The Evolving Standard of Care for Autoimmune Neuropsychiatric Illness

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In recent decades, there has been increasing biomedical and public understanding of the role of autoimmunity in neuropsychiatric illness. Popular media have highlighted patients with psychiatric illnesses who were eventually diagnosed with autoimmune neuropsychiatric illnesses such as anti–N-methyl-D-aspartate receptor encephalitis. Coverage of these cases has often drawn attention to the effects of misdiagnosis or delayed diagnosis of such diseases in psychiatric patients. Autoimmune encephalitis can have varied presentations and often involves evaluation and management from multiple medical specialties. As a result, there remains considerable uncertainty regarding how courts might gauge the legal standard of care with regard to psychiatric workup of new-onset psychiatric symptoms, and the degree to which autoimmune encephalitis must be considered. In this article we provide a brief overview of autoimmune encephalitis and autoimmune psychosis, including current diagnostic approaches to these conditions. We review case law regarding the standard of care for psychiatric disorders caused by general medical conditions. Finally, we provide a medicolegal perspective on the responsibilities of psychiatrists and other mental health professionals in the evaluation of possible autoimmune encephalitis.

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In recent decades, as the medical community has developed a greater understanding of the potential role of autoimmune pathophysiology in psychiatric illness, the lay community has also become increasingly aware that psychiatric illnesses can be caused by autoimmune disease. Susannah Cahalan's best-selling 2012 memoir, *Brain on Fire: My Month of Madness*, which has been made into a film, chronicled the author's experience of autoimmune encephalitis.[1] According to her book, she developed personality changes, paranoia, and hallucinations; was diagnosed as having alcohol withdrawal or bipolar disorder; and was then prescribed antipsychotic medication. Eventually, her behavior and function declined to the point of having multiple seizures and requiring hospitalization. After weeks of inpatient care in New York City, she was eventually diagnosed with anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis and treated with immunotherapy.[1]

Media outlets have examined additional cases where autoimmune encephalitis was initially diagnosed as a mental illness. For example, a 2022 BBC Ideas video titled "The misdiagnosis that sent me to psychiatric hospital" featured the experience of a woman with anti-NMDAR encephalitis who was initially hospitalized in a psychiatric unit before her diagnosis was updated weeks later.[2] Notably, this video acknowledged that while anti-NMDAR encephalitis can be misdiagnosed in this manner, psychiatric illnesses, such as functional neurological disorder (FND), can also be misdiagnosed as nonpsychiatric illnesses.

A 2023 Washington Post article described a patient who was diagnosed with schizophrenia in

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her early 20s and eventually placed at a state psychiatric hospital, where she remained catatonic despite extensive medication treatment and electroconvulsive therapy.[3] According to the article, a medical reassessment conducted almost 20 years later found that she had signs of neuropsychiatric lupus, though her symptoms were indistinguishable from those of schizophrenia. The article noted that after multiple rounds of intravenous steroids, cyclophosphamide, and rituximab, the patient improved enough to be able to move to a rehabilitation center. The author wrote: "While it is likely that only a subset of people diagnosed with schizophrenia and psychotic disorders have an underlying autoimmune condition, [. . .] there are probably many more patients whose psychiatric conditions are caused or exacerbated by autoimmune issues" (Ref. 3, p 9).

Increasing public awareness of and interest in autoimmune neuropsychiatric illness may enable patients and families to advocate more effectively for appropriate diagnoses, connect patients with necessary care, and bolster research funding and allocation of clinical resources. At the same time, while conditions such as anti-NMDAR encephalitis are relatively rare, the possibility of a missed or delayed diagnosis may have legal implications for mental health professionals. Such conditions raise a significant question for psychiatrists and other practitioners who encounter psychiatric symptoms in many patients on a daily basis regarding the standard of psychiatric care for the workup of autoimmune neuropsychiatric illness. This article provides a brief overview of autoimmune encephalitis and autoimmune psychosis, including current diagnostic approaches. We review case law regarding the standard of care for psychiatric disorders caused by general medical conditions. Finally, we provide a medicolegal perspective on the responsibilities of psychiatrists and other mental health professionals in the evaluation of autoimmune neuropsychiatric illness. These standard-of-care considerations likely have broad implications for other types of neuropsychiatric illnesses.

