MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy

To the Editor: Pope et al. retrospectively reviewed 14 patients with recurrent high-grade gliomas (HGG) treated with chemotherapy and bevacizumab.[1] Fifty percent of patients responded to treatment determined by post-treatment MRI. Several aspects of this report merit commentary. All patients in the study previously failed primary therapy and one prior salvage therapy. The number of patients treated within 3 months of radiotherapy was unclear. Though the protocol specified at least 4 weeks elapsed since administration of radiotherapy, it is recognized that early delayed radiotherapy changes seen on MRI may simulate tumor progression and resolve over time.[2] The performance of MRI to assess response to therapy in patients with recurrent HGG is customarily performed every 2 months and coordinated with chemotherapy cycles. In this report, first post-treatment MRI appears desynchronized with chemotherapy administration. As response rates were based on first post-treatment MRI, response appears not to be bevacizumab dose dependent.

To this author's knowledge, there has not been a single agent trial of bevacizumab for recurrent HGG though trials in other solid cancers indicate a less than 10% single agent response rate. The rationale for combining bevacizumab with CPT-11 was not mentioned in this article. A number of reports evaluating CPT-11 as a single agent for recurrent glioblastoma have concluded the agent has little efficacy.[3] The first report by Stark-Vance indicating response to the combination of bevacizumab and CPT-11 for recurrent HGG was not cited.[4]

The durability of response was also not reported. Clinical trials in recurrent HGG report response duration by overall survival, time to tumor progression, and 6-month progression free survival. Fifteen percent 6-month progression free survival for patients with recurrent glioblastoma is used as the standard by which new trials are compared with respect to efficacy.[5]

A variety of methods have been utilized to assess response to anti-angiogenic agents including dynamic contrast enhanced MRI. These methods provide proof of principle by quantifying tumor blood volume or perfusion. Pope et al. do not report whether the observed response represents an anti-angiogenic effect on tumor vasculature or an effect on blood brain barrier disruption with normalization of peritumoral edema and diminished tumor contrast enhancement.

Pope et al emphasize the complexity of treating recurrent HGG and remind neurologists that the approach to malignant gliomas continues to evolve and will increasingly utilize targeted therapies such as antiangiogenic agents.

Marc C. Chamberlain, *Tampa, FL*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: Dr. Chamberlain raises several important issues, some of which are directly addressed in our article. Our study reported the early MR imaging findings of patients with recurrent malignant glioma following chemotherapy/bevacizumab combination treatment. The study was not a clinical trial of the effectiveness of this therapy for recurrent malignant glioma. Therefore, the durability of response as measured by the length of survival, time to tumor progression, and 6-month progression free survival was not reported. When a sufficient amount of time has passed to make meaningful conclusions regarding this therapy in relationship to patient survival, we or others will report these data.

The most important question raised by Dr. Chamberlain is whether the response to chemotherapy/bevacizumab therapy could be attributed to resolving radiation changes. We do not believe this is possible. Of the 14 patients reported, all had failed prior radiation therapy. Only one patient initiated treatment within 3 months of completion of radiation therapy. The median time between completion of radiation therapy and initiating chemotherapy/bevacizumab in this patient group was 40 weeks. All patients were scanned within 45 days of treatment. In the article cited by Dr. Chamberlain,[2] only 2 of 32 patients treated for glioma showed spontaneous improvement, suggesting that even if all our patients had been treated within 3 months of radiation therapy, the MR imaging findings of our study would not be explained by radiation change.

Another important question raised by Dr. Chamberlain is whether the observed response represents normalization of the blood brain barrier, a direct effect on tumor, or a combination of the two. We were unable to fully address this issue in our report, due to the space limitations of the journal. We found that for some patients reduction of tumor bulk was clear even on the T2W images, and therefore not simply a result of changes in enhancement due to re-establishment of the blood brain barrier. However, the reduction in edema is likely related to changes in vascular permeability, as VEGF is a potent mediator of increased vessel permeability as noted in our report. We are currently analyzing data obtained from dynamic contrast enhanced MRI to further investigate the effects of chemotherapy/bevacizumab treatment on tumor hemodynamics.

