Psychosis Secondary to Anti-N-methyl-D-Aspartate Receptor Encephalitis

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CASE HISTORY

Presentation in Emergency Room (Days 1–2)

Ms. B is a 24-year-old, single, black woman with a past medical history of dysfunctional uterine bleeding and no previous psychiatric history, who was sent to the emergency department by her coworkers for evaluation of acute memory loss and psychological distress. Her coworkers were concerned about her abnormal behavior, such as arriving to work distressed and tearful, and repeatedly stating that she did not remember how she got there. The previous day she had a similar presentation and was taken to another hospital's emergency department, where a noncontrast head CT scan revealed no significant findings; she was discharged for outpatient workup. Until that point, she was reported to have been a productive and conscientious worker, and her current presentation was felt to be unprecedented and atypical.

On psychiatric interview, she repeatedly asked why she was in the hospital, often within one minute of asking previously. She exhibited a labile mood and was initially guarded and somewhat paranoid. Over a period of several minutes however, she became more relaxed and was able to communicate more successfully. She attributed her presentation to "anxiety" and explained that she had been too busy to be able to seek appropriate mental health treatment. She was unable to detail acute stressors beyond financial matters. She remarked she had persistent anxiety for the past five years, which had slowly progressed to the point of preventing her from driving or from leaving her apartment (except when necessary, as for work). She noted that prior to this time she had been quite social, exemplified by going dancing, singing, and traveling. She also endorsed depression for years, though never to the extent of suicidal ideation or attempts, and had no thoughts of self-harm at the time of the interview. She reported racing thoughts and a decreased need for sleep (generally sleeping only a few hours a night), though she vaguely mentioned that these symptoms had been occurring for years. She remarked that she was able to hear her next-door neighbors' conversations as though they were in her head. Other sounds, such as others' conversations and laughter, felt intrusive to her, and she found them louder than her own thoughts and very distracting. She denied any visual hallucinations or command auditory hallucinations. She did express some paranoia—in particular, that her coworkers were speaking about her behind her back and that she was going to lose her job.

She had no known family history of psychiatric or neurologic disease, though she was in foster care since age 8 and had limited knowledge of her biological parents. She stated that she had few supports beyond her roommate, though aunts and cousins visited her in the emergency department, and they commented that she was close with her grandmother. Substance abuse history was notable only for cigarette smoking and rare alcohol consumption. She did have a significant trauma history of sexual abuse from her foster father at age 16 resulting in pregnancy, for which she underwent an elective termination. She has since had nightmares with frequent flashbacks, avoidance, and paranoia of men in general. She was followed by gynecology for dysfunctional uterine bleeding that developed after reinitiation of injectable medroxyprogesterone following elective termination six months earlier. At that time, a pelvic ultrasound was notable only for a 0.6 cm calcified echogenic focus with posterior shadowing on her left ovary.

Further mental status examination revealed her to be somewhat inattentive, with pressured and fragmented speech, and near flight of ideas. Cognitive exam was notable for good memory registration but poor recall (recalled 0/3 words after a few minutes, 1/3 with multiple choice). Otherwise, her calculations, fund of knowledge, naming, repetition, and orientation were appropriate. Neurologic exam and vital signs were normal at this time.

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At the time of her emergency room evaluation, her presentation was felt to most closely resemble an acutely manic state with psychotic symptoms. Her presentation was thought to be somewhat atypical, as her main symptoms were amnesia and distractibility. She appeared to improve with a trial of risperidone and lorazepam overnight in the emergency department, though she continued to display anterograde amnesia and inattention. Due to concern for her potential inability to care for herself at the time and less than satisfactory improvement, she was admitted involuntarily to an inpatient psychiatric facility.

Psychiatric Inpatient Course (Days 2–10)

Ms. B was treated at the psychiatric facility with standing olanzapine up-titrated to 20 mg at bedtime and additional medications, as needed, for worsening agitation. Antipsychotics appeared to fail in reducing her symptoms, and her agitation was only mildly responsive to benzodiazepines. In particular, she had inadequate responses to risperidone, haloperidol, quetiapine, and diphenhydramine. Worsening memory and confusion, along with episodic dissociation, were felt inconsistent with a typical first episode of agitated psychosis, and the practitioners caring for her decided to pursue a neurologic evaluation. Unfortunately, due to her agitated and disorganized nature, she was not able to participate in diagnostic studies such as head imaging or electroencephalogram. She was therefore transferred to a tertiary facility for neurologic assessment and diagnostic evaluation under sedation.

