Encephalopathy: Approach to Diagnosis and Care

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Table of Contents

Applying A Systemic Approach ........................................... 2
The Presenting Complaint and History ............................... 3
The Physical and Neurologic Examinations ......................... 6
Laboratory and Imaging Studies .......................................... 9
Conclusion ......................................................................... 14
References ........................................................................ 14

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Applying a Systematic Approach

A request for the evaluation of a patient with altered mental status is one of the most common reasons for a neurology consultation. A wide range of conditions can result in this clinical presentation—from primary neurologic disorders (seizure, stroke) to systemic diseases (urinary tract infection, hyponatremia). The neurologist must be able to quickly clarify the nature of the cognitive change, prioritize the diagnostic possibilities, decide on an expeditious work-up, and start appropriate therapy, as early treatment is critical for many of these conditions (eg, prompt administration of intravenous antibiotics for meningococcal meningitis). Because the scope of potential causes of encephalopathy is broad and the time for action is frequently short, following a systematic approach to evaluation is critical.

Recognizing Encephalopathy

One of the first challenges is to recognize a patient with altered sensorium and to distinguish the disorder as encephalopathy. The neurologist’s use of the term altered mental status is generally synonymous with encephalopathy and conforms, in broad terms, with the psychiatrist’s definition of delirium (ie, a disturbance of consciousness that develops over hours to days and that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia). Encephalopathy, therefore, is a generalized cortical dysfunction characterized by an acute-to-subacute course (hours to days), prominent fluctuations in the level of consciousness, poor attention, frequent hallucinations and delusions, and changes in the level of psychomotor activity (generally increased but at times decreased).

A study assessing housestaff awareness of risks for delirium among older hospitalized patients found that clinical trainees had poor knowledge of patient orientation to place and time. In a large retrospective study, only 4% of patients had a recorded diagnosis of delirium, yet an episode may occur in up to 56% of older hospitalized patients. Some studies have emphasized the need for standard cognitive assessment of all inpatients, such as the Confusion Assessment Method (CAM), to improve clinician awareness of delirium.

Characterizing the Cognitive Change

Once encephalopathy is recognized, the next step is to characterize the precise nature of the cognitive change, which directs the subsequent work-up. This step requires characterizing the time course as acute, subacute, or chronic and as monophasic or multiphasic (single or multiple episodes) and determining whether generalized cortical dysfunction is accompanied by focal neurologic signs and symptoms.

Distinguishing the nature of the illness has implications for the urgency of treatment, which is usually much less in the case of a chronic, progressive condition such as dementia. One must be wary of delirium complicating the course of dementia, a disorder typically characterized by chronicity, a normal level of consciousness, relatively normal psychomotor activity, better preservation of attention, and, usually, less frequent hallucinations and delusions until late in the course of the illness. Various studies estimate the prevalence of delirium in community-dwelling and hospitalized patients with dementia to be from 22% to 89%. Moreover, changes over the course of minutes to hours can occasionally be inherent to a dementing illness. For example, patients with Lewy body dementia are known to have prominent fluctuations in awareness (attention/vigilance) and vivid visual hallucinations during the day. It is even more important to be aware of focal deficits that can be mistaken for encephalopathic changes. For example, patients with embolic distal left middle cerebral artery (MCA) distribution strokes can be erroneously classified as “demented” when their “cognitive difficulties” are primarily limited to their language, and patients with right MCA/parietal strokes can occasionally present primarily with agitation.

Narrowing the Differential

Once encephalopathy/delirium is determined to be present, further evaluation of the patient is aimed at defining the range of etiologic possibilities. Simply hearing the presenting complaint will allow one to narrow the differential significantly. Nonetheless, having a systematic approach ensures that no potential diagnosis...
is missed. One useful mnemonic is shown in the Table. Thus, after recognizing encephalopathy and developing a broad differential, the history, examination, and ancillary studies can be used to narrow the differential to make a diagnosis and formulate a treatment plan. In the following series of cases, we describe the application of such a systematic approach to the evaluation of patients in whom multiple etiologic processes may be at work.

THE PRESENTING COMPLAINT AND HISTORY

CASE 1: A 51-YEAR-OLD MAN WITH ACUTE EPISODIC CONFUSION

A 51-year-old right-handed man is brought to the emergency department (ED) for evaluation of episodes of confusion over the past month. The neurology consult service is called to evaluate the patient.

Although the patient cannot recall all the episodes, he reports that they usually occur in the evening and consist of him asking his wife “stupid questions.” The patient is unclear whether the episodes last seconds, minutes, or hours. Although the patient’s wife did not accompany him, she is available by telephone to provide additional history. She describes episodes lasting 15 minutes to as long as an hour, during which the patient speaks “gibberish,” impulsively (and incorrectly) uses various appliances and electronic equipment, and walks up and down the stairs. She states that the spells are not accompanied by loss of consciousness, shaking, tongue biting, or urinary incontinence. However, she notes that after a spell the patient often complains of a headache and goes to sleep.

This patient’s presenting complaint and history thus far suggest several diagnostic possibilities. Of the following, which is least likely?

A) Migraine
B) Frontotemporal dementia (FTD)
C) Transient global amnesia (TGA)
D) Transient ischemic attack (TIA)
E) Seizure

One of the first issues in characterizing the cognitive change is to define the time course of illness. In this case, the description of the presenting complaint—multiple episodes of confusion over approximately 1 month, generally occurring in the evenings, with partial recall and without other obvious clinical signs—suggests an episodic process that is not rapidly progressive. The differential diagnosis, therefore, should be shaped by the fact that the illness is acute and multiphasic.

Another prominent feature of this patient’s history is that he is unable to describe the episodes of confusion. By the nature of their illness (ie, the accompanying inattention and alteration in consciousness), encephalopathic patients are rarely able to give a complete history. There are infrequent reports of encephalopathic patients who are able to describe their experiences while altered.10 Such reports indicate misperceptions and delusions. Whether a patient’s self-reported descriptions are helpful in the work-up is less clear, although they should be taken seriously in defining the nature of the disturbance. The interaction with the patient should consist of clear, directed language in an optimized environment (eg, with adequate lighting, with the patient’s hearing aids/glasses in place). Accordingly, of utmost importance is finding a reliable collateral informant; a report from an outside observer, whether a family member or health care professional, may be the only useful historical information to aide in the diagnosis.

