Correspondence

High prevalence of neurovascular instability in neurodegenerative dementias

To the Editor: AD is associated with neuronal loss in areas related to central regulation of cardiovascular autonomic reflexes (CVAR). The neurovascular instability report by Ballard et al.¹ could be related to abnormal integration of CVAR. We studied heart rate (HR) change on deep breath (HRdb), initial HR increase on standing (beats/min) (HRst), and 30:15 ratio in 20 AD patients (age 56–79 years) and 20 age-matched controls (table). Mann-Whitney and Student *t*-test were used.

Table Results of autonomic tests in AD patients and controls

Test	AD	Controls	<i>p</i> Value
HRdb	11.1 ± 9.5	14.5 ± 7.1	0.10
HRst	13.3 ± 5.8	16.2 ± 7.9	0.10
30:15 ratio	1.05 ± 0.07	1.18 ± 0.1	0.001

Values are mean ± SD.

HR = heart rate; db = deep breath; st = standing.

We found patients with normal HRdb showing normal cardio-vagal brainstem reflexes. Patients also had normal HRst but without subsequent HR decrease (30:15 ratio), indicating normal initial vagal modulation but defective further HR regulation.² It is possible that cardioinhibitory carotid sinus hypersensitivity in AD patients¹ could be explained by normality of afferent limb of the carotid sinus reflex and of cardiac vagal brainstem function but with loss of inhibition from cortical regions. Cardiovascular instability with spontaneous hypotension accompanied by slow cortical EEG activity and normal HRdb was reported in one AD patient.³ The clinical relevance of abnormal CVAR integration in AD needs further study.

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Dopamine agonists reorient visual exploration away from the neglected hemisphere

To the Editor: I read with interest Grujic et al.'s recent article on the effect of bromocriptine on visual exploratory behavior in patients with visuospatial neglect after right hemisphere stroke.¹ As the authors note, my colleagues and I also observed that bromocriptine can increase ipsilesional motor-intentional bias.² Our patient took 20 mg daily at the time when we assessed his performance, and other studies of bromocriptine treatment for neglect in humans^{3,4} have slowly increased the daily dose to a presumed therapeutic range of at least 15 mg/d.

Grujic et al. do not discuss why they chose a small dose (2.5 mg), and I wonder if they would be willing to explain. It would seem, based on their findings, that clinicians using bromocriptine for neglect may wish to reassess soon after instituting therapy as well as at "therapeutic dose."

Anna M. Barrett, MD, *Gainesville, FL*

To the Editor: The study by Grujic et al.¹ on the role of the dopaminergic system in visual exploration in unilateral neglect is interesting not only for its implications on clinical practice and rehabilitation, but also for its theoretical aspects, which bear on the pathophysiology of directed attention in unilateral neglect. Although animal studies have shown that the dopaminergic system is involved in explorative behavior,^{5,6} studies on humans in this area are limited.^{3,7}

Grujic et al. show that a single dose of the dopaminagonist bromocriptine accentuates exploration on the side ipsilateral to the lesion, resulting in worsening of left neglect. This finding conflicts with the results of Fleet et al.³ who reported an improvement in human unilateral neglect with chronic administration of bromocriptine. Grujic et al. also found that dopaminergic stimulation has different effects on the exploratory-motor and sensory-perceptual components of directed attention. This aspect was explored in our own study⁷ in which acute stimulation with apomorphine produced a transitory improvement in unilateral neglect, particularly in its premotor aspects. Grujic et al.'s findings apparently contradict the results of animal studies, as well as those of Fleet et al.³ and our own study with apomorphine.⁷ Consequently, we have several comments.

1. The patients studied by Grujic et al. did not, at the time of the bromocriptine challenges, present clinical signs of unilateral neglect, although they had all manifested such signs in the past. In such patients it is likely that some neuronal reorganization has occurred. This might explain Grujic et al.'s unexpected findings.

2. Animal studies have shown that dopaminergic fibers implicated in sensory neglect project to the frontal lobes.⁸ Most of Grujic et al.'s patients had relatively extensive lesions also involving frontal structures. Thus, the postsynaptic targets of the dopaminergic projections from subcortical structures may have been extensively compromised and dopaminagonists may have been unable to exert a frontal effect.