Autoimmune Encephalitis and Psychosis

Reports of psychiatric illness associated with autoimmune encephalitis (AE) have increased in the medical literature over the last two decades. A variety of autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, thyrotoxicosis, Sjögren syndrome, and vasculitis, can cause psychiatric symptoms ranging from subtle personality changes to psychosis and catatonia.[4] In 2001 and 2006, Diamond and colleagues published research implicating autoantibodies against the N-methyl-D-aspartate (NMDA) receptor in the neuropsychiatric manifestations of lupus.[5,6] In 2005, Dalmau and colleagues[7] described four cases of young women patients with subacute or acute psychiatric symptoms, including behavioral and personality changes, rapid neurological deterioration including seizures, and altered mental status. In addition to abnormalities seen on brain magnetic resonance (MRI) and positron emission tomography imaging, the patients' spinal fluid contained antibodies against an unknown protein present in hippocampal neurons. Notably, all four patients were eventually diagnosed with ovarian teratoma. In 2007, Dalmau *et al.* identified the antigens as subunits of the N-methyl-D-aspartate receptor (NMDAR) and characterized the clinical syndrome as paraneoplastic autoimmune NMDAR-related encephalitis,[8] now known as anti-NMDAR encephalitis. Of the 12 patients described in the 2007 report, three presented initially with short-term memory loss followed by onset of psychiatric symptoms or altered mental status. Nine of the twelve initially had psychiatric symptoms such as personality or behavioral change, agitation, or paranoia; six of the twelve had initially been evaluated by psychiatrists; and five of the twelve had been admitted to psychiatric units.[8]

Since 2007, numerous additional etiologies for AE have been characterized, with pathogenic antibodies against a variety of neuronal intracellular antigens (including Hu and glutamic acid decarboxylase (GAD)), synaptic receptors (including NMDA and AMPA), or cell-surface proteins (including leucine-rich glioma-inactivated 1 (LGI-1), myelin oligodendrocyte glycoprotein antibody (MOG), and Aquaporin 4).[9] In light of these findings, clinicians must now consider AE as part of the differential diagnosis for acute psychiatric illness, particularly in cases of psychosis that are atypical in onset or associated with other general medical concerns (e.g., emerging after a neoplasm or viral infection).[10] Of note, while anti-NMDAR encephalitis has become known in part for its prominent psychiatric phenotypes,[11] including psychosis, neuropsychiatric symptoms (particularly memory deficits or altered mental status) are common in other forms of AE, including limbic encephalitis.[9,11]

As summarized by Graus and Dalmau, the term "autoimmune psychosis" was originally coined "to designate patients with schizophrenia or [first episode

Table 1 Risk Stratification and Diagnostic Criteria for Autoimmune Encephalitis/Psychosis

Screening Tool: Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score (Dubey 2018)[14]

+1 point each:

- New-onset, rapidly progressive mental status changes (1–6 weeks) or new-onset seizures (past year)
- Neuropsychiatric symptoms
- Autonomic dysfunction

+2 points each:

- Viral prodrome
- Facial dyskinesias (if no faciobrachial dystonic seizures)
- Seizures refractory to >2 antiepileptic medications
- CSF findings of inflammation
- MRI showing demyelination or inflammation (such as T2/FLAIR medial temporal hyperintensity)
- Systemic cancer within 5 years of neurological symptom onset

+3 points: Faciobrachial dystonic seizures

APE2 score ≥4 suggests possible AE /autoimmune psychosis:

Possible AE *(Graus 2016)*[9]
Rapid progression (<3 mo) of working memory deficits, altered mental status, or psychiatric symptoms, *AND* at least one of:
- New focal CNS findings
- Unexplained seizures
- CSF pleocytosis (>5 WBCs/μL)
- Characteristic signs of demyelination or inflammation on brain T2 MRI

AND reasonable exclusion of alternative diagnoses

Possible autoimmune psychosis (Pollak 2020)[15]
Rapid progression (<3 mo) of current psychotic symptoms, *AND* at least one of:
- Current/recent tumor diagnosis
- Movement disorder
- Adverse response to antipsychotics (e.g., NMS)
- Significant cognitive dysfunction
- Decreased consciousness
- Unexplained seizures
- Autonomic dysfunction

Also see Graus et al 2016[9] for diagnostic criteria for autoantibody-negative but probable AE and other encephalitis syndromes.

