The Differential Diagnosis of Multiple Sclerosis and Bipolar Disorder

Sir: Pine et al.[1] described a series of patients hospitalized for mania who were also found to have multiple sclerosis, thus reminding us of the importance of considering multiple sclerosis in patients presenting with psychiatric symptoms plus neurologic abnormalities. We present a case illustrative of this point, yet raise the issue that magnetic resonance imaging (MRI) findings, commonly used to differentiate bipolar disorder from multiple sclerosis, are similar for both disorders. This complicates diagnosis and points to a similar etiology for symptoms that overlap both bipolar illness and multiple sclerosis.

Case report. Ms. A, a 48-year-old woman with a 10-year history of "mood swings," presented for her first psychiatric admission with symptoms of irritability, pressured speech, racing thoughts, circumstantiality, and persecutory delusions. Neuropsychological testing found difficulty with attention and concentration, poor short-term memory, and impaired perceptual-motor skills. Neurologic examination was normal other than for poor grip strength. Pharmacotherapy consisted of lithium carbonate 600 mg b.i.d. (serum lithium level = 0.84 mmol/L), haloperidol 5 mg q.h.s., and benztropine 1 mg q.h.s. Ms. A was discharged after 10 days following significant improvement of manic symptoms.

One month later, Ms. A was readmitted with a 10-day history of increasing lethargy, restlessness, difficulty concentrating, urinary incontinence, and periodic disorientation, although she was without manic symptoms. The patient's serum lithium level at readmission was 0.98 mmol/L. Her neurologic examination was significant for hyperreflexia, mildly decreased motor strength, clumsiness of the right upper extremity, and a Babinski reflex on the left. An MRI of the brain showed T_2 signal hyperintensities in the periventricular and subcortical white matter, corpus callosum, right cerebral peduncle, and right brain stem. While these lesions were suggestive of multiple sclerosis, none were enhanced with the addition of contrast and therefore were not thought to be acute. There were no prior studies available for comparison.

Lithium and haloperidol were discontinued, and Ms. A's delirium cleared over 4 days. Further investigation of her past medical history revealed an isolated episode of transient unilateral numbness, dysarthria, and blurry vision 12 years previously. Prophylactic treatment of mania was begun with divalproex sodium 250 mg t.i.d. and perphenazine 8 mg q.h.s. Follow-up at 5 weeks revealed no mania, psychosis, or delirium.

The association between multiple sclerosis and mood changes is well known. It is important to distinguish between primary and secondary mood disorders because the indicated treatments are different, e.g., steroids may be needed to control acute demyelination, or psychotropic medications may cause adverse effects in patients such as ours, who have significant neurologic damage. According to the Poser and Paty criteria,[2] a definitive diagnosis of multiple sclerosis requires two distinct episodes of neurologic deficits with clinical evidence of two separate lesions, or two episodes with clinical evidence of one lesion and paraclinical evidence (including MRI) of another lesion. A single episode can meet criteria if associated with increased cerebrospinal fluid immunoglobulin G (IgG). Other paraclinical evidence in the Poser and Paty criteria includes results of evoked response studies, the hot bath test, and expert urological assessment, although these tests were not pursued in this case. Furthermore, psychopathology associated with multiple sclerosis typically occurs during or immediately after the onset of neurologic symptoms.[1] A clear history of the course of symptoms can further help to differentiate secondary mania from primary mania.

Although it is still possible to make the diagnosis of multiple sclerosis in this patient based on the Poser and Paty criteria by using clinical data alone, MRI is increasingly used to differentiate primary psychiatric symptoms from those secondary to multiple sclerosis.[3] The MRI findings of this patient, however, are consistent with both multiple sclerosis and bipolar disorder.

Eight studies are reported in the literature describing increased rates of either periventricular subcortical gray matter or deep white matter lesions in bipolar disorder.[4] Therefore, white matter abnormalities are associated with both primary and secondary mood disorders. Increased abnormal white matter in bipolar patients has been associated with increased cognitive impairment, and it has been suggested that this subset of bipolar mood disorders results from anomalous myelination.[5] This complicates the differential diagnosis of bipolar disorder from multiple sclerosis and further blurs the boundary between primary and secondary mania.

