Association Between Glutamate Blockade and Fatigue in Patients With Multiple Sclerosis

Excitotoxicity, primarily mediated by excessive glutamate release, is one of the main proposed mechanisms for neurodegeneration in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis.1 However, a few clinical trials of medications with glutamate-blocking properties have not yet shown beneficial effects in patients with MS.

Fatigue is one of the most frequently reported MS symptoms and the underlying mechanisms of this potentially debilitating symptom are not well understood.2 Here, we report the effects of riluzole, a medication with glutamate-blocking properties, on fatigue in a randomized clinical trial in patients with early MS.

Methods | This is an analysis of a randomized, double-blind, placebo-controlled trial assessing the possible neuroprotective effects of riluzole in combination with intramuscular interferon β-1a that was conducted at 2 centers. The methods, including inclusion and exclusion criteria, the details of the randomization, and the results of primary and secondary outcomes of the study, are reported elsewhere.3 The institutional review boards at the University of California–San Francisco and Oregon Health and Science University approved this study; written informed consent was obtained from all participants.

In summary, 43 patients with clinically isolated syndrome or MS with symptom onset within the previous 12 months and with at least 2 silent T2 hyperintensities in the deep white matter on a clinical brain or cervical magnetic resonance imaging scan were invited to participate in the study. Patients were randomized to receive 50 mg of riluzole or placebo twice daily. After 3 months taking the study drug, patients also initiated weekly intramuscular interferon β-1a. Fatigue was evaluated by the Modified Fatigue Impact Scale (MFIS).4 The MFIS was administered at baseline; months 3, 6, 12, 18, and 24; and, in the first half of patients who completed the study, months 30 and 36.

To analyze the effect of riluzole on the MFIS score, a mixed-effects regression model was used with the treatment allocation (in an intent-to-treat analysis) as the predictor and the MFIS score as the outcome. The mixed model allowed patient-specific intercepts and slopes to accommodate the repeated-measures nature of the data and possible time trends during the course of the study. All analyses were conducted in Stata version 13.1 (StataCorp).

Results | Baseline characteristics of patients who were recruited in the study are shown in the Table. Twenty-two patients were randomized to riluzole and 21 patients to placebo. The mean MFIS score in the riluzole and placebo groups were 24.1 and 33.2, respectively. Compared with the placebo group, the MFIS score worsened by 4.6 points per year in the riluzole group (95% CI, 1.1-8.1; P = .01) (Figure). Adjusting for baseline MFIS score or age (that was significantly different between the 2 groups at baseline) or T2 lesion volume and normalized gray matter volume (the primary study outcome was adjusted for these variables owing to baseline imbalance) did not change the results.

Discussion | Despite increasing evidence of involvement of glutamate excitotoxicity in the pathogenesis of neurodegeneration in MS, pharmacologic blockade of glutamate in human studies have not shown clinical benefits and may have detrimental effects on patients’ symptoms. A 16-week clinical trial examining the symptomatic effects of memantine, a noncompetitive antagonist of glutamate N-methyl-D-aspartate receptor, on cognitive function of patients with MS reported statistically important worsening of fatigue as measured by a fatigue severity scale in the memantine group.5 Another clinical trial to assess the effect of memantine on neuropsychological performance in MS was prematurely halted after 9 patients reported a worsening of neurological symptoms. Interestingly, 4 of 7 patients in the memantine group reported worsening fatigue.6

While our results including appropriate adjustments might be a false-positive finding related to multiple comparisons, they are in line with previous reports of worsening fatigue in patients with MS receiving a medication with anti-glutamatergic properties. In our case, the trend over time of fatigue worsening during the 36-month trial questions the...
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OBSERVATION

Non-N-Methyl-D-Aspartate Receptor Antibody Encephalitis With Cerebellitis With Associated Ovarian Teratoma

The incidence of autoimmune and paraneoplastic encephalitis is increasing with improved recognition of clinical syndromes and diagnostic testing. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been well described in young women with ovarian teratoma.1 The classic presentation of this syndrome is a subacute encephalopathy with mood disturbances, including psychosis, with variability of seizures and movement disorders. However, to our knowledge, there have been no reported associations between ovarian teratomas and paraneoplastic cerebellitis. Typically, paraneoplastic cerebellar degeneration or cerebellitis has been linked to anti-Yo antibody. More recently, cases of autoimmune and paraneoplastic cerebellitis have been reported with associated anti-Homer-3 and anti-metabotropic glutamate receptor 1 antibodies. Metabotropic glutamate receptor 1 has been associated with Hodgkin lymphoma, but there have been no reported neoplasms in cases of cerebellitis with positive Homer-3 antibodies.2,3

We present a case of meningoencephalitis with cerebellitis in a previously healthy woman with bilateral ovarian teratomas. Based on diagnostic evaluation and treatment response, we postulate a novel paraneoplastic cerebellitis with associated ovarian teratomas.

Report of a Case | A woman in her mid-20s with no medical history presented with 2 to 3 days of fever, headache, encephalopathy, and ataxia. Her examination was significant for fever, encephalopathy, dysarthria, hypophonia, ataxic speech, reduced visual acuity, truncal more than appendicular ataxia, and bilateral Babinski signs. Initial magnetic resonance imaging...