APE2 score ≥7 suggests probable or definite AE / autoimmune psychosis:

Probable anti-NMDAR encephalitis[9]
Rapid progression (<3 mo) of at least four of (or at least three if +teratoma):
- Behavioral or cognitive dysfunction
- Speech dysfunction
- Seizures
- Movement disorder
- Decreased level of consciousness
- Autonomic dysfunction or central hypoventilation

AND EEG abnormalities *AND/OR* CSF pleocytosis or oligoclonal bands

Definite anti-NMDAR encephalitis,[9]
1+ symptom groups from "Probable," *AND* serum and CSF IgG anti-GluN1 antibodies, or antibodies in serum with neuronal confirmatory tests

Definite autoimmune limbic encephalitis[9]
Rapid progression (<3 mo) of working memory deficits, seizures, or psychiatric symptoms suggesting limbic involvement
AND bilateral medial temporal lobe abnormalities on brain T2 MRI
AND EEG temporal lobe abnormalities *AND/OR* CSF pleocytosis
AND reasonable exclusion of alternative diagnoses

Probable autoimmune psychosis[15]
Criteria met for "Possible," *AND* at least one of:
- CSF pleocytosis (>5 WBCs/μL)
- Bilateral medial temporal lobe abnormalities on brain T2 MRI

AND/OR at least two of:
- EEG abnormalities
- CSF oligoclonal bands or increased IgG index
- Serum anti-neuronal antibody

AND reasonable exclusion of alternative diagnoses

Definite autoimmune psychosis[15]
Criteria met for "Probable," *AND* presence in CSF of IgG class anti-neuronal antibodies

psychosis] suspected to be autoimmune in origin on the basis of the detection of serum [. . .] neuronal autoantibodies" (Ref. 10, p 112). These antibodies (such as NMDAR antibodies), however, have been found in one to five percent of both patient groups and healthy controls, and without corresponding cerebrospinal fluid (CSF) antibody findings, or MRI or electroencephalogram (EEG) abnormalities, the presence of serum antibodies is not a specific finding for AE[12] and is not sufficient to warrant immunotherapy.[13]

Table 1 summarizes diagnostic approaches for AE and autoimmune psychosis. In 2016, Graus *et al.* provided a set of criteria for "possible" AE, based on presence of working memory deficits, altered mental status,

or psychiatric symptoms, as well as new focal central nervous system (CNS) findings, new or unexplained seizures, CSF pleocytosis, or MRI features.[9] The same paper also proposed criteria for "definite" AE subtypes, including anti-NMDAR encephalitis and autoimmune limbic encephalitis.[9] In 2018, Dubey *et al.* proposed the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score.[14] An APE2 score of four or more was 99 percent sensitive and 93 percent specific for the presence of neural-specific antibodies.[14] This score is routinely used in clinical practice to determine the risk of possible or definite AE.[16] In 2020, Pollak *et al.* proposed criteria, intended for use in psychiatric contexts, for the diagnosis of "possible," "probable," and "definite" psychosis of autoimmune origin.[15] A diagnosis of "probable" autoimmune psychosis requires CSF, MRI, or EEG findings; and "definite" autoimmune psychosis requires a finding of IgG class antineuronal antibodies in CSF. Autoimmune psychosis is arguably a variant of AE,[15] and Graus and Dalmau stated that "outside of the context of AE, psychosis [of] autoimmune origin has not been shown to exist" (Ref. 10, p 113). Terminological debate aside, a diagnosis of AE or autoimmune psychosis may have significant implications for a given patient's treatment and prognosis.

AE may initially present as another neurological or psychiatric condition. A 2018 study retrospectively examined the initial presentations of 50 patients who were eventually diagnosed with AE. In 34 of 50, the admission diagnoses were different: ten patients (20%) had been diagnosed with epilepsy, eight (16%) had been diagnosed with psychiatric disorders, and two (4%) had been diagnosed with dementia.[17] A 2020 case report[18] described a patient who received a diagnosis of functional neurological disorder, and later was diagnosed with unspecified tic disorder, adjustment disorder, and mild cognitive impairment, before eventually being diagnosed with anti-LGI-1 limbic encephalitis. The authors stated that the delay in obtaining a lumbar puncture and CSF analysis delayed the diagnosis of limbic encephalitis.[18]

