The spectrum of presentations of venous infarction caused by deep cerebral vein thrombosis

To the Editor: Van den Bergh et al.1 illustrated important features related to cerebral venous thrombosis (CVT) and specifically deep cerebral venous thrombosis (DCVT). Their four cases occurred in women. CVT is more common in women, and DCVT has a female to male ratio of 8.3:1. All women were taking oral contraceptives (OCP). It has been shown that OCP, even at low doses, increases the risk of CVT. In the presence of congenital thrombophilia, this risk is 100 times higher.2 Diagnosis is difficult in DCVT because there are many clinical and radiologic presentations. DCVT should be considered in a patient presenting with headache, altered mental status, neurologic symptoms not easily localized to an arterial supply, and imaging abnormalities seen bilaterally in thalamus and basal ganglia. These areas are well perfused via small branches from both anterior and posterior circulations, so an arterial stroke is not the culprit.3,5

Zeyad Morcos, Granad Island, NE

Reply from the Authors: We thank Dr. Morcos for his interest in our article. We agree that DCVT is a diagnostic challenge; especially in the case of partial thrombosis or sufficient collateral.1 The recommendations made by Dr. Morcos are appropriate—to consider DCVT in case of headache, altered mental status, neurologic symptoms not easily localized to an arterial supply accompanied by thalamus and basal ganglia abnormalities, especially if bilateral. It is unclear whether known risk factors for CVT in general can be directly applied to DCVT, but it seems to be more common in women. However, it is difficult to establish the role of OCP usage as an additional risk factor since its use is extremely common among women in the reproductive age.4,6 The change in the sex ratio of cases of sinus thrombosis over time provides indirect evidence.

Bilateral involvement of a single cranial nerve: Analysis of 578 cases

To the Editor: We read Dr. Keane’s article with interest.1 Dr. Keane’s analysis of the inpatients he personally examined over a 34-year period at the Los Angeles County/University of Southern California Medical Center suggested that bilateral involvement of the same cranial nerve is uncommon and is usually associated with cranial nerve VI damage.

However, the most rostral of cranial nerves, the olfactory nerve, was not mentioned. Inclusion of this cranial nerve may have substantially changed his results. Bilateral cranial nerve I damage is frequently seen associated with head trauma, including up to 60% of those with severe head injury. Likewise, a variety of other neurologic conditions induce bilateral olfactory deficits, including tumors, epilepsy, demyelinating disorder, degenerative disorders including Parkinson’s disease and senile dementia of the Alzheimer’s type, and migraine.1,2

Furthermore, inclusion of this cranial nerve would have markedly changed his results because, based on demographics alone, cranial nerve I dysfunction would have been substantial. It is estimated that half of those over the age of 65 and three-quarters of those over the age of 80 have a reduced ability to smell. Furthermore, many medications used in the treatment of neurologic conditions may have also been anticipated to impair his patients’ olfactory ability.

The lack of inclusion of cranial nerve I in Dr. Keane’s report highlights the widespread practice of overlooking cranial nerve I in the neurologic examination. In a retrospective study of 94 neurology inpatient consultations recorded in the hospital charts, only four had cranial nerve I testing (and those were described as “WNL”).4 A myriad of neurologic conditions manifest bilateral cranial nerve I dysfunction, and discovery of such loss is important for safety and quality of life.3

Alan R. Hirsch, MD, Stephanie Fulton, Thomas L. Wilding, Frances Groen, Chicago, IL

Reply from the Author: I agree with the authors on the importance of testing the olfactory nerve. I hope that their letter will be more persuasive than my harangues to the residents that the cranial nerves do not begin with II.

James R. Keane, Los Angeles, CA

References
Addendum to assessment: Prevention of post-lumbar puncture headaches: Report of the TTAS of the AAN

To the Editor: We read with interest the report of the Therapeutics and Technology Assessment (TTA) Subcommittee of the AAN providing an addendum to the assessment on the prevention of post-lumbar puncture headaches (PLPHAs) following diagnostic LPs. We were surprised that a consensus was reached for a Level A recommendation. Only one Class I article was cited.2

In the Strupp et al. study, 306 patients were allocated randomly to the “atraumatic” vs “traumatic” needle, yet 230 are evaluated, representing a drop-out rate of 25%. Of the 76 drop-outs, 25 did not return the evaluation sheet. Since the Subcommittee’s recommendation includes a mandate to enact widespread educational strategies to impact neurologic practice, we think an intention-to-treat analysis that incorporates all randomized patients would be important.