Overall, the episodic events in this case appear to be stereotyped, making seizure a definite diagnostic possibility. The lack of shaking and tongue biting would not be sufficient to rule out this diagnosis; partial complex seizures are a frequent seizure type in which observers often notice only a brief lack of responsiveness. Migraine, and specifically confusional migraine, is an additional possibility. A rare migraine variant that includes a confusional state, confusional migraine most commonly occurs in children and has been associated with head trauma. The confusion is characterized by inattention, distractibility, and difficulty with speech and motor activities. The confusion may last from minutes to several hours, can be followed by a headache, and commonly ends in sleep.11

Another possibility for this patient’s mental status

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**Table. Mnemonic for Potential Causes of Encephalopathy/Delirium**

| I   | Infections (central nervous system: meningitis/encephalitis; systemic: urinary tract infection, pneumonia, endocarditis, sepsis) |
| T   | Trauma, tumor/paraneoplastic |
| S   | Stroke, seizure, (p)sychiatric |
| D   | Drugs (intoxication or withdrawal), degenerative (decompensated dementia) |
| E   | Electrolytes, endocrine |
| L   | Low glucose, leukoencephalopathy |
| I   | Inflammatory (eg, acute disseminated encephalomyelitis) |
| R   | Rheumatologic (eg, vasculitis) |
| U   | Uremia |
| M   | Metabolic (hypoxia, hyperglycemia, hyperammonemia), malnutrition, mitochondrial |
change is TIA. The history thus far suggests distal left more likely than right MCA dysfunction, given the prominent confusion and change in speech content and the lack of prominent motor deficits. However, if the symptoms truly represented TIA, they most likely would not be embolic, as it is exceedingly rare that recurrent emboli (even from a source more distal than the heart, such as the carotid artery) would involve the same distal vessel. One possibility would be a flow-limiting atherothrombotic lesion, but as more episodes occur, the likelihood that they represent TIA without leading to a subsequent stroke significantly declines. Finally, the phenomenon of TGA deserves mention. This syndrome consists of an acute, primarily anterograde amnesia (persistence for 1–24 hours), in which patients frequently ask the same questions over and over but do not lose consciousness or self-awareness. While the origin of the syndrome is unclear (migrainous, epileptic, and ischemic etiologies have all been suggested), the recurrence rate is low (2.5% annually in 1 study13, and the risk of subsequent vascular events is small as compared with TIA. Even without a good description of the events in this case, the multiple episodes argue somewhat strongly against TGA.

FTD is the least likely possibility, largely due to the time course and nature of the clinical events. The episodes in this case last 15 minutes to 1 hour and involve stereotypical behaviors with sharp onset and offset. In contrast, FTD is characterized by progressive behavioral, language, cognitive, and functional deficits that evolve over months to years. Solely based on history, complex partial seizures would rank highest on the differential diagnosis list and would necessitate tests to confirm the diagnosis (eg, electroencephalogram [EEG]), to localize and delineate the nature of any underlying focal lesion, and to institute appropriate treatments (eg, antiepileptic medication and treatment of any identifiable causes). Nonetheless, this case illustrates the importance of initially considering a wider list of etiologic possibilities as the cause of multiphasic episodes of transient confusion with acute onset and short duration in order not to miss other potentially serious and treatable conditions.

CASE 2: A 75-YEAR-OLD WOMAN WITH SUBACUTE CONFUSION

A 75-year-old right-handed woman is hospitalized for confusion and found to have a urinary tract infection. The patient’s daughter reports that the patient has been increasingly confused during telephone conversations over the past week and stopped answering her telephone 2 days ago, which prompted the daughter to go to the patient’s apartment to check on her. The daughter found the patient lying in her bed, which was wet with urine.

Given this patient’s subacute presentation, which of the following medical conditions would not be a risk factor or precipitant for encephalopathy?
A) Vascular dementia
B) Parkinson’s disease
C) Recent bilateral hip arthroplasty
D) Depression
E) Obstructive sleep apnea

The patient’s past medical history can greatly inform the diagnosis of encephalopathy. Inouye et al found that among hospitalized patients aged 70 years or older, visual or auditory impairment and physical comorbidities all predisposed to delirium. While emphasizing significant methodologic problems with the studies reviewed, these authors also found evidence of increased risk for delirium in patients with a history of alcohol abuse or depression. Other risk factors for delirium most certainly exist. Meagher includes social isolation, a change to a novel (often, hospital) environment, the perioperative period following an emergent or prolonged procedure, and a history of previous encephalopathy. At times, encephalopathy risk factors and precipitants can overlap, and the independence of various factors can blur. For example, there is controversy as to whether the documented risk factor of older age can be fully disentangled from the confounder of physical frailty.

Vascular dementia can affect multiple cognitive domains and predispose to relatively small metabolic stressors to cause cognitive decompensation and lead to altered sensorium and confusion. In a study of neuropathologically confirmed cases of vascular dementia, episodes of delirium were reported in roughly 50% of patients. In Parkinson’s disease, nonmotor neuropsychiatric manifestations are being increasingly recognized, with studies reporting a prevalence of upward of 60%. These symptoms include mood and anxiety disorders, fatigue, apathy, hallucinations, dementia, and sleep disorders. All of these nonmotor symptoms may predispose the Parkinson’s patient to encephalopathy.

Of the medical problems listed, obstructive sleep apnea is least likely to predispose to encephalopathy in an otherwise cognitively intact individual. While this disorder can cause altered mentation and arousal due to associated hypoxia and hypercarbia, it usually would not be expected to cause long-lasting (days to weeks), continuous, and progressively worsening encephalopathy.

CASE 3: A 65-YEAR-OLD MAN ON MULTIPLE MEDICATIONS

A 65-year-old right-handed man with depression, anxiety, rheumatoid arthritis, and atrial
fibrillation presents to a neurology clinic stating that he believes he is developing Alzheimer’s disease and that for the last few months he has not been able to “think straight.” He asks about pills that can improve his memory. The patient’s current medication regimen is complex and includes cyclosporine 150 mg bid, lorazepam 0.5 mg taken at bedtime for many years, citalopram 40 mg qd, and digoxin 0.25 mg qd. The patient notes that he also has been taking jimsonweed “on and off” for the last 6 months.