A 2018 comparative study estimated the prevalence of probable or definite AE (based on the 2016 criteria[9]) as 13.7/100,000 person-years, similar to the prevalence of all infectious encephalitis (11.6/100,000) in the study population.[19] But, based on subsequent publications, the prevalence of definitive AE appears to be lower than previously thought, including in patients with psychosis (with or without neurological symptoms). In a 2021 prospective observational study of 105 patients with first-episode psychosis,[12] 20 percent of the patients fulfilled criteria for "possible" or "probable" autoimmune psychosis based on the 2020 criteria.[15] Despite this, none of these 105 patients had neuronal autoantibodies in their serum or CSF, and none were ultimately diagnosed with anti-NMDAR or another AE.[12] At a six-month follow-up, 101 of the patients had a primary psychiatric diagnosis (such as schizophrenia or bipolar I disorder).[12] The remaining four patients had diagnoses of frontotemporal dementia, HIV-associated encephalopathy, hyperthyroid encephalopathy, and encephalopathy secondary to suspected metabolic disease.[12]

A 2023 retrospective study examined 393 cases of patients who had been diagnosed with AE but subsequently received a different diagnosis at an autoimmune neurology clinic.[20] Of the 393, 107 patients were found to have been misdiagnosed, and 77 did not fulfill the diagnostic criteria for "possible" AE.[20] The updated diagnoses included functional neurological disorder (25% of the 107), neurodegenerative dementia (21%), psychiatric disease (18%), cognitive deficits from comorbidities (10%), cerebral neoplasm (9.5%), and other (17%).[20] These results are consistent with AE being rare. The authors of this study noted that the estimated cumulative incidence of AE is three to nine per million person-years, and it accounts for fewer than one percent of first-episode psychosis cases.[20]

While AE is far less common than primary psychiatric diseases, either a missed diagnosis or a misdiagnosis could delay appropriate treatment and result in harm to the patient. AE has high morbidity and mortality and can involve weeks or months of hospitalization, relapse, and persistent symptoms even after resolution of an acute episode.[11] The 2020 consensus criteria state that immunotherapy should be considered in cases of "probable" or "definite" autoimmune psychosis.[15] Treatment for AE is multimodal and involves plasma exchange and immunosuppression, such as high-dose steroids or agents such as methotrexate or rituximab, removal of tumor (if present), and seizure control.[15] Immunotherapy initiated within weeks after symptom onset is recommended to reduce relapses and cognitive impairment and improve functional outcomes.[11,15] A diagnosis of AE, however, may require a protracted period of symptom evolution, evaluation, and testing. Immunotherapy also has substantial side effect burden and cost. Management

of psychiatric symptoms associated with AE also requires psychiatric treatment, such as antipsychotic medications, to manage psychosis symptoms, even though patients with AE may be more susceptible to adverse reactions such as neuroleptic malignant syndrome (NMS).[15] Treatment for catatonia in AE may include benzodiazepines or electroconvulsive therapy.[15] Additional treatments include supportive care and rehabilitation: physical therapy, occupational therapy, and psychotherapy for emotional sequelae. Given both the rarity and morbidity of AE, combined with the risks of misdiagnosis and provision of inappropriate treatments, the careful evaluation of a patient with suspected AE carries great significance.

The Existing Standard of Care

A psychiatrist's duty to exercise due care in diagnosis includes a comprehensive interview and review of the patient's history, medical records, diagnostic tests, and collateral information.[21] The psychiatrist is also responsible for performing or referring a patient to a competent physician for a physical and neurological examination and clinically appropriate tests to rule out general medical conditions that could be causing the patient's mental illness.[21] As Noffsinger and Magalotti noted in 2022, a psychiatrist may be liable for a failure to evaluate for or diagnose a medical condition, for mistaking a psychiatric illness for another medical condition, or for a failure to manage a medical condition.[22]

Claims related to misdiagnosis or delayed diagnosis in psychiatric care may be resolved through settlement. A 1994 article reviewed 34 liability claims filed between 1978 and 1991 against the University of Texas System in its care of adult psychiatric patients.[23] One of these cases, which resulted in an out-of-court settlement with the largest monetary award of the claims surveyed, involved an allegation of negligent failure to diagnose Cushing's disease. The patient had developed acute psychosis, received three years of psychiatric treatment, including electroconvulsive therapy, and was subsequently diagnosed with Cushing's disease. The authors noted, "[I]t is vital for psychiatrists to consider organic disorders within a differential diagnosis to provide appropriate medical treatment and avoid this type of malpractice litigation" (Ref. 23, p 467). These findings suggest that for patients exhibiting atypical physical symptoms associated with psychiatric illness, psychiatrists may wish to seek consultation from primary care or other specialty physicians, with documentation of this consultation.