Neurology Inpatient Course (Days 10–36)

Ms. B was admitted to neurology service at a tertiary care teaching hospital, where she underwent diagnostic procedures, including the following: MRI of the brain with contrast, which revealed no abnormalities; lumbar puncture, which revealed WBC count of 8 (96% lymphocytes) but was otherwise normal; and EEG, which showed diffuse slowing consistent with encephalopathy but without seizures or epileptiform abnormalities. Given the combination of acute-onset psychiatric changes and amnesia, concern arose for anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. While awaiting the serum and CSF anti-NMDAR antibody studies and after performing further imaging of her ovaries, she was initiated on steroids (methylprednisolone 1 g/day for 5 days) and intravenous immunoglobulin (IVIg; 2g/kg over 5 days) due to high suspicion for autoimmune encephalitis.

Her mental status was initially agitated: she pulled out IV lines and attempted to strike or spit at staff, requiring four-point restraints at times. She developed repetitive stereotyped pouting movements of her mouth and repeated grimacing (orofacial dyskinesias) and dysautonomia (fluctuations in her heart rate and blood pressure) that was refractory to clonidine and propanolol and was then treated with IV labetalol. She became more somnolent over the next few days, with decreased arousability that ranged from following simple commands to being barely arousable to sternal rub. She appeared catatonic at times. The psychiatry team suggested a trial of lorazepam for her catatonia, but it appeared to have little effect on her mental status.

She developed worsening dysautonomia, including fever to 101F, hypertension to 160 mm Hg systolic, tachycardia to 110 beats per minute, and tachypnea with a rate of 40 breaths per minute accompanied by blood oxygen desaturations to 70%. She was therefore transferred to the neurologic intensive care unit on day 19 (10th day of neurology course). Her serum and CSF anti-NMDAR antibodies ultimately returned positive. Pelvic ultrasound and MRI did not reveal ovarian abnormalities, but a transvaginal ultrasound was suggestive of bilateral subtle ovarian abnormalities.

Oophorectomy was felt indicated for treatment of her condition, but the patient was not able to consent to this procedure. Legal proceedings granted her grandmother temporary guardianship, and her grandmother consented for bilateral oophorectomy on day 22 (12th day of neurology course). Pathology confirmed right ovarian, mature, cystic teratoma.

After surgery, she began to show clinical improvements. Her lorazepam requirements began to decrease; her dysautonomia began to resolve; and she became more interactive from her somnolent and withdrawn state. At postoperative day 6 she was transferred from the ICU to the floors. She subsequently developed mild agitation and paranoia, and suffered from anterograde amnestic symptoms that required frequent reorientation and explanation of her hospital stay. Her agitation was effectively treated with quetiapine. Upon her discharge from the hospital on postoperative day 14, she had greatly improved, with fluent speech, good eye contact, appropriate responsiveness to questions, resolving motor symptoms of catatonia, and resolution of psychotic symptoms. She continued to have retrograde amnesia, with no recollection of her hospital stay. She was discharged to a comprehensive, residential rehabilitation program.

Outpatient Follow-Up

Ms. B was seen three weeks after discharge from inpatient hospitalization and continued to have complete amnesia regarding her hospital stay, with resumption of her memory around the time of her rehabilitation. She made steady progress with speech therapy, occupational therapy, and physical therapy, and continued to be followed as an outpatient, with a focus primarily on cognition, as she continued to express difficulty multitasking.

In rehabilitation she was started on buspirone 10 mg/day, sertraline 100 mg/day, and trazodone 150 mg at bedtime for endorsed neurovegetative symptoms, including difficulty sleeping, decreased energy, and poor appetite. She feels the medications have been helpful. Her mental status exam showed persistent difficulty with memory: although she was

able to register 3/3 words on testing, she recalled only 1/3 and 2/3 with multiple-choice prompts. Otherwise, she was oriented, attentive, and fluent, with good fund of knowledge and a linear thought process without psychotic or delusional thought content. Her mood was still low at times because of her loss of fertility, though she understood both the necessity for the operation and the clinical judgment used.*

QUESTIONS TO THE CONSULTANTS

1. Neurology: What is the neurologic overview of anti-NMDA receptor encephalitis?
2. Psychosomatic medicine: Given Ms. B's initial presentation, was it right for Ms. B. to be admitted to a psychiatric hospital? When should an inpatient psychiatric hospital transfer a patient to a general medical hospital?
3. Forensic psychiatry: What legal complications present in this case should a physician be aware of?

