Correspondence

Abnormal vergence with upper brainstem infarcts: Pseudoabducens palsy

To the Editor: We read with interest the article by Pullicino et al.[1] on seven patients with pseudoabducens palsy. As all their patients showed an associated upgaze palsy, the authors emphasized the importance of a localization close to the riMLF for the production of pseudoabducens palsy. Regarding the role of the thalamus in vergence control, particularly in association with the production of esotropia, the authors argue that because localization in previous reports of "thalamic esotropia" was based only on axial scans without coronal views,[2] it still remains to be established beyond doubt that a lesion restricted to the thalamus can produce esotropia or pseudoabducens palsy.

While the article by Pullicino et al. was in press, we reported a patient with selective loss of vergence control, consistent with the clinical findings of bilateral pseudoabducens palsy.[3] Unlike previous reports, upgaze palsy was absent in our patient and MRI showed a symmetric paramedian thalamic infarction without midbrain lesion, documented by axial and coronal images. Our findings clearly demonstrate that exclusive paramedian thalamic lesions can produce esotropia or the clinical symptoms of pseudoabducens palsy. Like Pullicino et al. we suggest that these symptoms are caused by interruption of inhibitory convergence pathways as they traverse the paramedian thalamus.

Gerald Wiest, *Los Angeles, CA*

To the Editor: We read with interest the report of seven patients with pseudoabducens palsy and convergence-retraction nystagmus from basilar artery infarction in the midbrain-diencephalon junction.[1] The authors list a differential diagnosis of this presentation as latent esotropia, Duane's syndrome, voluntary convergence spasm, and divergence paralysis. We report a case of deep cerebral venous thrombosis (DCVT) presented with abnormal vergence.

Our patient was a 33-year-old right-handed male smoker who developed sudden onset vomiting, lethargy, dysarthria, right hemiparesis, and hemiataxia. He was initially hypotensive to 90/40, but with intravenous dopamine his blood pressure improved to 140/80 and his level of alertness and right hemiparesis and hemiataxia improved. On examination his pupils were 4 mm and reactive to accommodation but not to light. Visual fields were full. He had esotropia when alert and downward deviation of the eyes when lethargic. He demonstrated slowed but full abduction of both eyes with horizontal saccades but had paralysis of upgaze. Bell's phenomenon was noted to be absent. Upon attempted upgaze there was convergence-retraction nystagmus. There was no lid retraction or ptosis.

Initial head CT showed increased density in the torcula and at the junction of the straight sinus and vein of Galen (not shown). Angiogram showed a filling defect in the vein of Galen-straight sinus junction that was suspicious for thrombosis (not shown). No arterial abnormality was found. Because the patient was improving on intravenous heparin, no local thrombolytics were administered. MRI showed a small FLAIR hyperintensity in the left dorsal midbrain and diencephalon (figure). After 48 hours of anticoagulation, the syndrome resolved completely and the patient made a full recovery. No cause for the venous thrombosis was found despite intensive testing for prothrombotic state.

Our case shows that DCVT can cause pseudoabducens palsy and convergence retraction nystagmus as part of Parinaud syndrome.[4] We believe that DCVT should be on the differential diagnosis of this ocular motor syndrome, and we suggest that a negative arterial workup in the setting of sudden onset should prompt an intensive search for venous thrombosis. DCVT is a difficult diagnosis to ascertain,[5] but is important to consider, as treatment with anticoagulation may be beneficial.[6]

Richard Bernstein, MD, PhD, *San Francisco, CA*;
Gary L. Bernardini, MD, PhD, *Albany, NY*

Reply from the Authors: We thank Wiest for his comments and for drawing our attention to his case report.[3] This report of a patient with esotropia and bilateral pseudosixth palsies resulting from bilateral paramedian thalamic infarction is important. The infarction appears to be completely restricted to the thalami on a coronal T2 MRI scan and suggests that injury to a descending inhibitory vergence pathway in the thalamus is sufficient to produce a pseudosixth palsy.

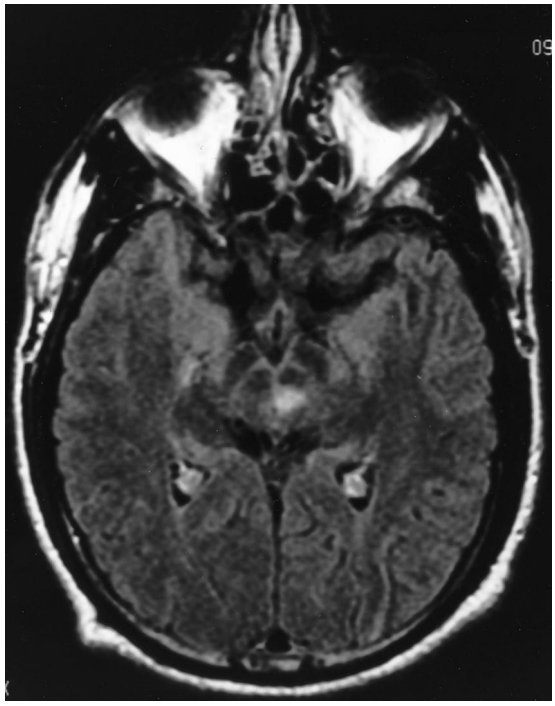

Figure. Fluid attenuated inversion recovery image showing hyperintensity in (A) the left dorsal midbrain and (B) the diencephalon of a patient with vein of Galen and straight sinus thrombosis.

