Adjunctive Modafinil in ALS

SIR: Amyotrophic lateral sclerosis (ALS) is a disease of upper and lower motor neuron degeneration that manifests itself by a progressive weakness of muscles, with resultant signs and symptoms that include difficulty with ambulation, speech, hand control, and swallowing, as well as persistent fatigue, twitching, and paralysis. There is no cure for ALS, and although the newly approved agent riluzole may prolong survival, treatment is more commonly supportive in nature. Below is described a patient who developed ALS while being treated for depression and in whom adjunctive modafinil proved of benefit in the treatment of fatigue, sleepiness, and lowered stamina.

Case Report

Ms. A., a 56-year-old woman, was initially seen for major depressive disorder in the context of several life stresses and a past history of major depression. Her medical history was positive for intermittent migraine, and she was on hormone replacement therapy with estrogen and progesterone. During treatment with nefazodone 350 mg and sertraline 50 mg, Ms. A.'s depression remitted, but she noted a sense of unilateral upper extremity weakness and twitching in addition to tripping and difficulty with speech. Because she attributed these problems to her psychotropic medications, sertraline was discontinued and nefazodone was initially reduced to 200 mg and ultimately discontinued, with mild subjective improvement in her physical symptoms but a return of depressive and anxiety complaints.

Because of the patient's continued difficulty with weakness of her arm, comprehensive neurologic evaluation was initiated, including electromyography and nerve-conduction studies, cervical and brain MRI, and extensive laboratory testing as well as speech and ambulation assessments. Four neurologists were consulted, and the ultimate diagnosis was ALS.

Ms. A. started riluzole for ALS and citalopram 20 mg/day for depressive symptoms. In spite of psychiatric benefit with citalopram, Ms. A.'s physical symptoms progressed and included severe daytime sleepiness, weakness, fatigue, and reduced ability to participate in her activities of daily living. Modafinil was prescribed and increased to a maximum tolerated dose of 300 mg daily, with marked improvement in alertness, energy, and ability to participate in both home and outside activities. On two occasions over 6 months, Ms. A. ran out of her supply of modafinil and experienced an immediate exacerbation of weakness, fatigue, and sedation, with rapid improvement upon restarting this medication.

Comment

Modafinil is a novel wake-promoting agent approved for use in narcolepsy, although reports[1,2] of benefits in other neurologic conditions suggested consideration of this agent in Ms. A. as adjunctive treatment for her ALS-associated fatigue, sleepiness, and weakness. Activation of hypothalamic arousal centers[3] is a proposed mechanism of action for this agent, which may also have potential antidepressant effects.[4] Ms. A.'s case suggests modafinil may be a useful adjunctive agent for ALS.

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Risk Factors for Treatment-Resistive Methamphetamine Psychosis

SIR: It is well known that methamphetamine abuse can cause a psychosis in long-term users. Most patients, however, respond well to neuroleptics, and psychiatric admissions to acute care facilities are generally short. Still, it is not uncommon for methamphetamine patients to be resistive to treatment, showing continued psychotic symptoms despite extended periods of abstinence.[1] These patients are often diagnosed as being schizophrenic, only later to have the symptoms clear up with continued treatment.

So far, there have not been studies on risk factors for development of treatment-resistive methamphetamine psychosis. One such potential risk factor is premorbid brain

dysfunction. According to Fujii,[2] the presentation after an injury to the brain results from an interaction between the type of brain injury and the premorbid brain. Thus it is hypothesized that patients with treatment-resistive psychosis secondary to methamphetamine abuse are likely to have a premorbid neurological condition.