Judicial precedent in this area of misdiagnosis, delayed diagnosis, or inadequate management of medical conditions in patients receiving psychiatric care includes cases where the plaintiff had an endocrine condition,[24–26] genetic disorder,[27] tumor,[28–30] stroke,[30,31] brain infection,[32,33] traumatic injury,[34,35] or complex medical history.[36] The cases highlighted below suggest courts will continue to face challenges in adjudicating malpractice claims as the field of psychiatry becomes more complex and intertwined with other medical specialties, as in the evaluation and management of AE.

A finding of malpractice typically requires finding that a physician's actions deviated from the accepted standard of care. This was reinforced in *Anderson v. House of Good Samaritan Hospital* in 2007,[33] wherein the plaintiff had received diagnoses of labyrinthitis and depression and was hospitalized involuntarily in a psychiatric ward. According to court records, the plaintiff became catatonic and was eventually transferred to a medical hospital, where he was diagnosed with acute disseminated encephalomyelitis secondary to a viral infection. The plaintiff alleged malpractice against the hospitals and treating psychiatrist.[33] The trial court jury was instructed to consider whether the physician had made an error in judgment, and the court found that none of the defendants were negligent. The Supreme Court of New York ruled that the trial court had erred, and that the "issue of fact" was instead whether the defendant's assessment and treatment fell short of the medically accepted standard of care.

The standard of care as determined by expert testimony may depend on whether the concern is diagnosis or management of a general medical condition. The 1997 ruling in *Vilcinkas v. Johnson*[32] considered the care of a patient who was hospitalized in a psychiatric unit, transferred to a medical intensive care unit, and diagnosed with herpes simplex encephalitis. The Supreme Court of Nebraska ruled that a family practice physician was able to testify regarding the standard of care for a medical doctor, including the defendant psychiatrist, who was treating a medical condition. In contrast, in another 1997 ruling, that of *Whaling v. Joyce,*[26] the plaintiff alleged a psychiatrist who had been treating her depression and anxiety was negligent in failing to diagnose her Graves disease. The plaintiff's expert witness was an

endocrinologist. The Circuit Court of the City of Fredericksburg, Virginia, granted the defendant psychiatrist's motion for summary judgment on the basis that the proposed expert testifying regarding the standard of care should have recent clinical experience and knowledge of standards in the defendant's specialty.

Physicians may be held liable for failing to use appropriate diagnostic procedures, as emphasized by the 1983 ruling in *Snow v. State.*[37] The courts have also recognized that the standard of care may depend on the time period during which a patient receives care. In the 1990 case of *East v. United States,*[24] the plaintiff's decedent had received treatment for severe depression. Court records stated he was eventually diagnosed with hypothyroidism, but despite treatment and normalization of his thyroid function, his depression persisted, worsened, and he eventually died by suicide. The plaintiff alleged that the decedent's physicians (including psychiatrists) failed to diagnose and treat his hypothyroidism in a timely manner, which proximately caused his severe depression and suicide. The U.S. District Court of Maryland ruled that "the standard of care between 1983-1985 [when the decedent was being treated] did not require a psychiatrist to perform a thyroid function test on all outpatients complaining of depression" unless they had "signs and symptoms suggestive of an organic illness involving the thyroid" (Ref. 24, p 17).

In order for a delayed diagnosis of a general medical condition to be ruled as malpractice, plaintiffs have had to demonstrate that the delayed diagnosis was a proximate cause of harm,[29] that an earlier diagnosis and treatment would have been beneficial,[28] or that physicians should have identified a diagnosis earlier based on the patient's signs and symptoms.[35] An adequate psychiatric evaluation may require a screening physical examination, the lack of which was relevant in *Zavalas v. State* in 1993[38] and was deemed a failure constituting inadequate outpatient care in *O'Sullivan v. Presbyterian Hospital* in 1995.[39] Addressing abnormal physical exam findings may be difficult, but no less crucial, in patients with chronic medical conditions and complex histories. In the 1995 case of *Deasy v. United States,*[36] physicians were found to have fallen below the standard of care when they treated the plaintiff patient for bipolar mania, disregarded his medical history including Ormond's disease (idiopathic retroperitoneal fibrosis) and the adverse effects of medications (including steroids), and failed to provide timely and appropriate treatment of his edema.