It is interesting that the thalamic infarcts in the Wiest et al. patient were also associated with a loss of convergence. Convergence is not necessarily impaired in the presence of a pseudosixth palsy because convergence was intact in our case 5 who had esotropia, pseudosixth palsy, and convergence-retraction nystagmus with a midbrain/diencephalic infarct.[1] This suggests that it may be too simplistic to ascribe both loss of convergence and signs of "convergence excess" (esotropia, pseudosixth palsy) to a lesion of a single descending vergence pathway.

Despite the presence of other signs of "convergence excess," Wiest et al.'s patient did not have convergence-retraction nystagmus. This is in keeping with our suggestion that a lesion close to the interstitial nucleus of Cajal is necessary for the production of convergence-retraction nystagmus.

Bernstein and Bernardini's interesting case illustrates that signs of "convergence excess" may point to midbrain/diencephalic dysfunction secondary to deep venous thrombosis. This is important because the signs are potentially reversible with anticoagulation, as in their patient.

Patrick Pullicino, MD, PhD, Norah Lincoff, MD, Bradley Truax, MD, *Buffalo, NY*

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A 1-year controlled trial of acetyl-L-carnitine in early-onset AD

To the Editor: I read with interest Thal et al.'s article on the use of acetyl-L-carnitine in early-onset dementia of the Alzheimer type.[1] However, I am puzzled by their classification of errors on the Folstein Mini-Mental State Examination (MMSE).[2]

They state that attentional differences accounted for better performance in the treated completer sample. It is, of course, surprising that a bedside test of attention would distinguish individuals with early AD. Unlike "attentional" or "intentional" dementias[3] that may be present with isolated frontal lobe abnormalities, dementia of the Alzheimer type rarely presents with distractibility, motor impersistence, defective response inhibition, or bradyphrenia/bradykinesis. "Cognitive" abnormalities such as acalculia, however, are a common early sign of AD, and checkbook or bill-paying errors are often elicited on initial history.

Although accurate serial seven subtractions require good vigilance and working memory, errors are not reliable evidence of inattention in normal subjects because they are influenced by calculation ability and a number of other factors.[4,5] Thus I would wonder how the authors can be sure that superior "serial 7s" in the treated group did not reflect better-preserved calculation ability. Preserving mathematical skills could improve patients' functional independence and quality of life, though further study and correlation with instrumental activities of daily living are needed.

How we classify errors on mental status testing is important because it implies impairment in specific neuroanatomic systems. Therefore, calling figure copying "praxis" can also be misleading unless the specific term, "constructional praxis," is used to distinguish it from evaluation of skilled, learned purposive movements.

Anna M. Barrett, MD, *Hershey, PA*

Reply from the Authors: I thank Dr. Barrett for her comments regarding the report in which we demonstrated that acetyl-L-carnitine in early-onset AD resulted in less deterioration on the attention item on the MMSE.[1] In the study we noted a trend towards less deterioration on the MMSE which reached significance in the completer population. Because a similar finding had been noted in a previous study, an item analysis was carried out. In any given trial, the total amount of data available is limited. Nevertheless, in both the trial reported here[1] and in the Spagnoli trial,[6] less deterioration was noted on a putative measure of attention. Although calculation may be influenced by many factors, spelling the word "world" backwards, as done in this study, is a reasonably pure attentional task. Unfortunately, other more specific tasks of attention were not available from this database. Thus, the conclusion was tentatively drawn that acetyl-L-carnitine might act by improving attention, a function not adequately measured on the Alzheimer's Disease Assessment Scale–Cognitive Component. Similar effects have also been noted in other ALCAR trials including less decline on a visual search of digit task[6] and less decline in timed cancellation tasks and digit span.[7] Thus, the overall weight of the evidence does support the contention that treatment with acetyl-L-carnitine is associated with less decline in attention.

Leon J. Thal, MD, *La Jolla, CA*

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Response of leptomeningeal metastases from breast cancer to hormonal therapy

To the Editor: Boogerd et al. describe two patients with breast cancer, neurologic signs and symptoms consistent with leptomeningeal metastases (LM), and CSF cytology positive for tumor cells who were treated with oral tamoxifen.[1] Both patients had durable clinical responses notwithstanding the decision to forgo intra-CSF chemotherapy [I-CSF]. Several issues relevant to the treatment of LM were discussed and warrant comment.