To examine this hypothesis, charts of 29 consecutive state hospital inpatients who were admitted for psychosis after methamphetamine abuse and had no family history of mental illness were reviewed for history of traumatic brain injury, learning disabilities, birth complications, or soft neurological signs. There were 26 males and 3 females. The mean age of the patients was 32 years. Of the 29 patients, 23 ($\chi^2 = 9.97$, $P < 0.01$) demonstrated evidence of at least one neurological disorder; 15 sustained at least one head injury, 10 reported placement in special education, 3 were diagnosed with attention-deficit/hyperactivity disorder, 2 reported birth complications or prematurity associated with signs of hyperactivity and learning problems, and 2 reported pathological left-handedness. For 19 patients, the onset of the neurological disorder was during childhood. Of the 10 patients who sustained a traumatic brain injury during the time of their methamphetamine abuse, 6 developed psychotic symptoms within a year.

These data suggest that the existence of a previous neurological disorder may be a risk factor for developing a treatment-resistive psychosis in methamphetamine abusers. It is of particular interest that a majority of the patients sustained their disorder during childhood. These findings support Fujii's[2] hypothesis of the interaction between brain injury and the premorbid brain.

To the author's knowledge, this is the first report of a relationship between previous neurological disorder and risk for treatment-resistive methamphetamine-induced psychosis. Some issues for future investigation include base rates of previous neurological disorders in patients who are not treatment-resistive, as well as the effects of premorbid neurological disorders on the duration and frequency of methamphetamine abuse that are required to induce a psychosis. In the interim, questions about prior neurological disorders would seem to be important during intake interviews with this population because this information may be predictive of course of illness.

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Temporal Lobe Structural Lesion in a Case of Posttraumatic Stress Disorder

SIR: Few studies have documented gross structural abnormalities in posttraumatic stress disorder (PTSD). In one magnetic resonance imaging (MRI) study, a developmental variant known as cavum septum pellucidum was found in half of PTSD subjects but in only 14% of control subjects.[1] In another study, gross abnormalities (cortical atrophy, focal white matter lesions) were reported in PTSD subjects (10 of 42 subjects), but not in control subjects.[2] Of particular interest has been the finding of reduced hippocampal volume in PTSD, and a question that arises is whether hippocampal injury is an outcome of the disorder or is a preexisting vulnerability to its development.

This report briefly highlights MRI findings of mesial temporal sclerosis (MTS) in a 16-year-old female with PTSD.

Case Report

Ms. A., age 16 years, presented with PTSD after being raped by her grandfather at age 6 years. Since the age of 10, she had made several attempts to injure herself (cutting her wrists and breasts, overdoses of pills). Of note on medical examination was an ability to dissociate readily and a history of several dissociative episodes per day in the past year. During exploration of the rape, she appeared to go into a light trance. She reported vivid flashbacks, nightmares, irritability, and insomnia. There were no impairments in short-term or long-term memory. She had no history of epilepsy or other medical illness and no history of drug use.

Ms. A. did not improve with cognitive-behavioral therapy. There was also little improvement with various medications: (i) citalopram 40 mg/day + risperidone 4 mg/day; (ii) fluoxetine 60 mg/day + quetiapine (Seroquel) 400 mg/day + valproic acid 100 mg/day; (iii) fluoxetine 60 mg/day + lamotrigine 200 mg/day + risperidone 3 mg/day; and (iv) fluoxetine 80 mg/day + quetiapine 600 mg/day + valproic acid 700 mg/day. Side effects included extrapyramidal effects (risperidone 3–4 mg/day), akathisia (fluoxetine 60–80 mg/day), and galactorrhea (quetiapine 300–600 mg/day). On a treatment regimen of fluoxetine 20 mg/day + quetiapine

200 mg/day + valproic acid 700 mg/day, there was some improvement in flashbacks and self-mutilation. In view of her frequent dissociations, electroencephalography (EEG) and MRI were requested. EEG and Holter-EEG were normal. MRI displayed mesial temporal sclerosis: right hippocampal atrophy and amygdala asymmetry.

Comment

MRI findings in adult victims of child physical/sexual abuse[3,4] and in combat veterans[5] suggest that PTSD patients exposed to early life trauma have greater left hippocampal volume reduction, while those exposed to later life trauma (combat veterans) have bilateral or right hippocampal atrophy. In sexually abused women with PTSD, a correlation has been found between the degree of atrophy and dissociative symptoms.