When further assessing the Strupp et al. article, the control event rate of 24% vs experimental event rate of 12% translates to a relative risk reduction of 50% and absolute risk reduction of 12% (NNT = 8.3). However, the CI calculates to 0.12 ± 0.1 (i.e., an absolute risk reduction of 0.02 to 0.22).

The new conclusion—now also one study providing Class I evidence in a patient population undergoing diagnostic LPs with a 22-gauge needle supports the use of an atraumatic spinal needle to reduce the frequency of PLPHA—is unlikely. Additionally, the studies leading to the addendum do not provide data higher than Class II evidence addressing other relevant primary outcomes (e.g., occurrence of back pain, technical variables between the two procedures).

We question the new conclusion that supports the use of an atraumatic spinal needle to reduce the frequency of PLPHA, and the recommendations to develop and disseminate standardized training materials for practitioners, and to track acceptance and implementation within the neurologic community.

Phillip L. Pearl, William M. McClintock, Washington, DC

Reply from the Authors: We thank Drs. Pearl and McClintock for their comments and appreciate this opportunity to respond. Pearl and McClintock state that 306 patients were randomized. The authors of the original article2 state that 51 patients did not meet the inclusion criteria and were not randomized. Therefore, 255 subjects were randomized. Of the randomized patients, 25 did not return the evaluation sheet—12 from the traumatic group and 13 from the atraumatic group. The 230 patients who returned the evaluation sheets were equally divided and the results for them are reported using intention-to-treat analysis. A 10% drop-out rate is acceptable and does not change the evidence class.

We agree with Pearl and McClintock that the number needed to treat to prevent one PLPHA by using a 22-G atraumatic needle rather than a 22-G traumatic needle, based on the article in question,2 is eight, and indicated this in the Discussion. We agree also that a reduction from 24% to 12% represents a relative risk reduction of 50% and an absolute risk reduction of 12%. We elected to present the information only in terms of numbers needed to treat, because we consider that number to be easier to understand than RR or ARR.

Pearl and McClintock state that the CI on the absolute risk reduction of 12% is 2% to 22%, without providing the basis for their statement. If they are correct, the best estimate for the absolute risk reduction remains 12%; eight is the most likely estimate of the “number needed to treat,” and the likelihood that the true number is greater than eight is the same as the likelihood that it is smaller than eight.

The original assessment and the addendum discussed technical aspects within the Discussion. The presence of a learning curve to the use of a new technology is not considered, in general, a “primary outcome” of the use of that technology. Pearl and McClintock suggest also that the occurrence of back pain should be considered an additional relevant primary outcome. We point out that there can be only one primary outcome, while recognizing the need to be aware of secondary outcomes that might detract from the value of benefits measured within the primary outcome.

The decision for a Level A recommendation was based on available evidence for post-LP headache. It took into consideration not only the new (2001) Class I evidence in diagnostic LPs, but also the Class I evidence in spinal anesthesia studies, all pointing to the reduction in the frequency of PLPHA by using non-cutting needles.

The recommendation to develop training materials and track acceptance are consistent with the mission of the AAN to serve its constituent members as they, in turn, serve patients with neurologic diseases. We stand by our original conclusions and recommendations.

Considering Drs. Pearl and McClintock’s affiliation, we point out that our recommendations pertain to the adult population, in which there are high quality data, and make no comments about the pediatric population.

Carmel Armon, Randolph W. Evans, MD, for the Therapeutics and Technology Assessment Subcommittee, Springfield, MA

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References

Camptocormia: Pathogenesis, classification, and response to therapy

To the Editor: Azher et al. concluded that of 16 patients diagnosed with camptocormia, 11 developed it in association with Parkinson disease (PD). Four had dystonia and one had Tourette syndrome. However, they did not report or perhaps did not perform electrodiagnostic testing and more specifically needle electromyography (EMG) examination of the thoracic paraspinal muscles in the individuals with isolated camptocormia and cervical paraspinal muscles in those who also manifested head drop.

The authors noted that no specific neuroimaging abnormalities were seen except for a thoracic syrinx in one patient. They did not report or did not perform thoracic or cervical spine MRI or CT imaging in each of the 16 patients and did not specifically remark about the signal characteristics of the extensor muscles in any case. These are significant limitations of their study.

The authors’ reference in their Discussion to previous studies demonstrating that thoracic extensor myopathy can cause camptocormia and one study of four patients with PD and camptocormia caused by this disorder. This mirrors our experience in patients with camptocormia including those with PD and other movement disorders. A thorough evaluation that includes nerve conduction study, repetitive stimulation, EMG of limbs and involved extensor muscles, MR imaging of the spine with attention not only to bony and neural elements but also the signal characteristics of the paravertebral muscles, and possibly muscle biopsy of limb or paravertebral muscle often uncovers a neuromuscular cause.

