Treatment-Resistant Self-Mutilation, Tics, and Obsessive-Compulsive Disorder in Neuroacanthocytosis: A Mouth Guard as a Therapeutic Approach

Sir: The term neuroacanthocytosis describes a group of phenotypically and genetically heterogeneous disorders associated with choreatic movements, psychiatric abnormalities, and cognitive decline. Patients with neuroacanthocytosis may develop dementia, schizophrenia, obsessive-compulsive disorder (OCD), tourettism, and self-mutilation. We present the case of a patient with neuroacanthocytosis who developed treatment-resistant oral self-mutilation behaviors, phonic tics, OCD, and a severe lack of initiative (i.e., abulia). This syndrome responded to the regular use of a mouth guard, an unusual therapeutic approach for this complex psychiatric phenotype.

Case report. Mr. A, a 32-year-old white physical therapist, sought diagnostic evaluation at our center in a state of severe undernourishment. He had a 3-year history of progressive self-neglect, lack of initiative, and morbid adherence to rules and schedules. He persistently worried about missing the “correct time” for taking his meals and medication. The presence of complex vocal tics (including slurs, grunting, squeaking, and sucking sounds) and severe lip-biting behaviors was a major complaint, which was also disclosed during his mental status assessment. In a desperate attempt to avoid self-mutilation, Mr. A kept a scarf in his mouth several times a day.

Blood examinations disclosed acanthocytes and increased muscle creatine phosphokinase. Magnetic resonance imaging revealed atrophy of both caudate nuclei. Electromyography and nerve conduction studies evidenced a mononeuropathy multiplex of axonal type. Unfortunately, no chorein Western Blot testing was available at the time of his evaluation.

Given the severity of Mr. A’s oral self-injurious behaviors, this condition took relative precedence over other psychiatric symptoms and was considered a primary treatment target. Mr. A was initially treated with fluoxetine, up to 60 mg/day, for more than a year, along with quetiapine, 300 mg/day (for 8 weeks), clozapine, 200 mg/day (for 8 weeks), topiramate, 75 mg/day (for 6 weeks), and clonazepam, up to 6 mg/day (for 12 months), all employed as augmentation strategies for fluoxetine in a sequential fashion and after adequate periods of treatment. Unfortunately, though, Mr. A reported no significant improvement of his symptoms.

In an attempt to treat Mr. A’s drug-resistant self-mutilation, a soft mouth guard was employed to prevent the destruction of perioral soft tissues. Surprisingly, not only did this strategy result in the remission of self-injurious behaviors but it also improved other psychiatric symptoms, including phonic tics, obsessive-compulsive symptoms, and lack of initiative. After using his mouth guard, Mr. A resumed several of his daily activities, such as getting in touch with his friends or even going to the beach. He displayed fewer phonic tics and became less preoccupied with daytime schedules.

The predilection of atrophy in the head of the caudate nucleus argues for a particular vulnerability of this part of the striatum in neuroacanthocytosis and is in agreement with the complex psychiatric syndrome presented by our patient. In fact, the disorders referred to in this report (i.e., impulsive aggres-

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The Continuum Hypothesis of Mood Disorders

Sir: The recent (November 2007) article by Laursen et al. tested the continuum between mood and psychotic disorders. The authors state that, using “selected risk factors” (i.e., some family, environmental, and birth variables), “differences between the phenotypes were quantitative rather than qualitative” but that differences between genders and between “age-specific incidences” favored instead the Kraepelian dichotomy between “manic-depressive insanity,” including most DSM-IV-TR mood disorders, and “dementia praecox,” including several DSM-IV-TR psychotic disorders). The variables chosen are questionable. Among classic diagnostic validators, age at onset, boundaries between syndromes (i.e., bimodal distribution of distinguishing features), course, psychometric (multivariate) analyses, and, most of all, psychiatric family history (in this case, of bipolar, unipolar, psychotic disorders) figure prominently. The “environmental” variables used by the authors seem weak when compared with these classic validators, allowing one to question the authors’ speculations about the continuum/dichotomy hypotheses resulting from “quantitative” (and not “qualitative”) differences found.