Finally, we neglected to cite Stark-Vance's abstract[4] on CPT-11 and bevacizumab. We appreciate Dr. Chamberlain's remarks as they allow us to appropriately acknowledge this work.

Whitney B. Pope, MD, PhD, Tim Cloughesy, MD, *Los Angeles, CA*

Disclosure: The authors report no conflicts of interest.

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Cerebral vasculopathy with aneurysm formation in HIV-infected young adults

To the Editor: Kossorotoff et al.[1] describe cerebral vasculopathy with aneurysm of unknown etiology in two HIV-infected adults. However, both of these cases are almost certainly varicella zoster virus (VZV) vasculopathy. The second patient had recurrent zoster before developing vasculopathy. Neither zoster rash[2] nor a CSF pleocytosis[3] is always present, and the development of aneurysm in patients with VZV vasculopathy is well documented.[4,5]

Nearly all adults have serum antibody to VZV, making serum of no value in the evaluation of patients for VZV vasculopathy. Furthermore, the CSF is usually PCR negative for VZV DNA and thus of limited value in diagnosing VZV vasculopathy, unlike highly sensitive PCR testing to diagnose HSV encephalitis. In cases in which VZV DNA was absent in the CSF, the diagnosis of VZV vasculopathy was ultimately confirmed by the detection of anti-VZV IgG antibody in the CSF.[2,3] Consequently, we reviewed our virologically verified cases of VZV vasculopathy as well as those in the literature and found that the detection of anti-VZV IgG antibody in CSF is a far more sensitive test than detection of VZV DNA in CSF (manuscript submitted for publication).

Donald H. Gilden, Maria A. Nagel, MD, *Denver, CO*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Gilden and Nagel for their interesting comments, but do not share their diagnostic certainty concerning our two HIV-infected adults with cerebral vasculopathy and aneurysm formation (CVA).[1] Due to the immune system deficiency, various ubiquitous viruses such as VZV can cause vasculitis in patients with HIV. As we discussed in our article, CVA in such patients could have some link with VZV infection but this has yet to be proven.

We agree that our biological investigations for VZV in two patients were not as accurate as other published cases with cerebral vasculitis.[3] However, the etiologic diagnosis of cerebral vasculitis is one of the most challenging offered to neurologists and biology cannot be considered as the single argument for it, particularly in HIV-infected patients who are prone to cumulate several infections together. Peculiar angiographic patterns may therefore play some crucial role in the diagnosis.[6] Our goal was to warn neurologists about a particular radiologic picture.

VZV vasculopathy usually presents as a stenotic arterial disease which is either unifocal in elderly immunocompetent persons or multifocal in immunocompromised persons.[3] Exceptionally, a focal vasculopathy with aneurysm formation on the basilar artery[4] or the intrapetrosal portion of the internal carotid artery[5] can occur during VZV infection.

These patterns are distinct from the multiple aneurysms formation observed in our two patients. To our knowledge, such multiple aneurysms formation was not previously associated with any cerebral vasculopathy due to infection, except in HIV-infected children. Indeed, CVA was reported in approximately 15 young HIV-infected patients aged from 1 day to 12 years[7] but not in adults. In this condition, aneurysms are bilateral and located on Willis circle arteries. The presentation was very typical in our Patient 1 while more distal cerebral arteries were involved in Patient 2.

CVA could have some pathophysiologic links with the systemic aneurysmal vasculopathy involving arteries as large as aorta also in HIV-infected young adults, for which no relationship with VZV was suspected.[8] However, an association between CVA and systemic arterial aneurysms has not yet been reported.

Mathieu Zuber, Emmanuel Touzé, Manoëlle Kossorotoff, *Paris, France*

Disclosure: The authors report no conflicts of interest.