Of this patient’s current medications, which are likely to have an effect on his cognition? Which 2 drugs raise concern about interaction?
A) Cyclosporine  D) Digoxin
B) Lorazepam     E) Jimsonweed
C) Citalopram

Inouye et al found that use of multiple medications increases the risk of encephalopathy, and this case highlights the importance of obtaining a thorough medication history when trying to ascertain the etiology of cognitive change. In collecting the history, it is important to determine the use of over-the-counter medicines and herbal supplements, as these presumptively innocuous medicines can have profound clinical impacts. The Beers criteria are a useful guide to medications that should be avoided in persons 65 years or older due to a high risk of adverse drug events.18

In this patient, cyclosporine-related side effects may potentially be at play, as this medication has been associated with confusion, cortical blindness, and seizures19 as well as with systemic complications. Digoxin toxicity, itself associated with altered mental status, may be exacerbated by concurrent use of cyclosporine, which is known to elevate digoxin levels. Macrolides and tetracycline are also known to elevate digoxin levels and should be used with caution in patients currently taking digoxin.20

Other drugs in this patient’s current medication list may also be contributing to cognitive changes. Lorazepam, which is frequently prescribed for its anxiolytic and sedative properties, can exacerbate encephalopathy and may cause paradoxical over-excitation and agitation in cognitively susceptible and demented individuals.21 Special note of the serotonin syndrome should be made, as the patient is on citalopram (a selective serotonin reuptake inhibitor). Serotonin syndrome is a toxic hyperserotonergic state that occurs as a result of excess agonism of serotonergic receptors.22 The syndrome is potentially life-threatening and characterized in its mild form by motor signs (tremor, hyperreflexia), autonomic signs (tachycardia, diaphoresis), and mild encephalopathy. The syndrome can progress, however, to cause hyperthermia, clonus, increased muscle tone, shock, or even death. Serotonin syndrome requires a high index of clinical suspicion, as there are no confirmatory laboratory tests.

Finally, jimsonweed may very likely affect this patient’s cognition. This herbal supplement is used to improve breathing in asthma and bronchitis.23 Jimsonweed has anticholinergic properties, and such drugs have a tendency to exacerbate or provoke encephalopathy.24 Therefore, efforts should be made to reduce or eliminate these agents from an at-risk patient’s medication list.

CASE 4: A 45-YEAR-OLD MAN DELIRIOUS AFTER ORTHOPAEDIC SURGERY

A 45-year-old right-handed man with no known history of major medical problems undergoes uncomplicated shoulder replacement surgery under general anesthesia. Two days postoperatively, the patient is noted to be extremely belligerent, combative, and disoriented. His son reports that, while in the hospital, the patient has been sweating and nauseated and has been unable to hold utensils due to a new hand tremor. He also has begun commenting about seeing people and animals that were clearly not in the room. In addition, the care team has noted mild tachycardia and elevated blood pressures on daily rounds, but these were attributed to postoperative pain. However, 3 days postoperatively, the patient has a generalized tonic-clonic seizure, requires intubation, and is transferred to the intensive care unit.

Which of the following findings on social history would be most helpful in determining the etiology of this patient’s confusion?
A) He has several cats
B) He drinks “several” vodka martinis and 2 glasses of wine per night
C) He smokes 1 to 2 packs of cigarettes per night
D) He used nasal cocaine 10 years ago
E) He lives near wooded areas and is an avid deer hunter

The social history can be important in helping to identify possible causes of delirium. Pet contacts can yield important diagnostic clues. In this case, the patient’s several cats potentially could be linked with exposure to diseases that can affect the central nervous system (CNS), such as toxoplasmosis, cat-scratch disease (Bartonella henselae), or rabies.23 Heavy tobacco use indicates an increased risk for cancer and paraneoplastic encephalopathy (eg, antineuronal antibody [anti-Hu]–associated limbic encephalopathy in the setting of small cell lung cancer). Westover et al found that cocaine use more than doubled the risk of both hemorrhagic and ischemic stroke, and that amphetamine abuse was associated with a five-fold greater risk of hemorrhagic stroke.
but not ischemic stroke. Stimulant drugs such as cocaine and amphetamines are thought to produce strokes by direct effects on the cerebral circulation, such as elevation of blood pressure, vasospasm, or accelerated arteriosclerosis. Exposure to wooded areas with deer suggests risk for tick-borne diseases associated with cognitive deficits, namely Lyme disease. Travel history also can provide rich information. For example, a recent trip to Africa might suggest exposure to pathogens that can cause encephalitis, such as West Nile virus. Furthermore, a sexual history is important to reveal risk factors for syphilis and HIV, diseases that can produce encephalopathy.

In this case, however, the most helpful aspect of the social history would be knowledge of excessive alcohol intake. Knowing this patient’s alcohol history at the outset of his hospital stay would have allowed for preventive measures to combat serious complications of alcohol withdrawal (cardiac arrhythmias, respiratory arrest, seizures) and for initiation of evaluation, counseling, and treatment of alcohol dependence and highly associated conditions such as anxiety and depression. Hospitals should have alcohol withdrawal prevention and treatment protocols that include treatment with long-acting benzodiazepines; frequent monitoring of vital signs and neurologic status; aspiration and seizure precautions; and supplementation with a multivitamin, thiamine, vitamin B₁₂, and folic acid. Evidence for alcohol withdrawal includes sweating, nausea/vomiting, anxiety, hallucinations, psychomotor agitation, tremulousness, encephalopathy, and generalized tonic-clonic seizures, all of which occurred in this patient. Often it can be difficult to obtain a reliable alcohol history, but this case clearly illustrates the importance of this information. Upon recognition of alcohol withdrawal symptoms, therapy must be initiated immediately despite the diminished likelihood that it will be successful in alleviating or preventing all major sequelae.

Data to support a genetic component to alcoholism, initially from studies showing higher concordance of alcoholism in monozygotic twins than in dizygotic twins, and more recently from the identification of susceptibility genes involved in the metabolism of alcohol and in its neurotransmitter systems.

Carnitine is an amino acid that is required for the transport of long-chain fatty acids into the mitochondria; persons with carnitine deficiency are unable to metabolize long-chain fatty acids, the major source of metabolic energy. Infection or fasting can trigger a metabolic decompensation that can present as a hypoketotic hyperglycemic encephalopathy. Primary carnitine deficiency typically presents in childhood and is due primarily to a faulty mitochondrial carnitine transporter. Secondary carnitine deficiency can occur in adulthood and most commonly arises from a block in a mitochondrial enzymatic pathway, leading to a buildup of acyl compounds. These compounds bind to carnitine and promote its excretion in the kidneys. Huntington’s disease is an autosomal dominant inherited neurodegenerative disease that often presents as a hyperkinetic movement disorder but in up to a third of individuals can present as neuropsychiatric and mood symptoms, including florid psychosis years before a clear movement disorder emerges.

In this case, the least helpful information on family history would be a cousin with Parkinson’s disease, as this disease appears to be more sporadic than inherited, and affected individuals would not present with early agitated delirium or seizure.

