioperative strokes after general surgery occur. We agree with Dr. Ballotta that a statistically more powerful study would help identify any subgroups of patients with asymptomatic carotid stenosis that might benefit from prophylactic endarterectomy before an unrelated surgical procedure. This would need to be a carefully conducted, prospective cohort in a randomized trial.

Bruce A. Evans, MD, Eelco F.M. Wijicks, MD, Rochester, MN

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Clinical features of withdrawal headache following overuse of triptans and other headache drugs

To the Editor: I commend Katsarava et al.¹ for undertaking the difficult task of a prospective study that involved hospitalizing a large number of patients, and for producing an incredible long-term success rate of 97%. However, I wish the authors had taken the extra step of double-blinding the trial. My concern is that their report describes clinical features of a condition that may not exist. Although withdrawal from caffeine has been shown to cause headaches in a double-blind experiment,² the existence of withdrawal or rebound headaches due to daily use of a simple analgesic, ergotamine, or a triptan has never been demonstrated scientifically. It may be that a number of anecdotal reports have created a myth of headache from medication overuse that is not supported by facts. In the study under discussion, there are plausible alternative explanations of the observed phenomena. Hospitalizing a patient under close observation for 14 days is a major intervention that should cause improvement in a significant number of patients even without other treatment. Caffeine is another variable that must be considered. The prolonged duration of withdrawal headaches in the group of patients using combination analgesics (most of which contain caffeine) as compared with the triptan group is consistent with my clinical impression that the daily use of caffeine-containing drugs almost always causes rebound headaches, whereas daily use of triptans almost never does.

Alexander Mauskop, MD, FAAN, New York, NY

Reply from the Authors: We appreciate the interest of Dr. Mauskop in our study. Firstly, we would like to emphasize that the entity of medication overuse headache (MOH) cannot seriously be called into question. After dozens of clinical descriptions (begin-

ning in the early 1950s,³ for review see a meta-analysis including 29 studies with 2612 patients⁴), the International Headache Society (IHS) integrated MOH (initially as drug-induced headache) into its classification of 1988 as an entity of its own.⁵

Secondly, from our point of view, the existence of withdrawal headache is well established.^{4,6} However, we agree that withdrawal headache is studied less, mainly because most centers use replacement therapy during the withdrawal period. In our population, we could clearly observe an increase of headache intensity (beyond the normal MOH intensity) between days 2 and 4 and a steady decrease afterwards. Because our patients did not receive any replacement therapy, a blinding of the study was not possible. In contrast, Silverman et al.⁷ aimed to confirm the existence of withdrawal symptoms after discontinuation of chronic caffeine administration, which allowed a double-blind approach (caffeine vs placebo). This, however, was not the issue of our study. Our goal, rather, was to characterize clinical differences of withdrawal symptoms due to different drugs.

The success rate of 97% does not reflect the long-term success rate but rather confirms the diagnosis of MOH, as defined by the IHS (reduction of headache days per month of at least 50%). The long-term success is clearly lower and depends mainly on the time of the follow-up and several other aspects. The few available studies evaluating long-term success rates suggest a relapse rate of 30 to 40% in the first year after withdrawal. For our group of patients, the 1-year follow-up data are now available (unpublished data) and show a relapse rate of 35%.

We agree that hospitalization of patients under close observation may itself influence (improve) the headache. Because all patients, regardless the type of overused medication, underwent withdrawal under the same conditions, the hospitalization itself is unlikely to influence the results.

Finally, as an important result of our study, we found that patients overusing analgesics (mostly containing caffeine or co-

deine) had a longer and more severe withdrawal than patients overusing ergots or triptans. Whether the additional withdrawal from caffeine and codeine worsened the withdrawal symptoms is an interesting aspect that cannot be excluded but warrants further study.

Z. Katsarava, G. Fritsche, M. Muessig, H.C. Diener, V. Limmroth, *Essen, Germany*

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Rapid infusion of intravenous immunoglobulin in patients with neuromuscular diseases

To the Editor: Grillo et al. reviewed the use of rapid infusion of IV immune globulin in patients with neuromuscular disorders.¹ Their abstract and discussion claim the safety and convenience of this practice in their population of patients, and the final sentence of their abstract states: “Rapid infusion IVIg can be given safely and conveniently in many patients with neuromuscular disorders.” Although this is accurate for the majority of their patients, the authors report 89 adverse events in 341 rapid infusions in 50 patients, 3.5% of which were considered “major.” This amounted to a major event in 11 out of 50 patients (22%).

These major events and their frequency are of concern to us, as these events included chest pain, myocardial infarction, congestive cardiac failure, severe headache requiring hospitalization, pulmonary embolism, and “transfusion related acute lung injury.” These serious occurrences are certainly related directly to the rapid infusion protocol (reaching as high as 800 mL/hour) in what

is essentially an at-risk population. Some of these adverse events are noted in the product information insert for the product used, and our own recent analysis of them, reported via pharmacovigilance, has identified rapid infusion of IV immune globulin as a possible risk factor.

It is strongly recommended that clinicians and other health care workers such as pharmacists and nurses who may be associated with the therapeutic administration of IV immune globulin read and understand the product insert and follow the noted recommendations related to the rate of infusion of this therapeutic agent.

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Reference

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Correction

Giant axonal neuropathy (GAN): Case report and two novel mutations in the gigaxonin gene

In the article, “Giant axonal neuropathy (GAN): Case report and two novel mutations in the gigaxonin gene” by Kühlenbaumer et al. (*Neurology* 2002;58:1273–1276), there was an error in the Results section, under the subsection “Molecular genetic analysis” (page 1275, line 18). “One of the patient’s brothers (II-3) inherited the exon 3 nonsense mutation from the *mother*” should read “. . . from the *father*.” The authors apologize for this error.

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Giant axonal neuropathy (GAN): Case report and two novel mutations in the gigaxonin gene

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