First, the evaluation of patients with LM in whom treatment is pursued usually entails imaging of the entire neuraxis because LM often coexists with bulky metastatic disease. Bulky subarachnoid or parenchymal disease and clinically symptomatic sites of disease are best managed with radiotherapy.

Second, outcome of patients treated with LM is clearly dependent upon a number of patient characteristics, including tumor histology.

Third, the best treatment for LM remains ill-defined. However, based on four Phase 3 randomized clinical trials of LM, standard therapy utilizes both radiotherapy and I-CSF.[2–5] Pending a randomized clinical trial comparing I-CSF to systemic hormonal/chemotherapy, I believe a primary role for systemic therapy remains speculative and with meager evidence-based data. However, I do recognize the limited palliative role of I-CSF and encourage further randomized clinical trials utilizing alternative drug delivery therapies.

Fourth, defining response to treatment in patients with LM is problematic. I concur that clinical disease status is extremely important in defining response to treatment, and time to neurologic disease progression best captures this clinical outcome.[4,5] Overall survival in patients with cancer is determined by a number of interacting processes such that success of treatment directed at CNS metastases is best defined by maintenance of neurologic status.

Finally, the issue of treatment-related toxicity is relevant because the majority of patients with LM have advanced systemic disease, and treatment of LM is therefore palliative. I-CSF results in both acute and delayed neurotoxicity. Although acute toxicity, manifested as aseptic meningitis, complicates one third of all treatment cycles, very few patients require hospitalization because oral agents easily manage this complication. Delayed toxicity caused by LM-directed therapy manifesting as a toxic leukodystrophy is in my experience infrequent [less than 3% of patients]. I agree that improved outcome and prolonged survival would result in a higher incidence of delayed neurotoxicities similar to that observed in the treatment of brain tumors. However, I believe that delayed neurotoxicity primarily results from radiotherapy and not I-CSF. Nonetheless, radiotherapy is an integral component in the treatment of LM, and its use should be judicious.

Marc C. Chamberlain, MD, *Baldwin Park, CA*

Reply from the Authors: We would like to comment on the points that Chamberlain raises in his letter. First, imaging of the entire neuraxis is useful if it is clinically relevant. Bulky metastatic disease will not respond to I-CSF chemotherapy. In patients treated with I-CSF chemotherapy, bulky disease can be treated with local radiotherapy. However, systemic therapy aimed to treat LM will also be active in bulky metastatic disease. So, imaging of the entire neuraxis for asymptomatic bulky disease is clinically irrelevant in patients treated with systemic therapy. We agree with Chamberlain that symptomatic bulky disease is preferably managed with local radiotherapy.

Second, indeed the outcome of patients with LM from breast cancer depends on a number of patient and tumor characteristics. As stated in our article, the positive receptor status and symptoms confined to the spinal level presumably contributed to the favorable course of disease in our patients.

Third, it is not possible to define the best treatment of LM from data in literature. Randomized trials of LM performed so far[2–5] only compared different agents for I-CSF treatment and do not imply that I-CSF treatment should be preferred to non-I-CSF treatment. Results of two clinical nonrandomized studies[6,7] showed similar responses to treatment and survival between patients with I-CSF and those without I-CSF treatment. However, non-I-CSF treatment significantly reduced the rate of treatment-related complications.[7]

Fourth, we agree with Chamberlain that response to treatment of LM is best defined by the neurologic disease status. Our patients showed a neurologic response of at least 12 months after oral hormonal treatment.

Finally, results of clinical studies in LM show a large variation in reported complications of treatment. In our experience, intraventricular MTX administered at low doses based on CSF MTX levels, without standard cranial irradiation, causes serious leukoencephalopathy in half of the long-term survivors.[6] In addition, we have observed histopathologically proven leukoencephalopathy after I-CSF MTX as single treatment modality.[8] So, in our opinion delayed neurotoxicity after treatment of LM is primarily related to I-CSF therapy, with radiotherapy as an important additional factor. For these reasons, combination of I-CSF treatment and radiotherapy as standard therapy for LM might be questioned. In selected cases systemic chemotherapy and even hormonal therapy might be considered as the primary treatment of LM from breast cancer.

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Correction

Treatment of agitation in AD: A randomized, placebo-controlled clinical trial
In the article "Treatment of agitation in AD: A randomized, placebo-controlled clinical trial" by Teri et al. (*Neurology* 2000;55: 1271–1278), the Alzheimer's Disease Cooperative Study was listed in the footnote and not the author line. The publisher apologizes for this error.

To: Treatment ofagitation in AD: A randomized, placebo-controlled clinical trial

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