Aaron Berkowitz, MD, PhD, and Maya Srikanth, MD, PhD

The syndrome of psychiatric symptoms, memory deficits, altered consciousness, and autonomic instability associated with anti-N-methyl D-aspartate receptor (NMDAR) antibodies was first described in 2007.[1] Since that time, anti-NMDAR encephalitis has become one of the most frequently diagnosed encephalitides, four times more common than viral causes of encephalitis and the second most common autoimmune cause of encephalitis after acute disseminated encephalomyelitis (ADEM).[2,3] Because the illness first manifests with psychiatric symptoms, many patients with this condition present first to psychiatrists.

Clinical presentation The core clinical features of this syndrome are best described in the largest cohort study of 577 cases of anti-NMDAR encephalitis.[4] Patients typically present with psychiatric symptoms such as delusional thoughts, paranoia, hallucinations, disorganized behavior, fear, agitation, or personality changes.[5] In children (≤18 years old), symptoms of mania (e.g., hyperactivity, irritability, and sleep disturbances) may also occur.[6] Since the median age at presentation is 21, many patients ultimately found to have anti-NMDAR encephalitis are initially thought to have the first manifestations of schizophrenia. Neuropsychiatric symptoms that would be atypical in early schizophrenia, such as short-term memory deficits, confusion, echolalia, and perseveration, should lead to consideration of anti-NMDAR encephalitis. In our patient, the presence of significant amnesia and confusion was an early indication that an underlying neurologic etiology for psychiatric symptoms should be considered. Additionally, up to 70% of patients initially experience a viral prodrome 1–2 weeks before the onset of psychiatric symptoms, with the prodrome consisting of malaise, fever, and either upper respiratory or gastrointestinal symptoms, which would also be atypical for primary psychiatric illness.[7] Additionally, anti-NMDAR encephalitis may occur following treatment of herpes simplex virus (HSV) encephalitis—a syndrome previously attributed to the relapse of HSV encephalitis or to the neuropsychiatric sequelae of the disease.[8]

The early psychiatric manifestations of anti-NMDAR encephalitis typically last 1–3 weeks, at which point neurological changes become more apparent, including the following: profound fluctuations in behavior between agitation and catatonia; movement disorders, including orofacial dyskinesias (55%), dystonic posturing (47%), and choreiform limb movements (47%); seizures (76%); and autonomic instability (69%), including hyperthermia, swings in blood pressure and heart rate, and central hypoventilation, often requiring ICU-level care.[5,7] The orofacial automatisms in our patient were characteristic of the disorder. Although orofacial dyskinesias can be seen in schizophrenia, these are due to long-term effects of treatment. Any movement disorder at onset of first psychiatric symptoms should raise concern for an underlying neurologic disease.

Since patients are often treated with antipsychotics for their initial symptoms, such changes may be attributed to the development of neuroleptic malignant syndrome. Indeed, our patient had an elevated creatine kinase (CK) of 4500 U/L (normal range, 26–192 U/L) but lacked other features of neuroleptic malignant syndrome such as hyperthermia and rigidity.[9] In addition, an inflammatory CSF profile with elevated WBCs is not characteristic of NMS. CK levels can also be elevated in anti-NMDAR encephalitis, with one study citing a range of 415–18,000 U/L.[6] This elevation may be due to seizure activity in some patients, but since our patient did not develop seizures, it is unclear what caused her CK elevation. Of note, the dysautonomia in anti-NMDAR encephalitis patients develops independently of administration of neuroleptics.

Epidemiology Anti-NMDAR encephalitis was initially described in women as a paraneoplastic syndrome associated with ovarian teratoma.[10] Only about half of affected patients, however, have an underlying tumor.[7] Affected individuals are primarily children and young adolescents (median age = 21), with women affected four times as frequently as men. In women over 18 with the disease, 50% have an underlying tumor, 96% of which are ovarian teratomas.[7] The incidence of associated ovarian teratomas is higher in African American females and lower in women under 18 (31%).[7] Only 5% of affected men are found to have an underlying tumor, primarily testicular germ cell tumors. The syndrome has also been reported with breast cancer, pancreatic cancer, neuroblastoma, and Hodgkin's lymphoma.