THE PHYSICAL AND NEUROLOGIC EXAMINATIONS

CASE 5: A 68-YEAR-OLD MAN POORLY RESPONSIVE AFTER DIALYSIS

A neurologist is urgently called to the dialysis unit to evaluate a 68-year-old man who slumped forward soon after dialysis and was unresponsive. On physical examination, temperature is 102.4°F, blood pressure is 210/94 mm Hg, pulse is regular at 77 bpm, respiratory rate is 12 breaths/min, and oxygen saturation is between 98% and 100% on room air. The general examination is notable for a thin man with clear lungs, mild papilledema on fundoscopic examination, a harsh 3/6 holosystolic murmur at the apex, and no evidence of photo/phonophobia or meningismus. The abdomen is diffusely and mildly tender, but there is no distention, hepatomegaly, or rebound tenderness. There is no cervical/axillary/inguinal lymphadenopathy. The arteriovenous (AV) fistula site is warm and erythematous.
of the extremities reveals tender nodules on the right second and third distal phalanges and nontender erythematous macules on the soles of the feet.

Based on this patient’s history and examination findings, which of the following is the least likely primarily causative diagnosis?

A) Hypertensive encephalopathy
B) Meningoencephalitis
C) Bacterial endocarditis
D) Dialysis disequilibrium syndrome
E) Idiopathic seizure

Given this patient’s chronic renal failure and markedly elevated blood pressure, hypertensive encephalopathy deserves consideration. The risk for hypertensive encephalopathy depends most on the tempo of blood pressure elevation and the difference in blood pressure relative to baseline, rather than the absolute value of the increased blood pressure. In a study by Hinchen et al, in which most patients experiencing blood pressure increases were peripartum, immunosuppressed, or renally impaired, 1 patient experienced symptoms at a systolic pressure of “only” 150 mm Hg. Thus, although the case patient’s blood pressure is elevated, to rule in a diagnosis of hypertensive encephalopathy would require a review of the patient’s previous blood pressures, a more detailed history to correlate increases in blood pressure with symptoms such as progressive headache, nausea, confusion, and visual disturbances, and neuroimaging (preferably magnetic resonance imaging [MRI]) to look for signs of cerebral edema, which can be subtle and restricted to occipital cortices and the temporoparieto-occipital junctions.

Meningoencephalitis also is a strong possibility. The patient has 2 components of the classic tetrad of fever (present), headache, meningismus, and altered mental status (present), and his chronic renal failure makes nonbacterial and atypical bacterial agents (eg, *Listeria monocytogenes*) more possible. Although the presence of mild papilledema is consistent with dialysis dysequilibrium syndrome—a disorder characterized by neurologic signs and symptoms, attributed to cerebral edema, during or shortly after intermittent aggressive hemodialysis—this syndrome is less frequently seen in patients on chronic hemodialysis. Endocarditis is the strongest possibility and is supported by the findings of cardiac murmur, a possibly infected AV fistula, and the presence of Osler’s nodes and Janeway lesions.

The diagnosis least supported by this patient’s history and examination findings is idiopathic seizure. While a provoked (secondary) seizure is a possibility given any of the diagnosable conditions listed, the history and absence of relevant findings (no evidence of physical injury consistent with convulsions, no tongue lacerations, and no bowel incontinence) make seizure of any cause a less likely possibility. Further, the evidence for both CNS and systemic illness and no known history of epilepsy virtually exclude the diagnosis of primary idiopathic seizure.

**Case 5 Conclusion**

A diagnosis of endocarditis is confirmed by positive blood cultures, an echocardiogram showing valvular vegetations, and observation of multiple septic emboli on brain MRI.

**CASE 6: A 58-YEAR-OLD MAN WITH A VIOLENT OUTBURST**

A 58-year-old man is taken to the ED for evaluation of extreme agitation and confusion following an incident in which he struck a police officer after being stopped for speeding in the breakdown lane. A neurologist is consulted to evaluate the patient.

The patient’s medical history is unknown, and there are no family contacts. On cognitive examination, the patient regards the examiner for a few minutes and then closes his eyes and falls asleep. After gently shaking the patient’s hand, the patient initially has difficulty keeping his eyes open but then becomes more awake. He is oriented to context (“doctor” and “hospital”) and year and month but not to day, time of day, exact time, or exact location (incorrect floor, hospital, and city). After several requests, the patient follows simple 2-step commands across midline but is unable to name the months of the year backward or to perform serial 7s. His responses are slow but his speech is fluent, without paraphasic errors, and he names high and low frequency objects and repeats correctly. There is no apraxia, neglect, or extinction to double simultaneous stimuli. However, his clock draw test is slow and labored in effort and highly disorganized, with only 50% of the numbers completed and several drawn outside the circle. Although long-term autobiographical memory appears intact, he can register only 1 of 3 objects verbally presented and recalls 1 of 3 objects after a 5-minute delay. Each time a female staff person enters the room, he jumps up from his seat and grasps at the air shouting, “I’m trying to catch all these fireflies!”

Which of the following accompaniments of encephalopathy is revealed in the cognitive evaluation of this patient?

A) Waxing and waning level of consciousness
B) Inattention
C) Poor impulse control and judgment
D) Poor organization and planning
E) All of the above
Level of consciousness was an issue during the cognitive evaluation of this patient, as evidenced by his initial inability to remain awake and alert and to comply with the examiner’s requests. Another prominent abnormality in encephalopathy is difficulty with attention and concentration, which may be characterized by easy distractibility and by difficulty following commands, concentrating to stay on task, and performing simple mental manipulations. Marked inattention makes it difficult to adequately assess learning and short- and intermediate-term memory performance. In this case, the patient had difficulty registering 3 words, thus preventing adequate assessment of his memory for a newly learned word list. Attention and memory difficulties can also manifest as a lack of temporal and spatial orientation, both of which require frequent updating and information storage. The patient had difficulty with fine-grade temporal and spatial orientation. His inappropriate comments revealed poor impulse control and judgment and, along with his abnormal clock draw test, showed lack of planning and organization, all of which are consistent with dysfunction of frontal executive and control systems.

Although the best answer is “all of the above,” it is important to remember that a hallmark of encephalopathic states is that they involve marked fluctuations in the level of consciousness and mental acuity—fluctuations that can occur over a period of minutes not just hours or days. The existence of “sundowning,” in which patients with baseline cognitive impairment appear well during the day but become delirious in the evening, is an example of a more stimulus-sensitive fluctuation in mental status. Questioning and counseling other health care providers and family members can not only provide valuable information with regard to precipitants and fluctuations, but can also help to establish an overall prevention and care plan.