References

1. Pine DS, Douglas CJ, Charles E, et al. Patients with multiple sclerosis presenting to psychiatric hospitals. J Clin Psychiatry 1995;56:297–306
2. Poser CM, Paty DW. New diagnosis criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231
3. Skegg K. Multiple sclerosis presenting as a pure psychiatric disorder. Psychol Med 1993;23:909–914
4. Altshuler LL, Curran JG, Hauser P, et al. T_2 Hyperintensities in bipolar disorder: magnetic resonance imaging comparison in literature meta-analysis. Am J Psychiatry 1995;152:1139–1144
5. Dupont DM, Jernigan TL, Butters N, et al. Magnetic resonance imaging and mood disorder. Arch Gen Psychiatry 1995;52:747–755

Carl R. Young, M.D.
Erica L. Weiss, M.D.
Malcolm B. Bowers, Jr., M.D.
Carolyn M. Mazure, Ph.D.
New Haven, Connecticut

Acute Angle-Closure Glaucoma and Paroxetine

Sir: Acute angle-closure glaucoma has been linked to use of tricyclic antidepressants[1–6] and monoamine oxidase inhibitors.[3] Susceptible patients are described as those with a history of angle-closure, age greater than 40 years, dilated pupils at initial examination, a personal or family history of glaucoma, and a history of ocular symptoms (visual abnormalities and/or eye pain).[4] While there is some debate about the role of antidepressant medication in exacerbating or causing glaucoma, clinicians have advocated use of serotonin selective reuptake inhibitors

(SSRIs) in treatment of high-risk patients.[5] We report a case of acute angle-closure glaucoma related to paroxetine use in a patient with mydriasis on examination prior to treatment but who had no personal or family history of glaucoma.

Case report. Ms. A, a 70-year-old widowed Hispanic woman, had required coronary artery bypass surgery several months prior to admission and had experienced progressive decline in functioning associated with depressed mood. Her associated symptoms included a 40-pound (18-kg) weight loss, crying spells, inability to perform activities of daily living, refusal to get out of bed, hopelessness, helplessness, decreased energy, impaired concentration, anhedonia, and marked somatic preoccupation. Ms. A did not use alcohol or illicit intoxicants. She had no previous psychiatric history and no family psychiatric or pertinent medical history. She was taking no medications known to be associated with exacerbation of glaucoma.

Ms. A was initially admitted to the medicine service where she underwent an extensive evaluation of multiple somatic complaints, including chest pain; shortness of breath; difficulty with recent and remote memory; abdominal, bladder, groin, and bilateral leg pain; nausea; and feeling that food was "stuck" in her throat. Assessments included magnetic resonance imaging (MRI) of the entire spine, computed tomography (CT) of the thoracic spine, mammography, bone scan, multiple electrocardiographs both at baseline and during episodes of chest pain, cystoscopy, barium swallow, gastric emptying study, CT and MRI of the head, lumbar puncture, echocardiograph, and extensive laboratory testing. None of these tests indicated abnormalities that explained Ms. A's symptoms. Somatic symptoms secondary to major depression were suspected, and Ms. A was transferred to the inpatient psychiatry service for further treatment.

Ms. A was observed for a 5-day medication-free period after admission to the psychiatry service. She continued to manifest symptoms of major depression and was started on paroxetine 10 mg q.d.; the dose was increased to 20 mg q.d. after 2 days. On the second day of 20-mg-q.d. treatment, the patient complained of severe pain and blurred vision in her left eye. Physical examination revealed a minimally reactive left pupil that was dilated to approximately 7 mm. The right pupil was reactive and measured 3.5 mm. Visual acuity was 20/100 OD, 20/400 OS (had been 20/100 bilaterally at admission); intraocular pressure was 15 mm HG OD, 85 mm HG OS. The patient underwent laser peripheral iridectomy, which decreased intraocular pressure. She was switched to sertraline 50 mg without adverse effect and transferred to the rehabilitation service where she did well, and her depression resolved.

We report here a case of acute angle-closure glaucoma in a patient treated with paroxetine. Acute angle-closure glaucoma has been reported after treatment with several classes of antidepressants, including monoamine oxidase inhibitors,[3] tricyclic antidepressants,[1–5] and SSRIs (fluoxetine).[7] To our knowledge, this is the first report of acute angle-closure glaucoma associated with paroxetine. The primary action of paroxetine is enhancement of serotonergic neurotransmission through selective inhibition of serotonin reuptake. Additionally, paroxetine exhibits affinity for muscarinic cholinergic receptors, an action which has been associated with mydriasis in vivo[8,9]; this effect is dose-dependent and has been observed at doses substantially higher than those used in standard practice. Nonetheless, the correlation between acute angle-closure glaucoma and paroxetine therapy in the present case is of potential clinical significance.