Diagnosis Definitive diagnosis is made by detecting the anti-NMDAR antibody in serum or cerebrospinal fluid in the appropriate clinical context. False-positive serum antibody test results have been reported with serum in patients who do

*The case history was prepared by Geoffrey Raynor, MD, Caroline Bader, MD, and Maya Srikanth, MD, PhD.

not have clinical features of the disease; CSF antibodies have been negative in nearly all such patients.[11,12] The sensitivity of CSF antibody testing nears 100%, whereas the sensitivity of serum antibody testing is only 65%–85%.[13] The specificity of the serum antibody is 97%–100%, with this variability attributed to differences in the methods used for antibody detection.[14]

Anti-NMDAR antibodies have also been detected in up to 10% of patients with schizophrenia, but the antibodies are typically IgA or IgM subtypes, as opposed to the IgG subtype seen in anti-NMDAR encephalitis; when IgG antibodies were detected in patients with schizophrenia, they were not specific to the NR1a subunit, as are the antibodies in the anti-NMDAR encephalitis, but also demonstrated reactivity to the NR2b subunit.[15] Importantly, in patients with schizophrenia whose CSF was examined, none had CSF antibodies to the NMDAR.[12] The significance of NMDAR antibodies in schizophrenia remains unclear, but the diversity of antibody subtypes and target epitopes suggests the possibility that these antibodies are an epiphenomenon rather than causative of schizophrenia (e.g., neuronal damage by the underlying pathogenic process in schizophrenia may expose NMDAR epitopes, leading to the development of antibodies).[12] Antibody results may take up to two weeks to return, but other diagnostic studies may sufficiently support the diagnosis to consider initiating treatment. MRI may demonstrate FLAIR hyperintensities in limbic regions (e.g., medial temporal lobes, insula), brainstem, basal ganglia, or cortex, but the results are normal in 50% of patients.[1] EEG is usually abnormal, but findings are typically nonspecific (slowing, seizures). Although a unique EEG pattern referred to as the "extreme delta brush" has been described in NMDAR encephalitis, it is seen only in 30% of patients.[16] CSF is abnormal in most patients, demonstrating a lymphocytic pleocytosis, elevated protein, or oligoclonal bands, although normal CSF is seen in 5% of cases and therefore does not eliminate the possibility of the disease.[5]

In women in whom the disease is suspected, an evaluation for ovarian teratoma should be undertaken; transvaginal ultrasound is the most sensitive study. Some patients with no radiologic evidence of teratoma, however, have been found to have small teratomas on pathologic examination when oophorectomy has been performed.[17]

Pathophysiology Anti-NMDAR antibodies (usually IgG1 or IgG3 subtypes) target the NR1 subunit of the NMDA receptor.[7] Binding of these antibodies to the receptor causes internalization, resulting in GABAergic neuron inactivation and subsequent glutamatergic hyperactivity.[18] Such glutamatergic hyperactivity in frontostriatal circuits is thought to result in the salient features of the syndrome.[7] CSF titers of these antibodies correlate with disease progression and recovery, suggesting that the antibodies themselves are pathogenic. This situation contrasts with other autoimmune encephalitides, such as Hashimoto encephalitis, in which anti-thyroid antibodies are believed to be a marker of disease but not directly causative of the clinical manifestations.

The discovery that anti-NMDAR antibodies are pathogenic in a condition that produces prominent psychotic symptomatology supports theories of NMDA receptor hypofunction as a mechanism underlying schizophrenia.[19] Indeed, subclasses of anti-NMDAR antibodies distinct from those associated with anti-NMDAR encephalitis have been detected in patients with schizophrenia, suggesting an even more intricate relationship between autoimmunity, NMDA dysfunction, and psychiatric disease.[15]