The only variable close to the classic validators is “age-specific incidence of admission,” for which the greatest difference between unipolar and bipolar disorders was found. On this basis, the continuum between mood and psychotic disorders was questioned, while there was a close similarity between unipolar disorder and schizophrenia in distributions of age-specific incidence of admission. Paradoxically, the Kraepelianaich dichotomy was questioned by using age at onset in this study, which was similar between “manic-depressive insanity” and “dementia praecox” (most onsets between age 20 and 30 years).

At the end of the article, the authors’ speculations lead to the unipolar-bipolar division (a DSM-IV-TR division, not a Kraepelian one). This categorical distinction, championed by Angst and others in the 1960s, was mainly based on age at onset, recurrences, and differences in family history of mania. At that time, bipolar II disorder was not diagnosed. Recent reviews and research articles (e.g., references 8–20) have shown that the basic requirement of a clear boundary (i.e., bimodality) between unipolar major depressive disorder (MDD) and bipolar II disorder was not met by diagnostic validators such as age at onset, bipolar family history, and recurrences. A dose-response relationship was found between bipolar family history loading and number of hypomanic symptoms during depression (i.e., mixed depression) in bipolar II disorder and MDD. A significant subgroup of patients with mixed MDD had an age at onset and a bipolar family history loading closer to those of bipolar disorders than to that of MDD.

Furthermore, age at onset did not have the expected bimodal distribution between bipolar II disorder and MDD.

An overlap between a significant proportion of MDD patients and bipolar II disorder patients was shown on the same classic diagnostic validators that had supported the splitting between bipolar I disorder and MDD. Co-occurrence of manic/hypomanic symptoms and depression (mixed depression) and of depressive symptoms in mania/hypomania (mixed mania/hypomania) by itself causes one to question any boundary between mood disorders. Mixed states (i.e., mania/hypomania and depression symptoms/syndromes co-occurring in the same episode) strongly support Kraepelin’s unitary view of “manic-depressive insanity.”

Bipolar II disorder and mixed depression may bridge the gap between bipolar I disorder and MDD, supporting a continuum of mood disorders that is further supported by the grading of manic/hypomanic/depressive symptoms in the community and in the longitudinal course of bipolar I/II and MDD. On these stronger grounds, preliminary conclusions on the continuum of mood disorders could be reached.

Dr. Benazzi reports no financial affiliation or other relationship relevant to the subject of this letter.

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Dr. Laursen and Colleagues Reply

Sir: We thank Dr. Benazzi for his interesting comments on the findings in our article.1 Psychiatric family history and course of the disorder are, as Dr. Benazzi states, among the more “classic” validators. In previous publications, using the same cohort, we have examined psychiatric family history as a risk factor. We found an overlap between bipolar disorder (ICD-8: 296.19 or 296.39; ICD-10 F30 or F31) and schizophrenia (ICD: 296.19 or 296.09; ICD-10 F20) in that bipolar disorder occurs in about 15% of the families of schizophrenic patients.2 Furthermore, we have examined the natural history of the long-term weekly symptomatic status of bipolar II disorder.3 We found a significant overlap between bipolar II disorder and schizophrenia.4 Moreover, we have found that the overlap between bipolar II disorder and schizophrenia is not confined to the more “classic” validators but includes a variety of other risk factors.5

Our conclusion was therefore that results were not conflictive when held up against other models (such as the continuum model). However, with the variables available and the setup used in this particular article,1 we did not find strong enough evidence to disregard the Kraepelinian dichotomization—not saying that the continuum model is not correct.

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The authors report no other financial affiliations or relationships relevant to the subject of this letter.

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Dr. Raj reports no financial affiliation or other relationship relevant to the subject of this letter.

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Parkinsonism and Akathisia With Quetiapine: Three Case Reports

Sir: Quetiapine, a dibenzothiazepine derivative produced by altering the structure of the clozapine molecule, has been shown to have low to moderate affinity for the D1, D2, 5-HT1A, and 5-HT2A receptors and moderate to high affinity for the α1- and α2-adrenergic receptors.1 Due to this receptor profile, quetiapine has been claimed to have a low incidence of extrapyramidal side effects. Large controlled trials have also shown that quetiapine is associated with placebo-level extrapyramidal side effects and akathisia in schizophrenia and bipolar disorder.2,3 However, evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness suggests that there is no difference in the incidence of extrapyramidal side effects and akathisia between quetiapine, olanzapine, and risperidone.4 A few case reports of akathisia, dystonia, and tardive dyskinesia with quetiapine have been published over the years.5,6; however, there is no literature in relation to parkinsonism with quetiapine. We report 2 cases of parkinsonism and 1 case of akathisia with quetiapine.

