

Editors' Note: In reference to "White matter hyperintensities on MRI in high-altitude U-2 pilots," Hellmann-Regen et al. identify potentially confounding factors, in addition to hypobaric, that are seen in military pilots, including high Gz stress and radiation exposure, and suggest a "regular pilot" control group. Author McGuire responds by sharing unpublished findings on a group of altitude-chamber technicians.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

ACUTE LATE-ONSET ENCEPHALOPATHY AFTER RADIOTHERAPY: AN UNUSUAL LIFE-THREATENING COMPLICATION

Paul J. Regal, Newcastle, Australia: Di Stefano et al.¹ reported 5 patients who developed steroid-responsive encephalopathy 9 months to 17 years after whole-brain radiotherapy for brain tumors. MRI, CSF, EEG, and other laboratory tests excluded almost all other potential causes for encephalopathy. The favorable response to IV methylprednisolone in 2–6 days further restricted the field of potential causes. The authors decided that brain biopsy, a potential gold standard, was not necessary. Brain autopsy on the 2 patients who died 2–2.5 years after autopsy was not undertaken. I wonder whether the authors estimated the denominator—the number of patients treated with whole-brain radiotherapy—to yield these 5 cases. In addition, it would be interesting to know the incidence of other forms of encephalopathy after radiotherapy. From my research in the Central Coast Australia Delirium Intervention Study—a prospective randomized controlled trial for subjects age 65+—both the informant-rated instrumental activities of daily living and informant-rated apathy evaluation score declined significantly in the days prior to delirium. Perhaps the authors could provide the cognitive scores before encephalopathy, on admission, and after recovery.

Author Response: Anna L. Di Stefano, Giulia Berzero, Enrico Marchioni, Pavia, Italy: We thank Dr. Regal for his comments. Peculiar characteristics of acute late-onset encephalopathy after radiotherapy (ALERT) syndrome are acute onset and rapid response to steroids. We agree with the value of neuropathologic findings in the setting of unusual complications of

radiation therapy. These were not available in our retrospective case series. Two patients did not show MRI abnormalities targetable by brain biopsy. In the remaining patients, brain biopsy was not performed because of patients' critical conditions at the time of ALERT syndrome and the subsequent improvement and MRI normalization after high-dose steroids. In this setting, we judged brain biopsy as an invasive procedure exposing patients to a disproportionate risk.

Patients 1 and 3 died at hospitals not within our site of acute respiratory distress due to pulmonary infection. They had no recent neurologic symptoms or MRI alterations. Although autopsy could have been informative, it was not performed. We intend to collect neuropathologic specimens from patients presenting with similar symptoms from all sites wishing to collaborate with us. As a retrospective study, neuropsychological tests were not serially performed.

From 1998 to 2011, patients were admitted into 4 different neurologic sites at the onset of neurologic symptoms. We cannot correctly estimate the number of patients receiving whole-brain radiotherapy in origin departments but we suggest that a more informative denominator would be the number of long-surviving patients after brain irradiation. To answer this, we are conducting a prospective clinical study on long survivors after brain irradiation to explore the underlying mechanisms of acute encephalopathy and its relationship with chronic postradiation complications.

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1. Di Stefano AL, Berzero G, Vitali P, et al. Acute late-onset encephalopathy after radiotherapy: an unusual life-threatening complication. *Neurology* 2013;81:1014–1017.

WHITE MATTER HYPERINTENSITIES ON MRI IN HIGH-ALTITUDE U-2 PILOTS

Julian Hellmann-Regen, Kim Hinkelmann, Francesca Regen, Berlin, Germany: McGuire et al.¹ presented interesting data on the prevalence and location of white matter hyperintensities (WMHs) in MRI scans of high-altitude pilots. The authors demonstrated that WMHs differ between the pilot group and a matched group of healthy controls. They concluded that these differences may be the result of hypobaric in the pilot group. While

their findings add to aviation and altitude-related risks, military pilots are also exposed to other potentially confounding factors, including exposure to high Gz stress, radiation, or use of stimulant drugs, which may contribute to unspecific brain lesions.²⁻⁴ With the inclusion of a “regular pilot” control group matched for these aviation-related factors, the suggested causal link between hypobaric and WMH development would be strengthened. In addition, previous reports indicating a trend of increased nonspecific brain lesions in pilots could be further confirmed.⁵

Author Response: Stephen A. McGuire, San Antonio, TX: Dr. Hellmann-Regen et al. made a relevant point: it would be ideal to compare our findings to those in another pilot group not exposed to high altitude. Even though this study has not yet been authorized, our unpublished results on 83 altitude-chamber technicians whose exposure occurred during their official duties as monitors for altitude-chamber exposure have demonstrated the same findings. They have

not been exposed to the stresses mentioned by Dr. Hellmann-Regen et al. We are in the process of preparing this study for publication.

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