The psychiatrist's scope of care may not necessarily include direct care of general medical conditions, but typically includes knowing whether the patient is under the care of other practitioners, and making appropriate referrals if the patient is not receiving necessary general medical care.[30,40] In the 1985 case of *Witt v. Agin,*[30] a plaintiff alleged malpractice in multiple physicians' failing to diagnose a growing nonmalignant brain tumor over two years. Court records showed the defendant psychiatrist's motion for summary judgment was granted on the basis that he did not commit malpractice, because he provided short-term care for the plaintiff's emotional problems and knew that she was under the care of other doctors for her other medical conditions. The 1988 case of *Wozniak v. Lipoff*[25] emphasized the importance of referring a patient for competent specialty care in a timely manner. According to court records, the defendant internist had been treating the decedent patient's Graves disease. Over a period of months the patient developed severe anxiety, paranoia, and depression.[25] The patient was eventually referred to an endocrinologist, and died by suicide a day after the endocrinology appointment.[25] An expert witness psychiatrist testified that the patient's depression was most likely related to the Graves disease, and the Supreme Court of Kansas affirmed in the ruling that negligence had occurred.

Psychiatric facilities routinely rely on a general medical hospital or emergency department (ED) to provide "medical clearance" prior to admission or may transfer a patient to an ED or medicine service for care of acute general medical conditions. But, depending on a psychiatric facility's own scope and resources, courts may consider if both the facility and clinicians working in the facility have a duty of directly evaluating patients' general medical conditions. In *Wilburn v. Cleveland Psychiatric Institute* in 1998,[41] the plaintiff alleged that the psychiatric facility's inadequate evaluation of the patient's stroke-like symptoms, which had been provisionally diagnosed as conversion disorder, resulted in the patient's second stroke. The trial court ruled that the facility was not negligent because it should not be held to the same standard of care as a general medical hospital in the diagnosis and treatment of stroke. But, the Court of Appeals of Ohio reversed the judgment on the basis

that the facility had claimed to have the capability to address patients' medical needs and did not provide the necessary evaluation to rule out conversion disorder. In the similar case of *Brodowski v. Ryave* in 2005,[31] a plaintiff with initial diagnosis of stroke versus conversion reaction was briefly admitted to a psychiatric unit and subsequently developed worsening stroke symptoms, with imaging findings showing an infarction and carotid artery clot. The trial court jury returned a verdict of "no negligence" against multiple defendant physicians and the Superior Court of Pennsylvania affirmed. But, a dissenting opinion stated there was evidence that the inpatient psychiatrist did not adequately screen the referral to the psychiatric unit.[31]

Litigation in Autoimmune Encephalitis

There are multiple cases of malpractice litigation regarding patients with infectious meningoencephalitis who had a missed diagnosis, delayed diagnosis, or delayed treatment.[32,33,42–44] Cases involving non-psychiatric patients with infectious meningitis have resulted in multimillion dollar verdicts or settlements for the plaintiffs.[42–44] To our knowledge, however, there is sparse judicial precedent regarding medical negligence in failing to diagnose or treat an AE in psychiatric contexts.

In the 2022 case of *Schultz v. Ercole,*[45] inpatient pediatricians were defendants in a suit alleging deliberate indifference toward a child patient who experienced neuropsychiatric symptoms including pain, facial paralysis, panic attacks, and hallucinations in 2019. The child was initially diagnosed with anxiety, and the differential diagnosis eventually included Pediatric Autoimmune Neuropsychiatric Syndrome (PANS), Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), AE, conversion disorder, and a stress or adjustment disorder.[45] Court records stated that the child was treated with intravenous immunoglobulin (IVIG). During a readmission, a consultant neurologist diagnosed the child with PANS. The lawsuit claimed that the defendant pediatricians were deliberately indifferent to the child's medical needs by disregarding the PANS/PANDAS diagnosis. The U.S. District Court for the Western District of Texas dismissed the claim and ruled that the defendants had considered multiple possible diagnoses, had considered the consultant's opinion, had consulted literature on PANS/PANDAS, and had ordered appropriate treatments. The court noted that the consultant who diagnosed PANS had not directly examined the child or performed diagnostic testing. The court also noted that negligence or malpractice do not constitute deliberate indifference, which is a particularly high standard to meet. The court stated that physicians do have a duty to explore "every possible explanation" (Ref. 45, p 8) for their patient's illness.