Treatment Definitive treatment requires removal of a tumor, if identified. Since up to half of patients have no tumor, initial treatment focuses on immunomodulatory therapy with steroids, intravenous immunoglobins (IVIg), or plasma exchange.[7] If clinical suspicion is high, patients are sometimes treated empirically while awaiting surgery or antibody laboratory results. Given our patient's rapidly worsening mental state and dysautonomia in the setting of high clinical suspicion for anti-NMDAR encephalitis, corticosteroids were initiated immediately, and IVIg after her lumbar puncture confirmed an inflammatory process. If there is no clinical response to those agents, rituximab, cyclophosphamide, or both are used—and are likely necessary to use when no underlying tumor is discovered. Also in such cases, ongoing immunosuppression is often necessary after the acute phase of the illness; steroid-sparing agents such as mycophenylate mofetil or azathioprine may be used. Although no consensus guidelines have been established on using second-line immunosuppression, a proposed treatment protocol suggests the initiation of second-line agents if no clinical improvement is seen after ten days, and to continue such immunosuppression for one year or until significant clinical improvement is seen.[7] Continued surveillance for the development of an underlying ovarian teratoma is also necessary, as the syndrome may precede radiologic evidence of an underlying tumor. Our patient demonstrated clinical improvement following removal of her teratoma, so second-line immunosuppression was not indicated.

In addition to immunotherapy, supportive therapies play a vital role. Many patients require ICU-level care when autonomic instability is a prominent feature of the clinical course. Intubation may be required for hypoventilation. Patients with anti-NMDAR encephalitis require multidisciplinary care throughout the illness and recovery, with close collaboration between neurologists and psychiatrists. For management of neuropsychiatric manifestations, neuroleptics and sedatives are often used, and benzodiazepines may be required to treat catatonia. Given the dyskinetic movement disorders that may occur, caution should be used with typical antipsychotics such as haloperidol, which may exacerbate abnormal movements.[20] Benzodiazepines and atypical neuroleptics such as quetiapine are preferred.[20]

CLINICAL COURSE Recovery occurs over a period of months, and evolves through a retracing of the illness in reverse, with stabilization of autonomic dysfunction, followed by normalization of dyskinesias and cessation of seizures before neuropsychiatric recovery.[7] Many patients (64%) have ongoing cognitive and behavioral deficits, including executive dysfunction, sleep dysregulation, and impulsive behavior.[5] Patients often recall very little from the acute phases of the illness, although a striking first-person narrative has been reported.[21] Relapse of psychiatric manifestations occurs in 20%–25% of patients and is more commonly seen in patients without an underlying tumor.[4] With treatment, about 75%–80% of patients ultimately recover fully or with minimal sequelae.[4] Our patient's recovery following her surgery recapitulated the phases of her illness in reverse, with stabilization of her dysautonomia followed by resolution of her orofacial dyskinesias and finally improvement in her mental status, though she had persistent amnesia for the period of her illness, which is common in the disorder.

Early intervention is associated with improved outcomes, with longer time to treatment initiation associated with fewer patients returning to the state of no or only slight disability (modified Rankin scale, 0–2).[4,22] Given that most patients present first to psychiatrists, early recognition by psychiatrists is essential for expediting diagnosis and treatment. The main differential diagnosis for anti-NMDAR encephalitis is a first presentation of schizophrenia, but early cognitive dysfunction (especially memory loss), movement disorders (especially orofacial dyskinesias), wide fluctuations between positive and negative psychiatric symptoms, lack of response to antipsychotics, and presence of a viral prodrome should all lead to consideration of anti-NMDAR encephalitis as a cause of the patient's symptoms. In our patient, prominent amnesia and fluctuations between psychosis and catatonia were deemed atypical for an initial presentation of psychiatric illness, and emergence of orofacial dyskinesias and dysautonomia provided sufficient clinical evidence to pursue diagnosis and initial empiric treatment while awaiting results of diagnostic studies.

New autoimmune encephalitides are being characterized yearly, with 12 now described—a situation that provides increasing opportunity for clinical and scientific collaboration between neurologists and psychiatrists in the diagnosis, management, and characterization of these diseases, their phenomenology, and their pathogenesis.[23]

David Kroll, MD

There remains so much we do not understand about the phenomenon we call *psychosis*. Even as the field of psychiatry advances toward uncovering various neurodevelopmental processes that might or might not underlie this umbrella term for a group of heterogeneous disorders, we are finding it harder and harder to define it nosologically.