One can hypothesize that in some cases of PTSD, psychological trauma predates neuronal changes but that in other cases, underlying neuronal dysfunction may predispose to its development. These processes are not mutually exclusive, and some combination of the two may be useful in explaining individual variations in trauma response. Although MTS has long been recognized as a common pathologic finding in patients with drug-resistant temporal lobe epilepsy, its etiology remains unknown. Hypotheses have included infectious etiologies and defects in energy metabolism. In a recent MRI study, the lesion was documented in patients with psychogenic nonepileptic seizures.[6] Histologically, MTS has been characterized by atrophy and gliosis of the hippocampus. Administration of epileptogenic agents has been shown to cause MTS and recurrent seizures in animals, perhaps on the basis of excessive release of excitatory amino acids such as glutamate. Interestingly, Ms. A. had no response on lamotrigine, a drug with antiglutamatergic properties.

The question of a relationship between MTS and PTSD cannot be answered by the data at hand. Nevertheless, we present this case to underscore the possible link between gross neurological lesions, more subtle impairments, and PTSD. Ultimately a comprehensive understanding of PTSD is likely to require more fine-grained analysis of dysfunction, including work at the molecular level. In the interim, the anomaly documented here is an interesting one to explore in patients with PTSD.

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Insight and Neurocognitive Function in Schizophrenia

SIR: Although impaired awareness of illness (poor insight) was already recognized as the single most common symptom in acute schizophrenia three decades ago, only recently have vigorous research efforts been made to uncover mechanisms associated with impaired insight. Neuropsychological accounts have focused on poor insight as a result of neurocognitive deficits secondary to the cerebral disease process in schizophrenia, specifically those associated with frontal lobe dysfunction. Consistent with these accounts, several studies have provided evidence of a relationship between poor insight and poor performance on neuropsychological tests sensitive to frontal lobe functioning,[1] although relationships with generalized cognitive deficits have also been described.[2] However, results of other studies regarding the relation between insight and neurocognitive function are equivocal.[3,4]

We investigated the relationship between insight and measures of short-term/working memory and source memory in 38 patients with schizophrenia who were also participants in a larger study on the neurocognitive basis of hallucinations. Insight was measured with item 12 of the general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS). We included measures of passive and active working memory: the Digit Span forward and backward (from the Wechsler Adult Intelligence Scale) and the Visual Elevator task (from the Test of Everday Attention), respectively. In addition, we included a measure of source mem-

ory;[5] this type of memory has been related to frontal cortex activation and to schizophrenia symptoms.

Multiple regression analysis showed that the four neurocognitive tests did not explain any significant portion of observed variance in insight ratings ($F_{model} = 1.88$, df = 37, $P = 0.14$). Individual partial correlations between the tests and insight ratings were neither significant (all $r < 0.27$, all $P > 0.10$). However, insight ratings did correlate significantly with the negative symptoms subscale of the PANSS ($r = 0.37$, $n = 38$, $P = 0.02$), in accordance with a very recent report by Buckley et al.[6] Negative symptoms might thus be a confounding factor for which previous studies have failed to control.

In sum, our findings provide additional evidence for the recent conclusion by Carroll et al.[4] that poor insight in schizophrenia may result directly from the disease process itself rather than being secondary to neurocognitive deficits.

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CORRECTION

In the Winter 2002 issue, pp. 88–89, the authors' affiliation was omitted from the letter ''Obsessive-Compulsive Disorder Associated With a Left Orbitofrontal Infarct.'' Ki Woong Kim, M.D., Ph.D., and Dong Young Lee, M.D., Ph.D., are affiliated with the Department of Neuropsychiatry, Kyunggi Provincial Hospital for the Elderly, Yongin City, Kyunggi-Do, Korea.