Depression occurs in a substantial number of elderly patients presenting to primary care physicians and to psychiatrists. These patients are at higher risk for intraocular events than the general population, since age is a risk factor for glaucoma.[4] SSRIs have been advocated as the preferred method of treatment for patients considered at high risk for development or exacerbation of glaucoma.[5] This case suggests that even the weak anticholinergic action of paroxetine may be of significance. Alternatively, the fact that a previous case report documented glaucoma associated with fluoxetine[7] suggests that a mechanism other than direct anticholinergic action may be involved. Ophthalmologic monitoring may be beneficial for patients with risk factors for glaucoma during treatment with paroxetine and, indeed, any psychotropic agent with anticholinergic activity. Further investigation and clarification of this issue are needed.

References

1. Rosselet E, Faggioni R. Glaucome et medicaments psychotropes. Opthalmologica Additamentum 1969;158:462–468
2. Hollister LE. Toxicity of psychotherapeutic drugs. Practitioner 1965; 194:72–84
3. Hermans G. L'effets nocifs des medications generales sur l'appareil visuel. Bull Soc Belge Ophtalmol 1972;160:15–85
4. Reid WH, Blouin P, Schemer M. A review of psychotropic medications and the glaucomas. International Pharmacopsychiatry 1976; 11:163–174
5. Epstein NE, Goldbloom DS. Oral imipramine and acute angle-closure glaucoma [letter]. Arch Ophthalmol 1995;113:698
6. Ritch R. The treatment of angle-closure glaucoma. Ann Ophthalmol 1979;11:1373–1375
7. Ahmed S. Fluoxetine and glaucoma [letter]. DICP, Ann Pharmacother 1991;25:436
8. Johnson AM. An overview of the animal pharmacology of paroxetine. Acta Psychiatr Scand Suppl 1989;80(suppl 350):14–20
9. Nemeroff CB. The clinical pharmacology and use of paroxetine, a new selective serotonin reuptake inhibitor. Pharmacotherapy 1994; 14:127–138

Catherine F. Lewis, M.D.
John R. DeQuardo, M.D.
Charles DuBose
Rajiv Tandon, M.D.
Ann Arbor, Michigan

Fluoxetine Efficacy in Social Phobia

Sir: The serotonin selective reuptake inhibitors (SSRIs) are establishing themselves as useful medications for the treatment of social phobia. While none are FDA approved for this indication, open reports and controlled trials suggest efficacy for all members of this class.[1] More than 2 years ago, Ringold[2] described two patients with social phobia who were successfully treated with paroxetine after failing to respond to fluoxetine and sertraline. Likewise, a patient I have been treating also showed a preferential response to one of the SSRIs, but in this case it was fluoxetine.

Case report. Mr. A, a man in his mid-20s, had a 10-year history of generalized social phobia without comorbid depression. He described difficulty socializing in most social settings and viewed his social anxiety as a daily problem. After failing to respond in a double-blind, placebo-controlled study of an SSRI, he was treated with sertraline in doses up to 200 mg/day for 3

months without benefit. He again failed to respond to treatment with paroxetine 40 mg daily for 3 months. Finally, he was treated with fluoxetine 20 mg for 6 weeks and then fluoxetine 40 mg for 3 weeks and improved markedly within days after the dose reached 60 mg daily. He reported feeling "like a changed person" and having confidence in social settings. He had a successful job interview and acquired better paying work. He is able to collaborate with coworkers in a manner inconceivable prior to his treatment. He has been able to attend social gatherings outside the workplace without his usual anxieties. For the first time, he was able to post a note on the Internet. Follow-up has been ongoing for 4 months, and while he continues to have some social anxieties, for example asking a woman out on a date, he views them as being entirely within the range of normal.

While it is possible that a higher dose of paroxetine may also have been effective, it is quite likely that this patient showed a preferential response to fluoxetine. This observation serves to further support the impression that there are efficacy differences among SSRIs.

References

1. Jefferson JW. Social phobia: a pharmacologic treatment overview. J Clin Psychiatry 1995;56(suppl 5):18–24
2. Ringold AL. Paroxetine efficacy in social phobia [letter]. J Clin Psychiatry 1994;55:363–364

Leslie v. H. Taylor, M.D.
Madison, Wisconsin

Dose-Related Thrombocytopenia and Macrocytic Anemia Associated With Valproate Use in Bipolar Disorder

Sir: A recent report on hematologic effects of anticonvulsants used for treating psychiatric inpatients showed a total absence of drug-related thrombocytopenia and anemia in 1251 patients treated with valproate.[1] In contradistinction, various authors report low platelet counts in adults and children treated for seizures and other neurologic disorders with valproate.[2–4] One study found a mean reduction in platelet count of 49,000/μL below baseline at doses near 1500 mg/day of valproate and of 69,000/μL at doses near 2800 mg/day.[4] Since thrombocytopenia has not been reported in a psychiatric population treated with valproate, I report a case of a patient with bipolar I disorder who developed thrombocytopenia and anemia associated with valproate treatment.