Case 6 Continued

On elemental neurologic examination, pupils are equally round and reactive, with no evidence of papilledema on fundoscopic examination. Visual fields are normal, but there is marked vertical gaze paresis with down-beating nystagmus. Facial sensation is intact, and smile is symmetric. Voice and palatal movement are normal. The tongue is tremulous but midline. On motor examination, bulk is diffusely decreased but tone is normal. There is a bilateral action tremor but no asterixis. Strength is full throughout. Reflexes including the jaw jerk are 3+ throughout except at the ankles, where they are 2+. Plantar responses are flexor bilaterally. Cold sensation is decreased to the midshin bilaterally, but other modalities are intact throughout. Finger-nose-finger and heel-knee-shin testing are normal. However, the patient’s gait is wide based, with marked truncal ataxia resulting in equal loss of balance in all directions.

Which of the following diagnoses is most likely based on this patient’s cognitive and elemental neurologic examination findings?
A) Thalamic stroke
B) Parasagittal meningioma
C) Wernicke’s encephalopathy
D) Normal pressure hydrocephalus
E) Progressive supranuclear palsy (PSP)

To summarize, the cognitive examination of this patient reveals marked and fluctuating abnormalities in level of consciousness, attention, psychomotor processing, and frontal executive, control, and behavioral systems; the elemental examination demonstrates upgaze paresis and gait ataxia. Normal pressure hydrocephalus typically presents as a dementing syndrome and not as fluctuating attention and hallucinations; in addition, the gait disorder is rigid or magnetic, not ataxic, and there is no ophthalmoplegia. A parasagittal meningioma could produce a frontal behavioral syndrome consistent with certain findings in this case but should not produce such eye movement abnormalities; instead, significant bilateral leg weakness and upper motor neuron signs would be expected. PSP is a neurodegenerative dementing disorder characterized by early frontal systems dysfunction, behavioral and personality changes, dysaesthesia, multiple falls, visual complaints, and limitations in vertical gaze (especially downgaze but also upgaze). However, patients with PSP usually have early parkinsonism and slurred speech and would not exhibit such dramatic and fluctuating disturbances in level of consciousness and attention until late-stage dementia. Thalamic strokes can produce a wide variety of cognitive deficits and can mimic many cortical syndromes. Certain rare thalamic strokes, namely lesions in the dorsomedian territory, can produce upgaze limitation and disinhibition syndromes but should not produce the type of gait ataxia seen in this patient.35

Of the choices listed, the most likely diagnosis would be Wernicke’s encephalopathy, a disorder caused by thiamine deficiency. Wernicke’s encephalitis is characterized by confusion, ataxia, and ophthalmoplegia. It is most often seen in alcoholics but can occur in disorders associated with malnutrition. Treatment is parenteral replacement of thiamine, which can cause rapid resolution of symptoms. However, if Wernicke’s encephalopathy is allowed to continue without treatment, it may progress to an irreversible cognitive state of severe anterograde memory loss and confabulation known as Korsakoff’s amnestic syndrome.
LABORATORY AND IMAGING STUDIES

CASE 7: A 22-YEAR-OLD MAN WITH EPISODIC AGITATION

A 22-year-old man with myoclonic epilepsy is brought to a neurology clinic by his parents for episodes of agitation over the past month. The patient has been seizure free during this period but reports some low-grade fevers without headaches or neck stiffness. One month prior, levetiracetam was added to his antiepileptic therapy and his valproic acid dosage was increased. He takes no other medicines, denies allergies, and denies any alcohol, tobacco, or illicit drug use. He is sexually active. The patient is adopted, and family history is unknown. His general and complete neurologic examinations are presently unremarkable.

Which of the following tests would be least helpful in the diagnostic work-up of this patient?
A) Liver function tests and ammonia level
B) Vitamin B₁₂ and methylmalonic acid levels
C) Antinuclear antibody (ANA) testing
D) Lactic acid level
E) Antiepileptic drug levels

Information gleaned from laboratory testing can complement the history and physical examination, revealing factors that may be contributing to or causing encephalopathy. The laboratory work-up of all patients with encephalopathy/delirium should include a complete blood count (CBC) with differential and a comprehensive metabolic panel (CMP). For example, an elevated white blood cell count (WBC) from the CBC can indicate an ongoing systemic infection to explain the encephalopathy. Important aspects of a CMP include sodium, blood urea nitrogen, creatinine, glucose, calcium, and magnesium levels, as abnormal values can trigger or contribute to encephalopathy, especially in susceptible individuals. In thrombotic thrombocytopenic purpura, patients often present with nonspecific confusion, but the CBC findings of anemia and thrombocytopenia and the CMP findings of renal failure make the diagnosis.

Routine laboratory testing should also check for elevated liver enzymes and ammonia levels, which can suggest a hepatic cause of delirium (as can be seen in patients on valproic acid), and for hypo- and hyperthyroidism, both of which can manifest or contribute to alterations in mental status.

Since 1824, when J.S. Combe described a case of fatal anemia associated with stomach degeneration—now known as pernicious anemia—the association between vitamin B₁₂ deficiency and cognitive deficits has been well documented. When B₁₂ is depressed, it fails to function effectively as a coenzyme in the metabolism of methylmalonic acid and homocysteine, thereby increasing the levels of these substances. The finding of elevated methylmalonic acid and homocysteine in the setting of low-normal vitamin B₁₂ levels (i.e., 150–350 pg/mL) may indicate functionally low B₁₂ that would benefit clinically from repletion. Healton et al. found that although 74% of patients with B₁₂ deficiency had neurologic symptoms, only 3% had psychiatric or cognitive symptoms. Thus, while vitamin B₁₂ deficiency rarely may be the primary cause of cognitive deficits, low B₁₂ levels may facilitate delirium and should be corrected.

A broad screen for infectious, inflammatory, and neoplastic conditions should be routinely included in the laboratory work-up of encephalopathy and should include erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) assays—both of which would be important in this case given the history of low-grade fevers. Other tests that may be essential to the work-up in specific situations include lead or heavy metal levels, testing for Lyme antibodies, serum ammonia levels, and a toxicology screen. The toxicology screen should include alcohol, antidepressants, amphetamines, barbiturates, benzodiazepines, cocaine, and levels of narcotics. In this case, antiepileptic drug levels would also be important to know, given that the patient takes both valproic acid and levitiracetam and there have been recent changes in his treatment regimen. Valproic acid can cause a dose-dependent hyperammonemia, and it is a potent hepatic enzyme inhibitor causing marked drug-drug interactions. In clinical studies of levetiracetam, 13.3% of patients experienced behavioral symptoms such as agitation, emotional lability, and anxiety.