Case 1. Ms. A, a 14-year-old girl, presented in April 2007 with an acute-onset illness of 4 weeks’ duration that was not preceded by any stressors, was continuous and fluctuating in nature, and was characterized by overeasiness, overactivity, grandiosity, incoherent speech with singing, occasional fearfulness, auditory hallucinations, visual hallucinations, reduced sleep, and increased appetite. Initially, she was treated with risperidone 1 mg/day and alprazolam 0.5 mg/day (both in tablet form), with which she showed significant improvement in all symptoms over a 1-week period. Her family stopped the medi-
cation, thinking that the patient had recovered. Following the stoppage of medication, a relapse of symptoms occurred, with the patient requiring admission.

Mental status examination at the admission revealed increased psychomotor activity, overcheerfulness, incoherent speech, echolalia, echopraxia, and auditory hallucinations of discussions about the patient. The DSM-IV diagnosis of mania with psychotic symptoms made at the initial admission was kept. Results of investigations in the form of hemogram, liver and renal function tests, thyroid function tests, electrocardiogram (ECG), and chest x-ray were normal. The patient was initially treated with risperidone 1 mg/day, which was increased to 2 mg/day. With this, she developed marked rigidity of the limbs, tremors of the hands, sialorrhea, masking of faces, and a decreased arm swing, without much improvement in psychopathology. Risperidone treatment was stopped, and quetiapine (in tablet form) was started in a dose of 25 mg/day and increased over a 2-week period to 150 mg/day. Over these 2 weeks, parkinsonian symptoms decreased and disappeared. As Ms. A’s psychiatric symptoms continued, the dose of quetiapine was increased to 200 mg/day after 1 week. At 200 mg/day, tremors of the hand and cogwheel rigidity reappeared. Over the period, the parkinsonian symptoms worsened, and there was a decrease in arm swing and masking of faces. However, her psychotic symptoms responded to quetiapine 200 mg/day. Trihexyphenidyl was started at 2 mg/day. Within 1 week, rigidity, tremors, and masking of faces disappeared.

Case 2. Ms. B, a 37-year-old housewife, presented in May 2007 with an insidious-onset illness of 5 years’ duration that had no precipitating factor and had a continuous course characterized by decreased interaction, decreased speech followed by mutism, posturing, rigidity, unprompted aggression, decreased sleep and appetite, and poor self-care. A DSM-IV diagnosis of catatonie schizophrenia was made. Results of investigations in the form of hemogram, liver and renal function tests, ECG, noncontrast computed tomography of the brain, EEG, and lipid profile were normal. She was initially treated with risperidone tablets (started at a dose of 2 mg and increased to 3 mg after 5 days) and electroconvulsive therapy.

Two weeks after starting risperidone, Ms. C was noted to have cogwheel rigidity, tremors of the hands, constipation, and pedal edema, which persisted despite a dose reduction to 2.5 mg and the addition of trihexyphenidyl 4 mg/day. Treatment with risperidone was then stopped, and treatment with quetiapine tablets was started at a dose of 50 mg/day and increased at 50-mg/day increments every week to a dose of 250 mg/day. Over the next 10 days, parkinsonian side effects and pedal edema decreased. When the patient was receiving a quetiapine dose of 200 mg/day, the parkinsonian side effects disappeared completely. However, within 1 week of Ms. C’s receiving a 250-mg/day quetiapine dose, rigidity and tremors appeared again. The dose of quetiapine was decreased to 200 mg/day, with which the parkinsonian symptoms disappeared.

Various mechanisms such as higher 5-HT2A/D2 receptor antagonism, fast dissociation of quetiapine from D2 receptors, and ability to normalize striatal tyrosine hydroxylase have been proposed as mechanisms by which quetiapine produces the lower incidence of extrapyramidal side effects among antipsychotics. However, recent reports have shown that akathisia, dystonia, and dyskinesia can occur with quetiapine and suggest the presence of other pathophysiologic mechanisms.

