Neurology® Clinical Practice

First seizure management: I can see clearly now?

Dana Ekstein, MD, PhD: I read with interest the article by Krumholz et al.[1] on the management of an unprovoked first seizure and the comments that followed, especially the one by Cole and Cascino,[2] which focused on treatment guidelines. The authors reported an absolute risk reduction in seizure recurrence of 35% during the first 2 years of treatment, based on the 5 studies that randomly divided the patients to receiving or not receiving treatment after the qualifying seizure. However, it seems that being randomly assigned to one of these treatment options yielded the best chances for the patient to remain seizure-free during this period. Overall, 522 out of 1,600 (33%) patients in the randomized studies had 1–2 years seizure recurrence (tables 1 and 2[1]), while 625 of 1,612 (39%) in the studies where physicians decided whether to recommend treatment, based on their clinical judgment, recurred (table 1[1]; $p < 0.001$, χ^2). This observation, which was not reported in the article, emphasizes the limitations of our current knowledge on the issue of treatment after a first seizure, and the complexity of factors taken into consideration while making treatment recommendations in this situation, other than the seizure prevention itself.

Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

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Authors Respond: **Allan Krumholz, MD; Samuel Wiebe, MD; David S. Gloss, MD; Shlomo Shinnar, MD, PhD; Jacqueline A. French, MD:** We appreciate Dr. Ekstein's interesting comment. Whereas her calculations are not a true meta-analysis, it would not be at all surprising to see a somewhat higher recurrence rate in patients who were not in randomized trials. If a physician has a high concern for seizure recurrence for any reason, the physician might not elect to enroll such a patient in a trial where treatment decisions are left to the flip of a coin. Randomized patients may have been those in whom physicians had more equipoise. In other words, anytime randomization is added to a study, generalizability likely suffers.

Also, data from the individual studies should not simply be combined. More typically, greater weights are given to more informative studies, because they are more likely to be closer to the true effect. There are many ways of doing this. Simply adding the results of the studies together is not one of them, except in narrow circumstances. Moreover, even though the 39% vs 33% difference Dr. Ekstein calculates may be statistically significant, we do not see its relevance for informing clinical decisions. Rather, it is reassuring that the data from nonrandomized studies are so similar to those from randomized clinical trials.

Maryland Epilepsy Center (AK), Baltimore, MD; University of Calgary (SW), Canada; CAMC Neurology (DSG), Charleston, WV; Albert Einstein College of Medicine (SS), Bronx, NY; New York University (JAF), New York.

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2. Cole AJ, Cascino GD. First seizure management: I can see clearly now? Neurol Clin Pract 2015;5: 368–369.

Differing trends in the incidence of vascular comorbidity in MS and the general population

Amin Zarghami, MD: Marrie et al.[1] revealed the rising trends of vascular comorbidities in multiple sclerosis (MS) in a large Canadian population-based study. The authors proposed 2 different explanations for this issue: (1) more health care visits for patients with MS could have led to higher diagnostic evaluation; and (2) the similarity between several predisposing factors of MS and vascular diseases (e.g., ischemic heart disease, hypertension, and diabetes mellitus), including smoking, obesity, and genetic predisposition. But the role of therapeutic and pharmacologic agents in the pathophysiology of these events was not discussed sufficiently.

Previous studies have suggested that high-dose corticosteroids are the standard treatment for acute relapses in patients with MS.[2] These drugs are prescribed for their immunomodulatory, immunosuppressive, and anti-inflammatory effects, so corticosteroid-induced negative side effects are also possible, especially in patients who take the drugs long term. It is well-known that glucocorticoid-associated side effects may involve various major organ systems including metabolic (i.e., diabetes mellitus, dyslipidemia, weight gain, lipodystrophy) and cardiovascular (i.e., hypertension, cardiovascular events) adverse events, which can be life-threatening and cause significant morbidity among long-term users.[3]

Marrie and colleagues' study provides valuable information about vascular comorbidity with MS and its great value relies on the large sample size and the well-conducted analyses. However, epidemiologic evidence on associations between MS pathophysiology and risk of other vascular related diseases by considering their type of treatment—particularly the role of therapeutic modalities and the duration of corticosteroid use—in rising morbidity is scarce. Further comparative assessments and future long-term follow-up studies are needed.

Babol University of Medical Sciences, Iran.

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Authors Respond: **Ruth Ann Marrie, MD, PhD; John Fisk, PhD; Scott B. Patten, MD, PhD:** Thank you for your interest in our work,[1] and for drawing attention to the potential role of treatment in the etiology of comorbidities.[4] However, it is unlikely that treatment with glucocorticoids contributes significantly to vascular comorbidity in the MS population. Glucocorticoids are used to treat relapses over short periods, not as a long-term therapy, and are much less likely to cause metabolic and cardiovascular disorders with short-term use. Glucocorticoid-induced hyperglycemia usually reverses with treatment discontinuation[5] and chronic glucocorticoid use was not associated with dyslipidemia in a study of 15,004 Americans.[6] We found that the incidence rates of diabetes, hypertension, and hyperlipidemia rose within the MS population over time, and the

incidence of diabetes rose more in the MS population than in the matched population. For glucocorticoids to play an etiologic role in these trends, their use would need to increase over time. As disease-modifying therapies that reduce relapse rates emerged early in the study period, this would be expected to reduce glucocorticoid use over time, as observed elsewhere.[2] To our knowledge, no existing chronic therapy with known effects on vascular comorbidity has increased in use in the MS population to fully account for our findings. Nonetheless, pharmacologic therapies are relevant and their role should be evaluated in future studies of this issue.

University of Manitoba (RAM), Winnipeg; Dalhousie University (JF), Halifax; and University of Calgary (SBP), Canada.

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