Elevated serum lactic acid levels can be a clue to an underlying mitochondrial cytopathy, and in this case one would be suspicious of MERRF (myoclonus epilepsy associated with ragged red fibers) syndrome, in which episodic encephalopathy has been described presumptively resulting from ischemic events in the brain. Mitochondrial disorders are typically maternally inherited, and in MERRF there is a point mutation at position 8344 in the mitochondrial genome for tRNA-Lys, thereby disrupting synthesis of proteins essential for oxidative phosphorylation. Finally, the patient should be tested for HIV infection. Although syphilis traditionally has been at the top of the differential for infectious causes of altered mental status, HIV/AIDS currently is the first consideration. The Centers for Disease Control and Prevention reports that in the United States in 2004, the estimated new cases of HIV in the 33 states reporting was 38,685, compared with only 7980 estimated new
cases of syphilis. Thus, while syphilis has been known as the “great imitator,” with varied clinical presentations including encephalopathy, the new “great imitator” may be acute HIV infection.

The least useful test at this time would be ANA, as there is no evidence to support a rheumatologic disorder, and an ESR and hsCRP will be used for screening. Although complications of systemic lupus erythematosus (SLE) can result in an encephalopathy, without other signs and symptoms of SLE there is little to support its investigation.

CASE 8: A 28-YEAR-OLD MAN WITH HEADACHES AND CONFUSION

A 28-year-old man with no prior medical history presents to a neurology clinic with a 2- to 3-month history of diffuse dull holoccephalic headaches, low-grade fever, stiff neck, and progressive confusion. When asked to describe his confusion in more detail, the patient states that he feels that everything he tries to do mentally is “slower and more effortful.” Review of systems reveals night sweats and a 15-lb unintentional weight loss in the last few months. The patient lives part-time in Connecticut and works in the Grand Canyon in the summer. He denies use of alcohol, tobacco, or other illicit substances. He reports multiple sexual partners. His family history is notable for Alzheimer’s dementia.

The general examination is normal. The cognitive examination reveals impaired attention but intact language and memory. The elemental neurologic examination, including fundoscopic examination, is normal. MRI of the brain with contrast reveals diffuse pachymeningitis, prompting lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis.

Which of the following CSF tests would be least useful in the diagnostic work-up of this patient?

A) Angiotensin-converting enzyme (ACE) level
B) Herpes simplex virus (HSV) polymerase chain reaction (PCR) analysis
C) Lyme antibody titer
D) Amyloid (Aβ42) protein level
E) Cytology, flow cytometry, and heavy chain gene rearrangement

CSF analysis is of paramount importance in guiding the diagnostic work-up for suspected meningitis. In all patients undergoing LP, an opening pressure should be obtained, and the CSF should be tested for cell counts, protein, glucose, and Gram stain and culture. Although this patient’s fundoscopic examination did not reveal papilledema, in patients with meningitis, elevated intracranial pressure is often seen and can precede changes in the fundus; thus, obtaining an opening pressure is important. CSF cell counts and differential are useful in that the degree of elevation in WBCs and the predominance of various WBC lines often reflect different pathologies. For example, a CSF WBC of 1000 cells/μL or greater with a polymorphonuclear cell predominance is typically seen in bacterial meningitis, whereas a CSF WBC less than 100 cells/μL and a lymphocyte predominance is typically seen in viral, fungal, or inflammatory meningitis. CSF protein is one of the most sensitive indicators of CSF pathology, and CSF-to-serum glucose ratio is often decreased in certain bacterial and fungal types of meningitis.

A patient with multiple sexual partners is at risk for certain causes of meningitis, including syphilis, HIV, and HSV. If the patient were immunocompromised, he would be at risk for cryptococcal meningitis, tuberculous meningitis, and other fungal meningitides. CSF VDRL is a highly sensitive (92%) and specific (100%) marker for syphilitic meningitis and is indicated in this case. Cryptococcal antigen testing is useful, as is AFB stain for tuberculosis and general fungal cultures.

Because the patient works in the southwestern United States, he is at risk for coccidioidomycosis, which can cause meningitis and would be diagnosed via fungal culture. Lyme meningitis can be a challenging diagnosis due to limitations in CSF testing. Blanc et al found that the intrathecal anti-Borreliia IgG index has a specificity of 97% but an only moderate sensitivity of 75%. CSF cultures for the causative spirochete are extremely difficult, and CSF PCR analysis for bacterial DNA has low sensitivity (~30%). Therefore, the American Academy of Neurology guidelines for diagnosis of nervous system Lyme disease incorporate patient history, general and neurologic examinations, serologic testing, and CSF testing. Sarcoi’dosis can present as a pachymeningitis, and CSF ACE levels are a sensitive and specific marker of neuropsychiatric disease.

Given the patient’s B symptoms, the differential diagnosis for the imaging findings would also include lymphomatous meningitis. Therefore, cytology would be useful as would a test for immunoglobulin heavy chain (IgH) gene rearrangement. CSF cytology may be abnormal, typically showing clumped pleomorphic cells with enlarged nuclei and coarse chromatin in 26% to 31% of primary CNS lymphoma patients. CSF testing for clonal rearrangement in the IgH gene can be approximately 20% to 40% sensitive but is 100% specific for diagnosis of primary CNS lymphoma.

The least useful test in this clinical scenario would be Aβ42 level. Although there is growing evidence to support this test in the diagnosis of Alzheimer’s disease, this patient’s clinical profile does not fit a neurodegenerative dementia.
Case 8 Conclusion

The patient undergoes extensive CSF testing, which is unrevealing. A dural biopsy with pathology is consistent with non-Hodgkin’s B-cell lymphoma.

CASE 9: A 50-YEAR-OLD WOMAN WITH PROGRESSIVE MUTISM

A 50-year-old right-handed woman is brought by her boyfriend to the ED for evaluation of progressive cognitive difficulty. Per the boyfriend, the patient was at her baseline state of good health until 1 week ago, when her car slid on the ice and crashed into a retaining wall at low speed. The patient did not lose consciousness. She returned to work but then developed dull bifrontal headaches and called in sick. Over the last 3 days she has had progression of headache, worst in the morning, and some low-grade fevers. She also has begun to complain of “odd smells” and memory difficulties and become more withdrawn, participating less in conversation. Over the past 24 hours she has been close to mute, providing only occasional “yes” or “no” answers when she appears to be emotionally aroused. Her medical history is notable for hepatitis C, anxiety, and hypothyroidism. The patient takes clonazepam and levothyroxine and has no medication allergies. The boyfriend states that the patient does not use alcohol, tobacco, or illicit drugs. Family history is notable only for hypothyroidism in her mother.

