Acute Viral Encephalitis Complicating a First Manic Episode

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The diagnosis of viral encephalitis in a patient with acute mania was difficult because of symptom overlap and inconclusive laboratory evaluations. Final differentiation was made clinically. Despite the generally assumed usefulness of diagnostic tests for encephalitis, only the electroencephalogram showed consistent sensitivity in this patient and in similar previously reported cases. Diagnosis was further complicated by the potential side effects of neuroleptic medications, which may mimic infection through extrapyramidal symptoms, fever, or altered blood counts. In addition, legitimate physical complaints were discounted as a result of the patient's psychiatric status.

The concurrence of major psychiatric and medical illnesses confounds clinical diagnosis and management. The nature of symptoms may vary, and valid medical complaints of psychiatric patients may be discounted, delaying appropriate care.

This paper presents a case of acute viral encephalitis complicating an initial episode of mania. It demonstrates that even within a psychiatric setting the psychologically disturbed patient may be medically compromised. The reasons are multifactorial: the differential diagnosis of organic and psychiatric illnesses, inadequate laboratory evaluations, complications of neuroleptic medications, and staff stereotyping of patients.

Case Report

A 28-year-old married white woman was hospitalized because of a ten-day history of disorganized behavior with poor judgment resulting in self-injury. Symptoms included elation, increased energy, lack of sleep, and poor nutritional intake. She experienced rapid thoughts with disturbing voices talking about other people and was preoccupied with religiosity and sexuality. Five days prior to admission she had impulsively filed for divorce. There was no significant history of substance abuse. Although she had no previous psychiatric treatment, mild episodic depressions over

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several years were reported. Family history was suggestive of an affective illness in her mother.

Physical examination revealed a healthy-looking woman who appeared her stated age. Vital signs included blood pressure 132/65 mmHg lying down without orthostatic changes, pulse 92 beats/min and regular, respirations regular at 16/min, temperature 37° C. There were superficial excoriations and ecchymoses over her lower extremities. She was normocephalic without trauma to the head. Fundi were benign with sharp discs. Tympanic membranes, nose, and throat were clear. Neck was supple without lymphadenopathy or masses, and thyroid was not palpable. There were no carotid bruits. All lung fields were clear to auscultation. Cardiovascular examination revealed normal rate and rhythm without gallop or murmur. Abdomen was soft without masses or hepatosplenomegaly. There was no articular edema or erythema. Neurological examination disclosed intact cranial nerves II through XII. Sensation was intact to light touch and pinprick. There was no dysdiadochokinesis, past-pointing, or tremor, although the test functions were performed with deliberation and concentration. Gait was normal. Deep tendon reflexes were symmetrical at 2/4 at biceps, supinator, patella, heel. There was plantar flexion upon plantar stimulation.

Mental status examination revealed an attractive, cooperative young woman with intact social graces and in good control. She was distractible, impulsively walking around trying to help others, and flirtatious. Affect was labile, alternately worried, anxious, and euphoric with inappropriate smiling. She reported moderate subjective distress, especially concerning auditory hallucinations, thought broadcasting, and a feeling of "going too fast." Conversation was intelligible with mild disorganization and blocking. There was no paranoia or suicidal or homicidal ideation. Memory for recent events was impaired, concentration was decreased, but sensorium was clear to orientation and abstraction.

Admission laboratory study results included hematocrit 40 percent, hemoglobin 13.9 g/dL, red blood cell count (RBC) $4.32 \times 10^6/\mu L$ with normal indices, white cell count (WBC) $5.3 \times 10^3/\mu L$, sodium 144 mEq/L, potassium 4.0 mEq/L, chloride 108 mEq/L, bicarbonate 24 mEq/L, total protein 5.8 g/dL, albumin 3.9 g/dL, calcium 8.8 mg/dL, glucose 93 mg/dL, blood urea nitrogen (BUN) 6 mg/dL, creatinine 0.9 mg/dL, total bilirubin 0.5 mg/dL, alkaline phosphatase 31 U, thyroid studies with T_4 by radioimmunoassay 7.2 μg/dL, T_3 uptake 44 percent, thyroid stimulating hormone (TSH) 4.5 μU/mL, clear urine toxicology screen, negative urine porphyrin screen, urinalysis with specific gravity of 1.016, pH of 6.5, negative protein, glucose, and ketones (but moderate occult blood with +1 RBC/HPF), no casts and negative culture, negative rapid plasma reagin (RPR) test for syphilis, negative blood culture, normal chest roentgenogram, and normal electrocardiogram. Since this was the patient's first psychotic episode, further neurological evaluation was performed. Computed tomographic (CT) scan of the head performed with 100 mL of Hypaque 60 percent was normal. Cerebrospinal fluid (CSF) from lumbar puncture disclosed glucose 74 mg/dL, protein 30 mg/dL, RBC 0/μL; WBC 4/μL with 25 percent neutrophils and 75 percent lymphocytes, and negative Gram stain and bacterial culture. A dexamethasone suppression test showed nonsuppression of serum cortisol (17 mg/dL) at 4 PM.