Schizophrenia spectrum has replaced *Schizophrenia* in the *Diagnostic and Statistical Manual of Mental Disorders*, and today's literature is punctuated with updated terms that attempt to capture relevant symptom presentations such as *first-episode psychosis*, *emerging psychosis*, and *prodromal symptoms*. How, then, can a general hospital psychiatrist view a patient like Ms. B, who presents with an apparent first-episode psychosis, and say whether her presentation is typical or atypical? Here is a woman with no clearly defined indicators of psychosis risk—no known family history and no clearly established track record of a major psychiatric illness, personality disorder, or identifiable prodromal symptoms—who apparently developed severe mental status abnormalities acutely, over a period of several days. To what template should we compare her?

Despite our broadening understanding of how heterogeneous the schizophrenia spectrum is, it is still important to start by asking the question, "Is this or isn't it first-episode schizophrenia (FES)?" Schizophrenia is a neurodegenerative process that typically emerges in early adulthood, often following a prodromal period of several years (which was absent from Ms. B's case).[24] This question of whether prodromal symptoms or other early indicators of psychosis risk are essential to a diagnosis of schizophrenia is a key one, even though they are not listed as diagnostic criteria by the DSM. An illness course that progresses from risk indicators, to prodrome, to first-episode psychosis, to progressive neurodegeneration is certainly common and is readily identifiable as a classic case of schizophrenia—and is what Kraeplin characterized when he coined the term *dementia praecox*. The literature describing the early stages of this illness is inconsistent and often vague, however, relying on such terms as *unspecific symptoms*.[25,26] Woodberry and colleagues[27] measured the frequency of patients with psychosis who had experienced nonspecific symptoms in childhood and found the frequency to be 57.5%, and 11% had childhood symptoms identifiable as *attenuated psychotic symptoms*.[27] Schultze-Lutter and colleagues[28] identified attenuated psychotic symptoms at least one month prior to onset of the psychotic episode in 98.4% of patients who presented for hospital admission with first-episode psychosis.[28] From their review of the literature, Debbané and colleagues[29] identified schizotypy as being another common risk indicator for psychosis, yet the term *schizotypy* remains vague and inconsistently applied.[29] These examples are by no means exhaustive of the existing data regarding the prevalence of premorbid symptoms, but they illustrate that premorbid symptoms, while difficult to define and not necessarily described in a uniform way, should be looked for when making a diagnosis of FES. They also tell us that the absence of premorbid symptoms does not make a diagnosis of FES impossible.

The abrupt onset of psychosis also warrants consideration of bipolar disorder, even though Ms. B's presentation was not strongly suggestive of acute mania. As for schizophrenia, prodromal symptoms that are varied and nonspecific have been commonly described, including emotional disturbances, anxiety, personality disorders, attention disorders, and substance abuse, but such symptoms are not absolutely necessary for

the diagnosis.[30,31] A recent, population-based study conducted by Serra and colleagues[31] identified psychopathological symptoms occurring prior to age 18 in 83.4% of patients with bipolar disorder.[31] A prior diagnosis of major depression is especially common (particularly if onset occurred in childhood), as is a family history of bipolar disorder.[32,33]

Ms. B.'s history was not notable for any such "clues" to a diagnosis of either schizophrenia or bipolar disorder. It would be fair to say that her history of anxiety and posttraumatic symptoms and her largely unknown family history (her involvement in the foster care system suggests possible psychopathology in her biological parents) place her at somewhat increased risk of major mental illness compared to the general population. But the atypical way in which she presented—abruptly and with severe cognitive deficits in addition to (and perhaps out of proportion to) her apparent positive psychotic symptoms, along with her weakly increased premorbid risk—demands a more thorough medical workup than might ordinarily be done prior to consideration of psychiatric hospitalization.

Of course, a comprehensive medical workup was done in the emergency department. Physical exam, vital signs, neurological exam, basic laboratory workup, and head imaging did not elucidate any medical or neuropsychiatric etiology for her symptoms, and meanwhile she appeared to respond favorably to an antipsychotic trial. Even if an FES or manic episode would be rare in the absence of premorbid indicators, NMDAR encephalitis is also exquisitely rare, and in the absence of foresight, performing a test for this condition seems low yielding, involves a relatively high morbidity, and delays potentially definitive psychiatric treatment. The decision to transfer her to a psychiatric hospital for further stabilization of Ms. B's presumed atypical first-episode psychosis after a fairly comprehensive medical workup and an initial appearance of responding to treatment was both reasonable and appropriate. But her case evolved after that. In the psychiatric hospital her symptoms did not respond robustly to antipsychotics. Her confusion grew worse instead of better, although that could have been caused by high-dose benzodiazepine exposure. The psychiatric hospital cited failure to improve with conventional treatments after eight days as the rationale for transfer to the general medical hospital.