The patient’s vital signs and general examination are unremarkable with the exception of a temperature of 102.5°F. Neurologic examination reveals an abulic woman who follows 3-step, midline-crossing commands easily but who is unable to repeat and who verbalizes only twice (“but,” “no”) during the 30-minute examination. Elementary examination is most notable for left-sided hyperreflexia and a Babinski response on the left. Basic laboratory testing with CBC and CMP are within normal limits. LP is attempted but is unsuccessful due to patient agitation despite sedatives.

Which of the following imaging studies of the brain would be least likely to assist in the initial diagnosis of this patient?

A) Computed tomography (CT) without contrast
B) MRI with contrast
C) Positron emission tomography (PET)
D) Magnetic resonance angiography (MRA)
E) Magnetic resonance spectroscopy (MRS)

In any patient with neurologic signs and symptoms, it is reasonable to order a screening CT scan of the brain. Although inferior to MRI in many respects, CT is useful in demonstrating significant pathology quickly, so that a treatment plan can be rapidly initiated. In a study by Kidwell et al., MRI and CT were equivalent for the diagnosis of acute hemorrhage, but MRI was better for detection of ischemic stroke and chronic hemorrhage. MRI of the brain with contrast is the best study to investigate for lesions such as stroke, tumor, or abscess, which are certainly in the initial differential diagnosis in this case. MRA of the brain could also be a useful study to investigate for vascular malformations or aneurysms that may be causing cognitive disturbance through direct mass effect or bleeding or possibly from being a seizure focus. MRS of the brain has proven useful in differentiating between abscess and tumor and can yield information regarding tumor grade. One of the foremost challenges for neuro-oncologists is differentiating tumor recurrence from radiation necrosis on MRI. In a study by Zeng et al., multivoxel 3D MRS technology distinguished tumor recurrence from radiation necrosis with 96.2% accuracy.

The least useful imaging study would be a PET scan of the brain, as it is most useful for answering specific questions when a differential diagnosis has already been narrowed. For example, in a patient who has completed treatment for a brain tumor, a PET scan can be useful for determining whether there is residual tumor. PET studies can also help differentiate between various types of dementia. Since a PET scan requires nuclear tracers and is limited in answering specific clinical questions, it would not be suggested as part of the initial imaging work-up of this patient.

Would an EEG be useful if any of the following was the diagnosis?

A) Hepatic encephalopathy
B) Benzodiazepine overdose
C) Subacute sclerosing panencephalitis (SSPE)
D) Hashimoto’s encephalopathy
E) Creutzfeldt-Jakob disease (CJD)

In general, the prominent feature of the EEG record in encephalopathies is slowing of the normal background frequency, but the EEG may be completely normal. Hepatic encephalopathy has the electrographic marker of other toxic-metabolic encephalopathies, namely theta and delta slowing with triphasic waves. In benzodiazepine overdose, there is the presence of excessive beta activity with poor reactivity. SSPE is a progressive, neurodegenerative disorder caused by defective measles virus replication in the brain as a consequence of measles immunization. In SSPE, the EEG may demonstrate bilaterally synchronous, high-amplitude spike or slow-wave bursts that often correlate with clinical myoclonus. An EEG can be useful in making the diagnosis of CJD, as a 1 hertz spike and wave pattern is characteristic. Steinhoff et al. found that this EEG pattern had a sensitivity of 67% and a specificity of 86% for the diagnosis of CJD.
Hashimoto’s encephalopathy is defined by spontaneous subacute encephalopathy with raised thyroid autoantibody levels and a remarkable responsiveness to steroids. In the case of Hashimoto’s encephalopathy, there are no characteristic EEG patterns that would suggest the diagnosis, and EEG in this setting would be least helpful.

Case 9 Continued

As the patient is being brought by stretcher to the MRI machine, she becomes unresponsive and starts picking at her clothes with her left hand. Her head turns to the left, and then all her limbs shake for several minutes. The ED staff intubates the patient and administers lorazepam and fosphenytoin, which abort the convulsive movements. MRI of the brain with and without gadolinium is obtained. A representative fluid-attenuation, inversion recovery (FLAIR) sequence reveals increased signal intensity in the right temporal lobe that extends upward into the right frontal lobe (Figure 1).

LP is attempted while the patient is intubated and sedated on propofol. The CSF is clear and colorless, with a glucose level of 62 mg/dL (normal, 50–75 mg/dL) and protein level of 72 mg/dL (normal, 10–40 mg/dL). No red cells are present, but 27 white cells per high-power field are seen, 97% of which are lymphocytes. Gram stain reveals no organisms. Empiric therapy with ceftriaxone, vancomycin, ampicillin, and acyclovir is started. Several hours after the MRI and initiation of antibiotics off sedation, the patient remains unresponsive to voice, has intact brain stem reflexes, and withdraws weakly to pain response on the right, with no withdrawal on the left. An EEG reveals periodic lateralized epileptiform discharges (Figure 2).

Based on the EEG, imaging, and CSF results, what is the leading diagnosis?
A) Paraneoplastic limbic encephalitis
B) Acute demyelinating encephalomyelitis
C) Astrocytoma
D) Herpes encephalitis
E) Brain abscess or acute bacterial meningitis

Brain abscess, whose associated CSF findings would be dependent on both the organism and the extent of communication with the CSF space, would not be consistent with the MRI scan; one would expect to see a localized collection (or collections) with ring enhancement following administration of contrast rather than the relatively diffuse signal hyperintensity seen. The CSF lymphocytosis argues against acute bacterial meningitis, which would be associated with the presence of polymorphonuclear leukocytes. Astrocytoma could consistent with the MRI findings; Pace et al found that in 119 consecutive patients with supratentorial gliomas, 62 (52%) presented with seizures. However, the finding of CSF pleocytosis would not be consistent with astrocytoma. Acute demyelinating encephalomyelitis can present as progressive confusion and is associated with CSF lymphocytosis, but seizures and the MRI pattern of the lesion (affecting predominantly grey matter) would not be expected. Strong consideration must be given to paraneoplastic limbic encephalitis, as the imaging and CSF findings are consistent with this diagnosis. In addition, in a study of 50 patients with paraneoplastic limbic encephalitis, 25 suffered from seizures at some point during the course of illness. Arguing against paraneoplastic limbic encephalitis are the absence of an underlying malignancy (although the encephalitis is known to precede diagnosis of malignancy by as many as 3 years), the slower time course (although presentations after days can sometimes be seen), and the high fever.