With isolated head drop, the most common neuromuscular causes we have encountered are isolated cervical extensor myopathy, inclusion body myopathy, myasthenia gravis, and amyotrophic lateral sclerosis (ALS). For those with isolated camptocormia, the most common neuromuscular causes we have encountered are isolated thoracic extensor myopathy and ALS. For those with both the most common causes we have encountered are isolated extensor myopathy (cervical and thoracic) and ALS.

It is implicit that patients with PD or other movement disorders who develop camptocormia, head drop, or both as a result of a neuromuscular disorder will not respond to Sinemet or dopamine agonists nor will they respond to botulinum toxin of anterior neck or abdominal musculature. Camptocormia should not be assumed to be caused by a movement disorder until neuromuscular causes are excluded.

Leo F. McCluskey, Philadelphia, PA

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Marchiafava–Bignami disease: Diffusion-weighted MRI in corpus callosum and cortical lesions

To the Editor: Ménégon et al. recently reported abnormalities on diffusion-weighted MRI (DWI) in a series of six patients with Marchiafava–Bignami disease (MBD).1

Partial callosal signal abnormality is common on FLAIR and T2-weighted MRI in past reports.2,3 In this study, DWI lesions involved the entire corpus callosum (CC) in all patients, prompting the authors to suggest that complete affection of the CC may be obligatory in MBD. Although sensitivity of DWI is likely superior to conventional MRI, this hypothesis appears questionable on the background of histopathologic results reporting the sparing of callosal areas from demyelination or necrosis4 and recent studies showing partial involvement on both conventional MRI and DWI.1,5 Moreover, Ménégon et al. reportedly acquired conventional and DWI images in axial slices only, an important limitation for comprehensive evaluation of the entire CC.

The authors proposed that markedly reduced callosal apparent diffusion coefficient (ADC) may indicate poor prognosis, which contradicts recent reports.2 A prospective, multicenter MRI study including sagittal imaging may provide the most comprehensive results on the prognostic value of DWI in MBD. Correlative studies establishing a link between ADC changes and histologic findings in MBD would be important but difficult due to the lack of an appropriate animal model and decreasing autopsy rates in this rare disorder.

The lateral-frontal predilection of cortical diffusion abnormalities1,5 is consistent with the autopsy finding of Morel’s laminar sclerosis in the same areas.6,7 Nevertheless, evidence that diffusion abnormalities correspond to this highly specific form of cortical injury is insufficient as comparable DWI lesions consist of cytotoxic edema have also been demonstrated following cerebral hypoxia, prolonged seizure activity, or in Wernicke-Korsakoff disease, which may accompany severe cases of MBD.1,5

The discrepancy between MRI studies suggesting poor prognosis in cases with cortical involvement1,5 and autopsy series reporting Morel’s laminar sclerosis predominantly in cases with a mild course1 also stresses the need for direct comparison of cortical diffusion abnormalities with histopathologic findings. Assuming that the observed cortical MRI lesions reflect a pathology corresponding to Morel’s laminar sclerosis, demonstration of the latter in the acute stage would indicate that cortical pathology in MBD may not result from secondary cortical neuronal degeneration due to callosal lesions as proposed earlier.4

Reply from the Authors: We thank Drs. Khaw et al. for their comments on our article where we describe MRI abnormalities in the sub-acute phase of MBD using conventional and DWI in axial and sagittal planes.2 We observed diffuse corpus callosum abnormalities in all the cases but never suggested the complete lesion of the CC as a new mandatory diagnosis criteria of MBD.

The low number of subjects, the anatomic-pathologic data, and the recent descriptions of partial corpus callosum diffusion hyper-intensities in MBD do not allow us to draw this conclusion.2 Our results also suggested a relationship between the values of the ADC/NAWM ratio and the long-term prognosis but with possible bias related to the low number of subjects.