3. Bromocriptine mainly acts on D2 receptors. D1 receptors are stimulated by dopamine and other dopaminagonists such as apomorphine and pergolide, but not bromocriptine.⁹ It is likely that stimulation of D1 receptors is also necessary to achieve the full dopaminergic effect.

4. The mechanism of action of bromocriptine differs from that of apomorphine. It seems that when dopamine is depleted bromocriptine has a very weak effect.^{10,11} This implies that where a lesion has completely destroyed the presynaptic structures, there can be a greater effect on the nonlesioned side, resulting in a deterioration in exploration on the contralateral side, as observed by Grujic et al.¹

5. To elicit worsened neglect Grujic et al. used a single oral dose of bromocriptine (1.25 mg), whereas Fleet et al.³ used bromocriptine for 3 to 4 weeks at doses of 15 mg/day. Recalling that the availability of bromocriptine is around 6% of the oral dose,⁹ the effect with such a low dose might be to stimulate autoreceptors, resulting in inhibition of the dopaminergic system.¹² Very low doses of bromocriptine can also worsen the symptoms of PD. The authors themselves stress the need for studies on other doses of bromocriptine and other drugs. The important point is that all of these studies point firmly in the direction of an involvement of the dopaminergic system in spatial attention.

Giuliano Geminiani, MD, *Milan, Italy*

Reply from the Authors: We appreciate the comments by Drs. Barrett and Geminiani regarding our article on dopamine agonists and visuospatial neglect. A variety of factors may contribute to the findings in our study and these include not only the dose of medication, but also the location and size of the lesions and the duration and type of hemispatial neglect. We agree that further studies are necessary to clarify the dopaminergic system's role in hemispatial neglect.

Z. Grujic, MD, *Chicago, IL*

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Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin

To the Editor: We read with interest the retrospective evaluation of purple glove syndrome (PGS) in patients receiving intravenous phenytoin (PHT) by O'Brien et al.¹ and the accompanying editorial in the same issue.² We agree that PGS can be a serious adverse event (AE) related to IV PHT administration, and its incidence may well be under-reported.

We query why the "randomly chosen 3-month period" was 7 years ago. The introduction of fosphenytoin (FOS) (Cerebyx; Parke-Davis, Morris Plains, NJ) certainly heightened awareness of the potential complications associated with IV PHT use and may have increased the care with which the drug is administered; hence, the findings may not represent the current risk of PGS.

Using FOS instead of IV PHT is not the only way to avoid this complication, particularly considering a recent prospective evaluation of the potential role of phenytoin-equivalent (PE) compounds in the treatment of status epilepticus (SE).³ We also plead for rational consideration of the need for parenteral PE therapy when other drugs (e.g., benzodiazepines) may be more appropriate first-line treatments, or where enteral PHT use may be appropriate.⁴ The latter might prevent complications and reduce costs, and presumably could have spared three patients in the series this untoward event (Patients 1, 3, and 4 received IV PHT for "maintenance").

We agree that surrogate outcomes pale in lieu of cost-effectiveness analyses. A recent such study did not include any cases of PGS.⁵ Similarly, prospective evaluation at our institution did not identify any cases of PGS, and we found that other perceived advantages of FOS (e.g., faster administration time) did not shorten Emergency Department (ED) length of stay.⁶ As a footnote to our randomized open-label evaluation of 279 patient-doses of parenteral PHT or FOS in the ED, the incidence of AEs was similar, and the only serious AE occurred in a patient receiving FOS (hypotension).

A Pharmacy and Therapeutics Committee must consider many factors in deciding to completely replace a hospital's open formula with FOS instead of IV PHT. At our institution, such a change would substantially increase pharmacy costs when we are not seeing significant numbers of such serious complications and when the pharmacy is being asked to display austerity in its selection of agents. Thus, FOS is restricted for use in patients without IV access (as it can be given intramuscularly) or those in SE (given its faster administration time).

We are glad to see an attempted systematic assessment of this

serious complication, although we would prefer the study period to be more recent if not prospectively evaluated. We call for thoughtful evaluation of the possible use of enteral PHT. To paraphrase an old saying, there may be situations where one may be relatively safe with the "devil you know."