An Uncertain Standard of Care

Because of the rarity and variable presentations of AE, which many clinicians have never encountered or treated, patients with AE may experience progressive illness over weeks or months before they are able to receive appropriate treatment. In considering the possibility of AE as part of a differential diagnosis, one approach is to utilize the APE2 risk stratification score,[14] as well as the presence or absence of clinical "red flag" signs or symptoms as described by the authors of the 2020 Consensus Criteria.[15] Several "red flags" (recent tumor diagnosis, movement disorder, severe or disproportionate cognitive dysfunction, decreased consciousness, unexplained seizures, or significant autonomic dysfunction) would increase the APE2 score and also form part of the proposed diagnostic criteria for "possible" autoimmune psychosis. Other red flags (recent infection, new-onset or changed headache, focal neurological signs, unexplained hyponatremia, or a history of autoimmune disorders such as lupus or autoimmune thyroid disease) are less specific but would still raise suspicion and warrant consideration of medical contributors to the patient's psychiatric symptoms.[15]

But, an early presentation of AE may be limited to psychiatric symptoms, without clear red flags. Some patients may not even show characteristic MRI or EEG findings until later in the disease course.[18] A 2013 observational cohort study of 571 patients diagnosed with anti-NMDAR encephalitis found that 23 patients (4%) had isolated psychiatric symptoms (most commonly psychotic symptoms with a mood component) without neurological symptoms.[46] For five patients with isolated psychiatric symptoms who were eventually diagnosed with anti-NMDAR encephalitis, the time from symptom onset to treatment ranged from two to 60 weeks, with a median of nine weeks.[46] A significant limitation of the 2020 Consensus Criteria is that they may be less helpful in cases with isolated[10] or more chronic psychiatric symptoms.

If a delay in pursuing AE evaluation would be considered an error in judgment or a deviation from the acceptable standard of care would depend on the specific clinical circumstances. Substantial clinical judgment is involved in deciding whether to refer a patient for additional specialty care or additional testing. Additionally, factors outside the control of the treating physician can also affect the standard of care for what a "reasonable practitioner" would or could do in similar circumstances. Depending on the patient's geographic location, socioeconomic status, insurance status, and other characteristics, access to a neurologist and to diagnostic testing may be limited and may require referral to a facility at a significant distance from the original point of care. Disparities in access may be further heightened by socioeconomic disparities.

Even after a CSF sample is obtained, testing for neuronal autoantibodies in CSF may take weeks to obtain. According to the Mayo Clinic Laboratory's website, the Autoimmune/Paraneoplastic Encephalopathy panel takes eight to 12 days to obtain the results.[47] The Clinical Laboratories Test Directory at the University of California, San Francisco states the result time for this test is four to 10 days.[48] Whether a patient has access to a tertiary medical center with experience evaluating for AE, including familiarity with expediting the necessary send-out tests, could be an additional factor shaping a patient's care. Evaluation for AE is extensive, time-intensive, and costly,[49] as it involves specialists, invasive procedures, neuroimaging, and specialty laboratory tests, all before immunotherapy. Physicians must reconcile these diagnostic and care access challenges with ongoing systems pressure to practice cost-conscious care,[50,51] including not ordering unnecessary or low-yield interventions,[52] as well as pressure to shorten the lengths of hospitalizations.[53–55] Patients may also encounter difficulty with affording treatment. In 2015, a patient with AE filed suit against her health insurers and the New York State Department of Financial Services after they denied coverage for her rituximab and IVIG immunotherapy.[56] According to 2016 court records, the case was discontinued (additional information was not provided).

Discussion

Autoimmune neuropsychiatric illnesses such as AE present clear diagnostic challenges even for a diligent and up-to-date psychiatrist. Depending on the specific clinical scenario and jurisdiction, psychiatrists might be expected to consider an autoimmune contribution to a patient's psychiatric symptoms and, if suspected, take steps to pursue further evaluation and treatment referrals. In such situations, psychiatrists may want to utilize diagnostic guidance such as the APE2 score and the 2020 Consensus Criteria (Table 1). But, case law regarding the standard of care in psychiatric settings for the diagnosis and management of these conditions, including the psychiatrist's expected knowledge base and scope of practice, is still evolving. For example, a psychiatrist might evaluate a case of first-episode psychosis and, in considering the possibility of AE, obtain a brain MRI. It is unclear, however, how this would affect the psychiatrist's exposure to legal liability because a negative MRI scan (which does not exclude AE[15]) might provide false reassurance that a neurological disorder is not present.