The gold standard for such a study would be to compare the MRI data to the brain anatomic-pathologic lesions observed in subjects who died during follow-up. This would also answer questions concerning the molecular basis of the cortical lesions observed in our patients. Similar cortical lesions to those observed in our study have been reported in one case without history of seizure or cerebral anoxia. As in our report, this suggests a possible primary cortical involvement in MBD.4

Two arguments promote the hypothesis of poor prognosis associated with cortical lesions: the poor clinical outcome of patients in Johkura et al. study5 and of the three patients in our study and the high frequency of cortical lesions in autopsy series.5 We agree with the authors that a multicenter MRI study using the uniform modalities of DWI acquisition and analysis would provide more comprehensive results on the prognosis value of MRI in the early phase of MBD.4

P. Ménégon, I. Sibon, C. Fachai, J.M. Orgogozo, V. Dousset, Bordeaux, France

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References

Primary central nervous system lymphomas (PCNSL): MRI response criteria revised

To the Editor: Küker et al. propose revised response criteria for primary CNS lymphoma (PCNSL) after completion of tumor-directed therapy.1 Of 68 patients with contrast enhancing lesion after methotrexate (MTX) therapy, they identified four with small lesions (5 mm in diameter or “bandlike”) in the area of primary tumor, hemorrhage, biopsy, or infection. The lesions were not further treated and did not show any change at 9, 24, 32, and 54 months follow-up.

Such lesions may reflect “unconfirmed” complete remissions (CRu) and not residual tumor, as proposed by an international workshop on standards of baseline evaluation and response criteria for PCNSL.2 The limits of residual lesion size as proposed by Küker et al. are arbitrary. In their retrospective analysis, they do not include information on the 64/111 cases who met the criteria of partial remission (PR) and how decisions for either salvage therapy vs waiting were made in these cases.

In a series of 65 patients treated with a combined systemic and intraventricular chemotherapy, patients who met the criteria of a PR were not treated with salvage therapy irrespective of residual tumor size.3 From these cases (plus another 23 patients treated with the same regimen), we identified seven cases where the following criteria: completion of therapy, residual contrast enhancing lesion, no low grade lymphoma, and follow-up for at least 1 year. Among these, four matched the revised response criteria as proposed by Küker et al. and two of them showed an early relapse 3 and 6 months after completion of therapy. The other three showed a residual contrast enhancing lesion, all located within the primary tumor region, measuring 8 mm. These patients showed a progression free survival of 20+, 29, and 84+ months. Two of the patients showed spontaneous disappearance of the lesions and the other a partial involution.

We conclude that categorizing patients’ responses according to these revised criteria is not predictive of their individual course after therapy. Therefore, patients with CRu should be carefully observed with serial scans.2

Uwe Schlegel, Annika Jürgens, Hendrik Pels, Bochum, Germany

Reply from the Authors: We read Schlegel et al.’s letter with interest and thank them for the additional data. We agree with their final statement that all patients with PCNSL should be closely monitored. However, surveillance scanning cannot be restricted to patients classified as complete response (CR) with small residual lesions but has to include patients with CR as defined by the original MacDonald criteria. These patients have also been shown to relapse early after CR.

In the NOA-03 trial1 of 11 patients without any residual contrast enhancing lesion relapsed within the first 6 months after the completion of therapy. It is plausible that Schlegel et al.’s patients who relapsed early after unproven CR did so at the site of the contrast-enhancing residual. It is not surprising that relapses may occur in patients with residual lesions, as in those without. The crucial point about the new classification scheme is that this is not even most frequently the case. In our treatment trial, all patients with residual contrast-enhancing lesions who received further therapy several were treated unnecessarily.

This point is confirmed by Schlegel et al., who describe three patients with even larger lesions that did not progress over a long time in spite of a lack of treatment. The suggested new criteria for modified CR may even have to be expanded if more data become available.

As in all classifications, sensitivity has to be balanced against specificity, which in this case does seem to advocate a careful approach. Further work and the application of more sophisticated imaging modalities such as PET may be necessary to better define the presence of residual viable tumor tissue.

W. Ku ë er, Ulrich Herrlinger, Oxford, UK

References

Use of serum prolactin in diagnosing epileptic seizures: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

To the Editor: The AAN Therapeutics and Technology Assessment Subcommittee recently reported on the use of serum prolactin (PRL) in differentiating epileptic seizures from nonepileptic seizures (NES).1 The authors addressed two main concerns: whether serum PRL is useful in distinguishing individual epileptic seizures from nonepileptic seizures (NES); and whether serum PRL is useful in distinguishing individual epileptic seizures from other paroxysmal neurologic conditions.

The diagnosis and treatment of patients with psychological NES has long confounded neurologists, psychiatrists, and emergency department physicians. Currently, no randomized double blind, placebo controlled trial (RCT) has been completed for NES.2 A common concern with diagnoses in the Diagnostic and Statistical Manual of Mental Disorders—IV is that psychiatric diagnoses have no physiologic correlates. While aggregate data on depression and anxiety states have revealed alterations in the HPA axis, these findings are not applicable to the diagnosis of these with major depressive disorders or post traumatic stress disorder. However, NES are the exception to this rule, where they do so.