William M. Coplin, MD, Denise H. Rhoney, PharmD, Elizabeth A. Lyons, PharmD, Kellie R. Murry, PharmD, *Detroit, MI*

Reply from the Authors: We appreciate the comments of Coplin et al. regarding our study examining the incidence, risk factors, and long-term sequelae of PGS in patients receiving IV PHT. We are pleased that they concur that PGS is an important "serious adverse event related to IV PHT." We will address each issue in their letter:

1) We believe the study design, methods, and results of this investigation fully support its conclusions. The 3-month study period was determined based on the number of consecutive patients exposed to IV PHT (n = 152) at the Mayo Foundation Hospitals. One of the investigators (D.R.H.) initially reviewed all of the hospital and nursing records and demographic information. The analysis was limited to this period when nine individuals were identified with PGS. We are unable to speculate as to whether the incidence of this adverse effect would be different at present. However, this potential serious AE associated with IV PHT therapy was well described and characterized before August 1991 to October 1991.⁷⁻¹³ The pharmacokinetics and clinical use of IV PHT was presented in the 1970s.¹⁴

The constituents associated with IV PHT remain a concern. The drug is weakly acidic and poorly soluble at neutral pH. Sodium hydroxide is added to raise the pH of the solution. Propylene glycol and ethanol are added to enhance solubility. These agents are all highly irritating to soft tissues.^{7,15,16}

2) We agree that PGS may also be avoided by using an alternative antiepileptic drug (AED). The purpose of our study was not to evaluate the rationale use of IV PHT or fosphenytoin. Other AEDs may also be associated with toxicity when administered parenterally: sedation, hypotension, and respiratory depression related to benzodiazepine or barbiturate therapy.

3) We appreciate the observations of Drs. Coplin et al. concerning two recent studies that compared IV PHT and fosphenytoin. The first work had a different purpose than our analysis. Marchetti et al. examined the "pharmacoeconomic evaluation" of hydantoin therapy in the emergency room. The second study apparently has not yet been published in manuscript form.⁶

4) Finally, our study was not intended to determine the economic impact of fosphenytoin versus IV PHT. A comment regarding this pharmacoeconomic decision was only made in the accompanying editorial.

Terence J. O'Brien, Gregory D. Cascino, Elson L. So, Debra R. Hanna, *Rochester, MN*

Reply from the Authors: Coplin et al. cite a pharmacoeconomic study⁵ and suggest that it should be ignored because it did not include cases of PGS. However, the point of this study⁵ is the large economic advantage of fosphenytoin over phenytoin because fosphenytoin reduces the risks of common side effects such as hypotension and IV site reactions. The issue of what pharmacy committees should consider is indeed^{5,17} central to this discussion. Preoccupation with acquisition cost of a medication can lead to false economy. The key issues are total cost of treating a patient with status epilepticus and patient satisfaction. There is evidence that fosphenytoin is superior to phenytoin for both.

Thomas R. Browne, MD, *Boston, MA*

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Correction

In the article "Bilineal transmission in Tourette syndrome" by Hanna et al. (1999;53:813-818), references 25 through 41 cited in the text did not correspond with the correctly numbered entries 25 through 42 in the reference list. Reference 25 alludes to The Tourette Syndrome Association International Consortium on Genetics; all subsequent references should have been renumbered accordingly, and reference 42 should have been cited. A corrected version of the article appears on the *Neurology* website (www.neurology.org). The publisher apologizes for the error. Additionally, Dr. Hanna's current address is New Jersey Neuroscience Institute at JFK Medical Center, 65 James Street, Edison, NJ 08818.

Correction

In the article "Stroke and intracranial venous thrombosis during pregnancy and puerperium" by Lanska and Kryscio (1998;51:1622-1628), the risk of stroke per 100,000 deliveries listed in table 3 (page 1627) should have been given as follows (with the number of patients with stroke in the sample given in brackets):

Cannel and Bottrell, 1956	62.5 [15]
Fliegner et al., 1969	12.1 [17]
Minielly et al., 1979	4.0 [2]

The author apologizes for the errors.

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