Failure to improve seems like an arbitrary criterion by which to trigger this kind of a transfer, even if it led to the correct treatment. The truth is that there are no formal guidelines by which to make such a decision, and medical transfers out of psychiatric hospitals have been characterized by only a few studies. Since most free-standing psychiatric hospitals do not have the resources to offer medical interventions onsite, they have established formal relationships with local general hospitals for the management of emergent medical needs.[34] Roughly 2%–7% of psychiatric admissions ultimately require transfer and admission to medical hospitals, and acute changes in medical parameters—for example, infection, laboratory abnormalities, neurological changes, or cardiovascular symptoms—are more likely to precipitate a transfer than preexisting conditions or symptoms.[35–37] A review of medical transfers from a free-standing psychiatric hospital conducted by Manu and colleagues[36] noted that anemia, elevated blood urea nitrogen or low albumin levels, and age >64 were predictors of medical deterioration requiring admission to the general hospital.[36] Leung and colleagues[37] determined that, among patients transferred to general hospitals from free-standing psychiatric facilities, cardiovascular problems, infections, and laboratory abnormalities were the most common admission indications.[37] However, objective criteria by which to determine whether or not a patient should be transferred for emergency medical care—or for further workup of an insidious medical or neuropsychiatric etiology of symptoms—have not been developed. Notably, a recent study of the rapid-response system for identifying and managing potential medical emergencies in psychiatric inpatients found that subjective concern on the part of nursing staff and objective indicators of medical symptoms (e.g., chest pain, vital sign abnormalities) were comparably predictive of a medical admission.[35] This finding suggests that the question remains hard to answer systematically but also that inpatient psychiatrists should always be cautious, especially when a patient does not present or respond to treatment in a typical way.

Catatonic symptoms and dysautonomia developed shortly after Ms. B transferred to the medical hospital, and these symptoms might have been considered acute, objective indications for emergency medical evaluation. There is no indication, however, that they were present while she was still in the psychiatric hospital. Rather, what prompted her psychiatric team to transfer Ms. B in advance of these acute symptoms was the team's impression that her case was atypical for a primary psychiatric illness and that it was not responding to treatments that are conventionally used for primary psychiatric illnesses. It was a clinical decision rather than an algorithmic one that saved her life: Ms. B.'s case was too atypical, or perhaps she was just too young or too acute, not to keep asking questions about her diagnosis when the conventional treatment for that diagnosis was not working.

Thomas Gutheil, MD

This complex and challenging case provides an opportunity to review some of the essential elements of competence, decision making, and informed consent—a review that becomes particularly necessary when the brain is compromised. Beginning with the basics may be called for.

Basics of informed consent The basic information presumed relevant to consent to treatment is the following: the risks and benefits of proposed treatment; the risks and benefits of alternative treatments; and the risks and benefits of "no treatment."[38,39] Consultative experience indicates that clinicians are generally familiar with the risks and benefits of a proposed treatment, somewhat less familiar with the risks

and benefits of alternative treatments, and less often inclined to offer the pattern for "no treatment." In fact, some treatment refusals are based on the treater's failure to outline the pros and cons of having that treatment. In Massachusetts, the case of *Harnish v. Children's Hospital*[40] ruled that a physician owes his patient the duty to disclose in a reasonable manner all significant medical information that the physician possesses or reasonably should possess, which is material in order for the patient to make an intelligent decision whether or not to undergo a proposed procedure. The court elaborated the notion of "material" as follows:

> Appropriate information may include the nature of the patient's condition, the nature and probability of risks involved, the benefits to be reasonably expected, the inability of the physician to predict results, if that is the situation, the irreversibility of the procedure, if that be the case, the likely result of no treatment, and the available alternatives, including their risks and benefits.