Trimble first showed that generalized tonic clonic seizures (GTC), but not NES, raised serum PRL.3 Pooling the available data of the 10 studies of the inclusion criteria, the subcommittee authors found a sensitivity of 60% for GTC and 46% for complex partial seizures (CPS), and a specificity of ~96% for both. They found a positive predictive value of 93 to 99%.

Cragar et al. similarly found lack of PRL elevation has an average 89% sensitivity to psychological NES.4 Clinically, this translates into a strong confirmation of a diagnosis of epileptic seizures when an elevated PRL is found in patients with GTC or CPS-like events suspected of being NES. The authors concluded that serum PRL rise is probably a useful adjunct to differentiate GTC or CPS from NES.

This report is timely in light of the difficulty in management of patients with NES. Harden et al. found that neurologists and psychiatrists differ significantly in their opinion, with psychiatrists believing video-EEG was inaccurate in NES diagnosis, compared to neurologists.5

The committee from the recent NINDS/NIMH/AES sponsored NES Treatment Workshop is preparing a multi-site RCT for NES treatment. The AAN Subcommittee’s report on PRL as an adjunctive diagnostic measure for seizures bolsters the validity of the video-EEG established NES diagnosis. Hopefully this will increase the confidence of psychiatrists, psychologists, and other providers in treating patients with NES.

W. Curt LaFrance, Jr., MD, Providence, RI

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Reply from the Authors: We are grateful to Dr. LaFrance for his comments about our prolactin therapeutics and technology assessment article. As he points out, it was a critical compendium of prior work, and we prepared it in part because this potentially useful physiologic marker has never really “caught on” in clinical practice. Although the test can have excellent specificity and positive predictive value, this is true only in a setting of high suspicion for epileptic generalized tonic-clonic or complex partial seizures, and in the absence of several confounding factors.

Interpretation of the assay therefore is far from automatic, and still requires keen clinical judgment.

David Chen, Yuen T. So, MD, PhD, Robert S. Fisher, MD, PhD, Stanford, CA

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Correction

Plaque density on CT, a potential marker of ischemic stroke

In the article, “Plaque density on CT, a potential marker of ischemic stroke” (Neurology 2006;66:118–120) by J.-M. Serfaty et al., table 2 contains significant errors. The accurate table is as follows:

Table 2 Association between symptoms and plaque characteristics

<table>
<thead>
<tr>
<th>Soft-tissue density in HU</th>
<th>Symptomatic, no. (%)</th>
<th>Asymptomatic, no. (%)</th>
<th>Odds ratio for symptoms (95% CI)</th>
<th>Symptomatic, no. (%)</th>
<th>Asymptomatic, no. (%)</th>
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<tr>
<td>49&lt;TD&lt;96</td>
<td>1 (3.3)</td>
<td>25 (24.5)</td>
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<td>35&lt;TD&lt;49</td>
<td>5 (16.7)</td>
<td>22 (21.6)</td>
<td>5.7 (0.6–52)</td>
<td>5 (20.8)</td>
<td>16 (25.0)</td>
<td>4.7 (0.5–45)</td>
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<td>23&lt;TD&lt;35</td>
<td>8 (26.7)</td>
<td>17 (16.7)</td>
<td>11.8 (1.3–102)</td>
<td>7 (29.2)</td>
<td>12 (18.8)</td>
<td>8.8 (0.9–81)</td>
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<tr>
<td>−8&lt;TD&lt;23</td>
<td>12 (40.0)</td>
<td>16 (15.7)</td>
<td>18.8 (2.2–158)</td>
<td>8 (33.3)</td>
<td>8 (12.5)</td>
<td>15 (1.6–142)</td>
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<tr>
<td>Calcified plaques*</td>
<td>4 (13.3)</td>
<td>22 (21.6)</td>
<td>4.5 (0.5–44)</td>
<td>3 (12.5)</td>
<td>13 (20.3)</td>
<td>3.5 (0.3–37)</td>
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</table>

Each quartile of soft-tissue density and the excluded calcified carotid group (Reader 1): p = 0.004 (stenosis >50%) and p = 0.04 (stenosis >70%). Similar results were obtained for Reader 2.

* Two patients could not be included in this group as no reliable clinical information could be retrieved.

TD = tissue density.

References

Plaque density on CT, a potential marker of ischemic stroke

*Neurology* 2006;66;1288
DOI 10.1212/01.wnl.000022497.71324.e3

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