Case report. Ms. A, a 48-year-old woman, was first hospitalized at age 29 with a psychotic episode of mania. At age 39, she experienced a rapid-cycling pattern refractory to lithium, which was discontinued after development of severe nephrogenic diabetes insipidus and mild renal insufficiency. She manifested an allergic skin reaction (histiocytic perivasculitis) to carbamazepine. Acute and maintenance electroconvulsive treatments did not control her mood cycles. Ultimately a regimen of divalproex sodium 2250 mg/day, with a blood valproate level of 87.7 ng/mL, and thiothixene provided improved mood stability. Her platelet count at 219,000/μL was within normal limits.

After a gastroplasty procedure for obesity at age 46, the patient required higher doses of valproate to maintain the same blood levels that provided better mood control. After 3 years of valproate when her dose was 6000 mg/day and blood drug level was 95.4 ng/mL, her platelet count dropped to 102,000/μL. Her peripheral blood smear displayed macrocytosis of red cells, slightly decreased platelets of intermediate to large size, and poorly segmented polymorphonuclear cells revealing the Pelger-Huët anomaly. A bone marrow aspirate showed minimal dysplastic features in the red cell series and the megakaryocytes. Hemoglobin was 12.5 g/dL and white blood count (WBC) 7500/μL, with 41% neutrophils. Serum folate and B_{12} levels were within normal limits.

Her abnormal blood picture appeared to be related to the valproate, which was continued along with monthly blood counts. A few months later, the patient's thiothixene was discontinued because of worsening tardive dyskinesia, and her mood cycles became more severe. The patient was hospitalized when she became suicidally depressed while being maintained on 5000 mg/day of divalproex sodium at a blood level of 71.7 ng/mL. Her hemoglobin was 11.4 g/dL with a mean corpuscular volume (MCV) of 108 μ^3, and her platelet count was 69,000/μL. The platelets reached a nadir of 45,000/μL, and valproate was discontinued. Within 1 week, her platelet count rose to 70,000/μL, then to 148,000/μL in another week. Valproate was reinstituted at 3000 mg/day and haloperidol 0.5 mg/day was added to enhance mood stability. Three months later, her platelet count was 275,000/μL and WBC 6800/μL. Her hemoglobin was 13.5 g/dL, MCV 110 fL, and blood valproate level 74.5 ng/mL. One year later at a dose of 3500 mg/day, her blood drug level was 55.4 ng/mL and platelet count was 128,000/μL.

The finding of macrocytic anemia without decreased levels of folate or vitamin B_{12}, the Pelger-Huët anomaly in the neutrophil line, and thrombocytopenia associated with valproate was first described in 1990 in a pediatric population.[5] This cluster of findings points to a myelodysplastic effect of valproate, reflected also in this patient's minimally dysplastic bone marrow. Several reports indicate that thrombocytopenia is related to dosage level of valproate and that valproate may be safely used in lower doses in patients who develop this untoward effect, a strategy successfully employed in this case.[2,3,5] Serious thrombocytopenia related to valproate use is rare, but when it occurs, dosage reduction may alleviate the hazards.

References

1. Tohen M, Castillo J, Baldessarini RJ, et al. Blood dyscrasias with carbamazepine and valproate: a pharmacoepidemiologic study of 2228 patients at risk. Am J Psychiatry 1995;152:413–418
2. Loiseau P. Sodium valproate, platelet dysfunction, and bleeding. Epilepsia 1981;22:141–146
3. Hoffman LM. Sodium valproate and thrombocytopenia. CMA Journal 1982;126:358–359
4. Neophytides AN, Nutt JG, Lodish JR. Thrombocytopenia associated with sodium valproate treatment. Ann Neurol 1979;5:389–390
5. Ganick DJ, Sunder T, Finely JL. Severe hematologic toxicity of valproic acid. Am J Pediatr Hematol Oncol 1990;12:80–85

Robert G. Fawcett, M.D.
Petoskey, Michigan