At present, case law suggests it would be prudent of treating psychiatrists to consider each patient's general medical history as part of a comprehensive psychiatric assessment, including any recent physical and neurological examinations. In addition, case law indicates treating psychiatrists should consider pursuing additional examination, diagnostic testing, or referrals if a patient has symptoms or signs of a general medical condition that may be causing psychiatric symptoms. A psychiatrist who refers a patient to another practitioner should communicate the clinical concern and rationale for the referral.

Occasional cases of AE with isolated psychiatric symptoms or fluctuating neurological symptoms pose a particular medicolegal challenge, as these cases could appear indistinguishable from psychiatric illnesses not caused by other medical conditions. Pursuing usual psychiatric care (including care in a subacute mental health treatment setting, or voluntary or involuntary psychiatric hospitalization) without further neurological evaluation could have legal implications. In litigation regarding cases of AE presenting with psychiatric symptoms, claims of emotional damages, disability, or wrongful death could be alleged related to misdiagnosis, failure to diagnose, delayed treatment, inappropriate treatment (such as NMS caused by medication), or failure to offer appropriate treatment (such as electroconvulsive therapy for catatonia). Conversely, a wrongful diagnosis of AE, rather than an underlying psychiatric disorder, could also create legal liability if the patient experiences a negative outcome.

Depending on the clinical context, it may be important for psychiatrists to provide ongoing reassessment, with consideration of symptoms or signs not previously detected, and with revision of the differential diagnosis and referral for additional care as appropriate. Even if AE is high on the differential and the patient may have increased risk of adverse medication effects such as NMS, the psychiatrist should use clinical judgment in using psychiatric treatments, such as medication (e.g., antipsychotics, antidepressants, or benzodiazepines) or other interventions (such as electroconvulsive therapy) to relieve psychiatric symptoms. Assessment of the patient's response, including any atypical or adverse response to medication, may provide additional diagnostic clarity.

If a plaintiff alleges misdiagnosis or delayed diagnosis of AE, the attorney might argue that critical symptoms should have been assessed as clinically significant. In contrast, the defense might argue that because of AE's rarity and complexity, even an experienced psychiatrist would not have developed concern for AE sooner. Forensic experts might be asked to evaluate the plaintiff's ongoing symptoms and degree of impairment resulting from alleged misdiagnosis in AE. Litigation regarding possible damages might involve expert witness testimony by multiple specialists: general psychiatrists, neuropsychiatrists, neurologists, neuroradiologists, neuropathologists, endocrinologists, rheumatologists, or neuropsychologists. Because this is an area where medical knowledge is rapidly evolving, the standard of care at the time of a forensic evaluation may have changed significantly compared with the standard at the time of the treatment rendered. Given the rarity of these cases, it may also be difficult for forensic evaluators to have developed practical expertise in the evaluation and treatment of these conditions before opining or testifying about the treatment in specific cases. Finally, given the overlapping expertise of different specialties involved in management of these conditions, evaluators may need to submit reports or testify alongside or against experts from other disciplines.

Emerging knowledge about autoimmune neuropsychiatric illness is an exciting and challenging development. Although wider understanding of these conditions may allow clinicians to better meet the needs of patients, the evolving clinical and legal landscape of these conditions introduces considerable uncertainty for psychiatrists and other health professionals. AE is becoming part of the differential diagnosis of new-onset or atypical presentations of psychiatric illness. The increased systems emphasis on short-term stabilization and cost-efficient care, including pressure to return patients to outpatient settings as soon as possible, creates competing pressure for clinicians to consider when patients present with subtle symptoms that may represent AE but are not pathognomonic. The question remains to what degree courts will expect clinicians to consider these diagnoses and pursue additional care. These considerations regarding autoimmune encephalitis may also be relevant for clinical and forensic practice in other neuropsychiatric illnesses (such as dementias, epilepsies, Huntington's disease, and multiple sclerosis) for which psychiatric symptoms can be the earliest symptoms, and for which practice guidelines are also evolving due to ongoing neuroscientific advances.

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