Initially the patient was treated with 5 mg of haloperidol the evening of admission and again the next morning. She appeared calmer and less disorganized. A DSM-III diagnosis of major affective disorder, bipolar type, manic phase was made. Treatment with lithium carbonate (1,200 mg) and perphenazine (32 mg) was begun. During the initial two days of hospitalization the patient demonstrated continued improvement.

The third day she developed nausea, emesis, and sedation. The lithium dosage was decreased to avoid supposed gastric side effects. That evening she reported escalating emesis and headache minimally responsive to acetaminophen (650 mg every 3 hours). The next day gastric distress ceased, but increased headache and neck stiffness led her to refuse meals. She was lethargic, remaining in bed. Benztropine (4 mg) was without benefit. A temperature of 38.8° C was noted. Because she refused to take oral medication or food, lithium and perphenazine were discontinued and intramuscular haloperidol (20 mg) was instituted. Anorexia, headache, neck stiffness, lethargy, and fever persisted, however.

By the sixth day full medical consultation revealed a neck stiff to flexion, tachycardia of 100 beats/min and temperature of 37.8° C. Cranial nerves II through XII were normal. Sensation was

intact to two-point discrimination and sharp-dull distinction. Alternating hand movements and finger-nose were slow but appropriate, and there was no drift of arms. She refused to walk or stand. Deep tendon reflexes were 2/4 throughout and toes were downgoing. Strength was decreased but symmetrical in all extremities. Remainder of the physical examination was intact. She appeared acutely distressed. Her overt psychotic symptoms had cleared and her mood was mildly euphoric despite obvious distress. The differential diagnosis included acute extrapyramidal effects with torticollis vs a resolving acute viral encephalitis. Medical consultation reported a community epidemic of coxsackie viral encephalitis in young adults. Medications were discontinued, except the benztropine (6 mg), which continued to be nonbeneficial. Fluorescent antibody for herpes simplex and zoster and a viral culture screen were performed on the previously obtained CSF specimen and on fresh throat and rectal swabs. These cultures remained negative throughout hospitalization. An electroencephalogram (EEG) showed "marked diffuse disturbance of brain function with posterior prominence beyond possible residual medication effects." Results were consistent with an acute encephalitic process. The medical consultant did not recommend a repeat lumbar puncture because of the resolving symptoms, characteristic viral presentation, and appropriate timing of the first CSF specimen.

Over the next five days the patient steadily improved. She was treated with low doses of thioridazine (25 to 50 mg every four hours as needed) for persistent mild euphoria. Headache and neck stiffness persisted, but were well tolerated. She was discharged after two weeks of hospitalization and within two days discontinued the thioridazine. In clinic ten days later she reported depressive symptomatology. Lithium carbonate (1,200 mg) and amitriptyline (100 mg) were instituted for the next six months. She was then maintained euthymic with only lithium for another six months. Seven months after discontinuation of the lithium she experienced her second manic episode.

Discussion

The differential diagnosis included acute encephalitis superimposed on a bipolar episode vs an organically induced mania as a prodrome to encephalitis in an affectively predisposed individual. Mania in conjunction with systemic illness such as porphyria, pernicious anemia, or myocardial infarction, or following head injury has been well described.[1] Several cases of viral encephalitis producing a psychotic prodrome[2-4] and three cases associated with manic symptoms[5-7] have been reported. Review of these cases clarifies the diagnosis in the patient presented here. Koehler and Guth[7] described depression and mania without neurological signs in a patient with positive herpes serologies five weeks after herpes labialis. They attributed the bipolar episode to herpes encephalitis in an individual predisposed by a premorbid hyperthymic personality. Others describe an encephalitic prodrome comprising variable manic symptoms intermixed with delirium or neurological deficits.[5,6] A patient described by Raskin and Frank[3] presented with psychosis and catatonia, with the neurologic signs of herpes encephalitis reportedly evolving late in the course. Early signs of organic disease were evident in the presentation of mild seizure activity, however. Wilson's two cases of psychosis[4] also displayed early, although subtle, organic signs with hyper-reflexiveness, chills, and herpes labialis. Obvious neurologic signs, when they finally developed, were fulminant. Although another of his patients presented clear neurological involvement, negative laboratory evaluation led to a diagnosis of "functional" psychosis. Misra and Hay[2] presented three patients with truly uncomplicated psychotic syndromes who then developed encephalitis. Although the psychiatric and encephalitic symptoms appeared distinct, they attributed the psychoses to infection. The present patient presented in a fashion similar to that of their patients, but with mania. Whether the mania was induced by the encephalitis, as the previous studies allege, or was a concurrent, but independent, process is difficult to determine from the acute course. However, this patient had a premorbid history of depression, subsequently became depressed a few weeks after the onset of mania, and developed a second manic-depressive cycle 18 months after the first. Her course then suggests bipolar illness with an independent, superimposed encephalitis.