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REM sleep behavior disorder: A possible early marker for synucleinopathies

To the Editor: Boeve and Saper propose that REM sleep behavior disorder (RBD) be considered an early clinical marker for neurodegenerative diseases with α-synuclein aggregation,[1] a proposal advanced earlier by Boeve et al.[2]

While RBD can be a sentinel event in these diseases, it is not specific for synucleinopathy, even in the universe of neurodegenerative disorders. As noted in their editorial, RBD has been reported in patients with progressive supranuclear palsy.[3] We have followed several families in southeastern New England with Machado-Joseph disease (MJD) (SCA-3). The ataxin-3 protein which accumulates in MJD has an expanded polyglutamine domain, and is biochemically distinct from α-synuclein. In our patient population, clinical features suggestive of RBD were identified in a high proportion of affected individuals.[4] This association has been confirmed with polysomnography by Iranzo et al.[5]

Based on these findings, we suspect that RBD may be a frequent occurrence in other relatively rare diseases that do not involve α-synuclein. Moreover, the estimated prevalence of RBD in the adult population is 0.5%, which outweighs the aggregate burden of synucleinopathies.

One possible explanation for the occurrence of RBD in these distinct disorders is that it reflects degeneration or dysfunction in an anatomic network they share in common. Another possibility is that RBD may be a response to biochemical injury in a vulnerable neuronal population. Whatever the trigger, caution must be exercised in conflating the clinical phenomenon of RBD with α-synuclein pathology. They are commonly but not always associated.

Lewis Sudarsky, *Boston, MA*; Joseph Friedman, *Warwick, RI*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We appreciate the points raised by Drs. Sudarsky and Friedman in their letter regarding our editorial.[1] There are several issues relating to the diagnosis and specificity of RBD associated with neurodegenerative disease: 1) a conclusive diagnosis of RBD requires polysomnographic (PSG) proof of abnormalities in REM sleep electrophysiology and behavior[6]; 2) a conclusive diagnosis of any neurodegenerative disease requires neuropathologic proof of specific inclusions or findings and absence of other comorbid conditions identified by appropriate histologic and immunocytochemical techniques; 3) genetically identified patients with a specific non-synucleinopathy neurodegenerative disease can have concomitant Lewy body pathology[7]; 4) Lewy body pathology is often present in combination with other distinct neurodegenerative disorders; 5) neurologically asymptomatic individuals can have α-synuclein-positive pathology at autopsy[8]; and 6) the timing of RBD onset and neurologic symptom onset may have some diagnostic specificity.[9]

RBD is not specific for the synucleinopathies, and space limitations did not permit us to elaborate on RBD associated with spinocerebellar atrophy-type 3 (SCA-3) and other disorders. However, the issues described above have complicated the determination of the true frequency of RBD in the various neurodegenerative disorders. In our ongoing clinicopathologic analyses in patients with RBD associated with dementia or parkinsonism at the Mayo Clinic, 33/34 (97%) have had a synucleinopathy identified at autopsy (Boeve et al., unpublished data), but we have not specifically sought to enroll patients with RBD associated with other disorders such as SCA-3 in an autopsy program. Furthermore, the onset of RBD tends to precede the onset of parkinsonism and cognitive impairment in the synucleinopathies by years or decades[1,2,9] whereas it tends to present concurrently or years following the onset of neurologic symptoms in progressive supranuclear palsy (PSP)[3] and SCA-3.[4,5]

We agree that it is the dysfunctional neuronal network in the brainstem that is common to all patients who have RBD associated with neurodegenerative disease, and not specifically whether α-synuclein positive pathology is present. Recently, studies have identified mutually inhibitory REM-off and REM-on areas in the mesopontine tegmentum of the rat, and suggest that this represents a flip-flop switch mediating key aspects of REM sleep control.[10] Degeneration of REM-on neurons in the subcoeruleus region that are responsible for REM atonia could explain RBD. If degeneration of these neurons is confirmed in patients with RBD, elucidating the mechanisms for early selective vulnerability may offer

insights into the pathophysiology of specific neurodegenerative disorders.

Bradley F. Boeve, *Rochester, MN;* Clifford B. Saper, *Boston, MA*

Disclosure: The authors report no conflicts of interest.

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Correction

Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD

In the article "Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD" by Semrud-Clikeman et al. (Neurology 2006;67:1023–1027), the order of authors is incorrect. The author list should read as follows:

Margaret Semrud-Clikeman, PhD; Steven R. Pliszka, MD; Jack Lancaster, PhD; and Mario Liotti, MD, PhD

The publisher regrets the error.