Risk factors for the development of extrapyramidal side effects with neuroleptic use include age (younger age for dystonia and older age for parkinsonism), maleness, history of extrapyramidal symptoms with past neuroleptic use, presence of affective symptoms, use of high-potency neuroleptic medications, high dose of medication, and parenteral administration. In our cases, the following vulnerabilities for extrapyramidal symptoms existed: presence of affective symptoms (first case) and history of extrapyramidal symptoms with neuroleptic use (all cases). Further, development of extrapyramidal symptoms with lower doses of quetiapine may also be due to low levels of cytochrome P450 3A4 enzymes, which metabolize quetiapine, in these subjects.

These cases demonstrate 2 important facts. First, quetiapine can cause parkinsonism and akathisia, and second, the propensity to develop these side effects is guided not only by the type of antipsychotic but also by risk factors for the development of extrapyramidal symptoms. Hence, in the presence of vulnerability factors, the target dose of antipsychotics should be achieved by gradual titration and close monitoring for the development of these side effects.

The authors report no financial or other relationship relevant to the subject of this letter.

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Sir: Janicak et al. in their recent study have provided clear and excellent evidence in support of the use of transcranial magnetic stimulation for the treatment of major depressive disorder. The results of the study support the results of a recent study by Anderson et al., who showed that transcranial magnetic stimulation is more effective than sham treatment for the treatment of patients with depression. Interestingly, transcranial magnetic stimulation is increasingly being used for the management of various neurologic disorders as well as psychiatric disorders besides depression.

Transcranial magnetic stimulation has been shown to be effective in the management of panic disorder in patients with underlying major depression. Repetitive transcranial magnetic stimulation improves auditory hallucinations in patients with schizophrenia and is also effective in improving movement disorders such as Parkinson’s disease.

Recent studies support the application of transcranial magnetic stimulation in the management of Tourette syndrome. For instance, Mantovani et al. reported 2 cases, both of whom were treated with repetitive transcranial magnetic stimulation of the supplementary motor area. At the end of 2 weeks of treatment, both patients demonstrated significant improvement on the Yale Global Tic Severity Scale, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Yale-Brown Obsessive Compulsive Scale.

Repetitive transcranial magnetic stimulation over the parietal and temporal lobes is also effective in improving symptoms of tinnitus. Centenzo et al. in a recent study have shown that transcranial magnetic stimulation is effective in decreasing spasticity in patients with multiple sclerosis. Repetitive subthreshold transcranial magnetic stimulation applied at 10 Hz also significantly decreases pain scores in patients with chronic neuropathic pain.

Clearly, transcranial magnetic stimulation is a major development in the field of psychiatry as well as neurology. Hopefully, the next few years will see more extensive and larger studies to expand the role of transcranial magnetic stimulation in the management of other neurologic and psychiatric disorders besides depression.

Dr. Kapoor is no longer affiliated with the University of Illinois at Chicago. Dr. Kapoor reports no financial or other relationship relevant to the subject of this letter.

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Dr. Rado and Colleagues Reply

Sir: We agree with Dr. Kapoor’s assessment regarding the growing number of psychiatric and neurologic disorders for which transcranial magnetic stimulation (TMS) is proving...
useful. Of note, the recently published study of TMS was the largest (N = 302) randomized, sham-controlled trial to demonstrate efficacy in patients with major depression.\(^1\) Further, the treatment modality was well tolerated by a majority of patients, with a low incidence of side effects and a low discontinuation rate.\(^2\) Patients with acute bipolar mania and posttraumatic stress disorder have also experienced a reduction in their symptoms following TMS treatment.\(^3,4\)

TMS has also shown utility in substance dependence. For example, Camprodon et al.\(^5\) demonstrated a decrease in cocaine craving in addicted patients following 1 session of TMS. Administration of TMS has also been associated with decreased nicotine craving and cigarette smoking.\(^6,7\)

We predict that larger, well-designed studies will better characterize the potential role of TMS for various neuropsychiatric disorders.

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