Three considerations may guide the information shared with the patient. First, *seriousness*: information about serious effects and side effects should be provided, and questions answered; these data work together with the "open door policy."

Second, *common* expected reactions. One of the major triggers of suit is alliance-breaking surprise ("What is happening to me that he didn't tell me about!!??"), whereas experiencing a side effect that has been foreseen and identified by the treater actually strengthens the alliance ("Oh, yes, there is that muscle stiffness the doctor warned me about; she must know what she is doing.").

Third, an *individualized approach*, fitted to the concerns of the individual. A computer jockey might be very sensitive to blurred vision; a young athlete may fear muscle stiffness; and a member of an older generation may be most concerned about constipation. Attention to these three and an open door policy will be most likely to achieve the goals of informed consent.

The second element of informed consent is voluntarity—the "consent" in informed consent. This constitutes the willingness to accept the proposed treatment. If a hospitalized patient is told, "Unless you take this pill, we won't give you your pants back," the voluntarity might well be in question.

The final element of informed consent is *capacity*; this term is preferable to *competence* in the clinical realm since, technically, only a judge can formalize capacity as competence, whereas themselves may reach opinions about decision-making capacity. Many clinicians are unaware that upon identifying a patient as lacking capacity or full capacity, as here, they acquire the ethical burden of being a "case finder"; in other words, it becomes a medical duty to take steps to assure that some appropriate decision maker will stand in for the patient to give vicarious consent to make treatment decisions. This category may include a judge, a guardian, a health care proxy, or—in an urgent situation—a next of kin. Of course, in a true emergency, defined in one sense as a matter of very high urgency or of life and death, informed consent is not required.

The concept of vicarious consent as here applied goes back to English law. When a noble lost capacity through age or infirmity, alternative decision making was required to preserve land in an island country; the king or a delegate would have a role in such decision making.

THE PRESENT CASE In the present case example, the patient clearly lacked capacity to express consent. A patient in so profound an altered state of cognition could not even evince a choice, the lowest level of consent, nor, because of impairment of both cognition and memory, could she understand her situation or any planned procedure. Since the treaters were confronted with an ongoing and likely worsening situation, some action was obviously called for.

DETAILS OF THE HEARING Because of the urgency of the situation and the deterioration of the patient's condition, which the judge on the case clearly grasped (arriving the very next day with a clerk), the hearing was held in a conference room at the tertiary care teaching hospital rather than at court. The first step was to find an attorney to act as the patient's advocate. The judge heard the case with the following witnesses: the OB-GYN team; the neurologist; the grandmother; the patient's advocate; the hospital's lawyer; the ICU nurse; and the social worker who served as liaison to the legal department.

All parties appeared to be in agreement about the regrettable necessity of the bilateral operation, since there were tumors on both sides. Note finally that the hospital personnel (who would fully qualify as fact witnesses [direct observers]) were qualified by the judge as expert witnesses for the purpose of this hearing; as such, they would be permitted to present conclusions, not just observations. Court attendees noted that the cross-examination was more a fact-finding approach rather than the more familiar attempts at destroying the credibility of witnesses; in a case like this, with strong agreement among parties, the defense attorney may be more inclined to show due diligence, probing all the alternatives, rather than trying to impeach the witness entirely.

Finally, the Massachusetts standard for vicarious decision making is not the best interests of the patient but, instead, "substituted judgment"; by this standard the decision maker, here the judge, attempts to divine what the incompetent patient would have wanted, were she competent. Interestingly, the grandmother testified that the patient had indicated at an earlier point that she did not want children: a position reinforcing the sterilization decision by substituted judgment.

FINAL COMMENTS A question arises: could the grandmother as health care proxy consent by herself to so extensive an operation? In theory, probably so, but since the procedure ends by sterilizing a 24-year-old, single, childless woman, the court was appropriately involved. Many jurisdictions give courts

(i.e., judges) great leeway in making these decisions. Note also that sterilizations have long been identified by courts as "extraordinary procedures" that require the type of judicial oversight effected in the case.

The grandmother was judicially appointed temporary guardian of the person and vicariously consented to the operation, presumably after having been informed about the magnitude of the threat and the serious consequences of the procedure itself, as well as the consequences of doing alternative procedures and doing nothing. The present case serves as an excellent example of the complexities of competence assessment, of vicarious consent, and of legal proceedings in such cases.

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