Laboratory diagnosis can be inconclusive in the differential diagnosis. Fluorescent antibodies have

a sensitivity of 40 to 60 percent depending on the virus and sampling site, and not all viruses are detectable with this method.[8,9] Lymphocytes may take up the fluorescent stain, resulting in a false positive.[10] Viral cultures require a minimum of 24 hours, and false negatives are frequent because of the difficulties in the growth of certain viruses, obtaining samples after the shedding period, and inappropriate sampling sites. The CSF is almost always negative for virus isolation.[11] In none of the reviewed cases were viral cultures positive. Other CSF studies also frequently fail to indicate active infection, especially early in the course. The patients of Wilson[4] and Koehler and Guth[7] did demonstrate elevated CSF white counts, but only after three and five weeks, respectively, of illness. All of the other patients had negative CSF smears, microbiologies, and chemistries, as also noted in this case. Reportedly, CT scans with contrast will indicate encephalitis in most cases, yet the few scans done in these cited patients were negative despite definite neurological and EEG evidence of infection. Raskin and Frank's patient[3] even had a negative brain biopsy while comatose and seizing. Wilson's second case[4] had a negative biopsy when the EEG was grossly abnormal and there was clear clinical evidence of encephalitis. These discrepancies may represent poor choice of sampling site, as the temporal lobes are preferable with herpes, or inoptimal sampling time because of the chronicity of the illness.[12] Confirmatory diagnoses were made most often by electroencephalography. The EEG may indicate encephalitis before any of the other tests are diagnostic and even before clinical symptoms are evident. It is almost always positive in acute encephalitis,[13] the degree of abnormality reflecting the severity of infection, degree of cerebral involvement, and level of consciousness.[14] Different viral agents may produce characteristic patterns, especially herpes, although none is pathognomonic for the particular virus.[13] In addition, serial EEGs will indicate clinical improvement and prognosis. Despite such general usefulness, two of the cases did report negative EEGs. Wilson's third patient[4] did not manifest EEG changes until he developed temporal lobe status epilepticus. Since herpes characteristically infects the temporal lobe and the EEG often shows a characteristic pattern with temporal evolution,[13] although special nasopharyngeal electrodes may be required to detect the abnormalities,[15] this patient may have been inadequately evaluated. Steinberg et al[5] reported no EEG abnormalities "other than those that could be attributed to neuroleptic medications and level of consciousness." It is unclear from this statement that the EEG was in fact negative, as medications may have interfered.

Medication regimens further complicate care. Neck stiffness, emesis, headache, and sedation are all possible side effects of neuroleptics as well as signs of encephalitis. In addition, antipsychotics can depress the white blood count, and lithium can elevate it, while high-dose phenothiazines may produce malignant hyperthermia[16] or simple drug fever at lower dosages. Thus, neuroleptics can mimic infection. The confounding effect of medications on the EEG was demonstrated by Wilson's false case of chlorpromazine encephalopathy,[4] and the allegedly normal EEG in the case reported by Steinberg et al.[5]

The lack of positive laboratory tests early in the patient's course and the potential medication complications resulted in psychiatric staff minimization of subsequent symptoms, as may also occur in medical settings.[17] Prominent indicators of organic disease, such as fever, were discounted, as in the previously reviewed literature cases. The history of social problems, eg, this patient's marital conflicts, may suggest a psychiatric diagnosis, while mental status changes, eg, lethargy, may be interpreted as "avoidant" because of assumed poor self-esteem.[18] Therefore, appropriate medical intervention may be delayed in patients with psychiatric diagnoses, even if they do not have well-established psychiatric reputations, and the delay may lead to overusage of medical facilities.[19]

In summary, the coincidence of two major illnesses in this patient compromised her care. Suspected medication effects and the staff stereotyping of psychiatric illness obscured evidence of evolving encephalitis. The negative laboratory evaluation, especially the CSF, further misled the diagnosis. Only the EEG definitely indicated acute infection. Once the encephalitis was established, the differential diagnosis of encephalitis superimposed on bipolar illness from organic mania was possible on clinical grounds only. This case illustrates some difficulties in differentiating psychiatric and organic psychoses and the usefulness of the EEG as a sensitive diagnostic tool. It further emphasizes the need for full medical evaluations with any atypical psychiatric course.

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