Given all signs, symptoms, and laboratory, imaging, and EEG findings, the leading diagnosis is a viral encephalitis. The most common and most treatable (with acyclovir) of these remains herpes encephalitis. This patient’s acute-to-subacute onset accompanied by fever, encephalopathy, and focal neurologic findings referable to the temporal lobe are classic for HSV encephalitis. As described in Chaudhuri and Kennedy’s discussion of Kennedy’s 1988 retrospective study of 46 cases (29 confirmed by isolation of HSV from the brain), presenting symptoms include “a history of a prodromal
influenza-like illness (48%), rapid onset of headache, clouding of consciousness and confusion (52%), meningism (65%), raised intracranial pressure (33%), deep coma (35%), mutism or aphasia (46%), focal neurologic signs (89%), and seizures (61%). The MRI scan documents the classic finding of increased T2-weighted (in this case, FLAIR) signal in the temporal lobe. The EEG record demonstrates PLEDs (periodic lateralized epileptiform discharges) localized to the right temporal leads. PLEDs are EEG abnormalities consisting of repetitive spike or sharp wave discharges, which are focal or lateralized over one hemisphere and recur at regular intervals of 0.5 to 5 seconds. They are seen most frequently in the setting of acute unilateral lesions such as encephalitis. Convulsive seizures often occur when PLEDs are seen on the EEG, but they can also be associated with confusional states (as seen in this case). Herpes encephalitis presents quite commonly with seizures because of its predilection for the temporal lobe, and it is one of the most common etiologies of PLEDs seen on EEG. In a recent study of 32 Middle Eastern patients with encephalitis who were HSV-1 positive by CSF PCR assay, 24 (75%) suffered from seizures. It should be borne in mind that other viral encephalitides exist, as do treatments for them, including cytomegalovirus encephalitis (ganciclovir and foscarnet), varicella zoster virus encephalitis (acyclovir), and enteroviral encephalitis. Thus, thinking broadly is important.

**CASE 10: A 41-YEAR-OLD WOMAN WITH METASTATIC CANCER AND CONFUSION**

A 41-year-old woman with melanoma metastatic to the lung, liver, and brain is admitted to the palliative care service with 1 week of increasing and agitated confusion. The patient’s husband reports that the patient is spitting out her medicines and has begun kicking and screaming in the presence of her usual caregivers. An extended panel of serum testing for reversible forms of dementia is unrevealing, and CSF analysis and EEG are unremarkable. Imaging reveals progression of metastatic disease in the brain, leading the team to conclude that the patient’s altered mental status is secondary to the increased tumor burden.

![Image of EEG record showing periodic epileptiform discharges](image)

*Figure 2. Electroencephalogram in bipolar montage at 5μV/mm and 30 mm/sec showing periodic epileptiform discharges occurring over the right frontotemporal region approximately every 2 seconds.*

In a study by Fang et al of terminal cancer patients, 47% had delirium but in only 20% to 42% of these cases was the problem recognized and treatment initiated. It is not always clear how best to treat patients with encephalopathy, as few randomized controlled trials (RCTs) of symptomatic management have been conducted. In a meta-analysis, Weber and colleagues reported that there is little good evidence to guide management; this finding was confirmed by a Cochrane review of delirium in patients with preexisting cognitive impairment. In an RCT by Cole and colleagues, 227 patients were randomized to usual care or to consultation and follow-up with a study nurse and either a geriatrician or a psychiatrist. The specialists could implement their own recommendations; no treatment medications were specified, although the nursing staff used a checklist to make environmental, cognitive, and activity recommendations. Improvement was defined as “an increase in the Mini-Mental State Examination (MMSE) score of 2 or more points, with no decrease below baseline plus 2 points, or no decrease below a baseline MMSE score of 27.” By this measure, there was no significant difference in the percentage of improvement between study groups (48% in the intervention group versus 45% in the usual care group).

In a smaller study of 31 hospitalized AIDS patients,
Breitbart and colleagues found that haloperidol and chlorpromazine were efficacious but lorazepam was not in treating symptoms of delirium. Other studies have suggested efficacy for the atypical antipsychotics olanzapine and risperidone. A consensus statement of the American Psychiatric Association emphasizes use of haloperidol for its lack of anticholinergic side effects, lower incidence of extrapyramidal side effects, and lower likelihood of sedation and hypotension relative to other neuroleptics. The guidelines also note the possible utility of atypical antipsychotics, and they suggest reserving benzodiazepine treatment for alcohol or sedative-hypnotic withdrawal and for adjunctive treatment in patients who cannot tolerate effective doses of antipsychotics. Clonidine is least likely to be helpful as a treatment for agitation in this case.

Of course, these medications are symptomatic treatments that rarely treat the primary cause of the encephalopathy. Every effort should be made to treat the underlying etiology as well as to avoid significant side effects (especially sedation) that may cloud understanding of the evolution of an unknown disease process. Losing the ability to follow changes in the neurologic examination for iatrogenic reasons (eg, oversedation) can lead to unnecessary testing and missed opportunities to treat incipient illness. As always, excellent nursing care is extremely important and can potentially reduce the need for pharmacologic approaches. Efforts have been made to prevent delirium in at-risk patients by proactively modifying the environment. In their study of hospitalized elderly patients, Inouye et al specifically targeted issues of preexisting cognitive impairment, sleep deprivation, immobility, visual impairment, auditory impairment, and dehydration. Many of the interventions were intuitive: nighttime and early morning blood draws and medications were moved to minimize sleep disruption, cerumen disimpaction and portable amplifying devices were employed to reduce hearing difficulties, and early mobilization protocols were implemented. These straightforward risk-reduction strategies lowered the incidence of delirium to 9.9% in the intervention group versus 15.0% in the control group.

CONCLUSION

The approach to evaluation of encephalopathy is much like detective work, in that only through methodical gathering and synthesis of all data can a diagnosis be achieved. Of utmost importance is to maintain awareness of the mental state of patients so that encephalopathy does not go unrecognized. Then, one should quickly clarify the nature of the cognitive change: Is encephalopathy present? Are the symptoms acute, subacute, or chronic? Is the change mono- or multifocal? Because the cause of mental status change is often multifactorial, having a broad initial differential diagnosis helps to ensure that no possibilities are overlooked. One then works systematically through the history, examination, and ancillary studies to prioritize the diagnostic possibilities, with emphasis on the inclusion or exclusion of emergent or life-threatening diagnoses. Work-up should be initiated promptly, and the decision to start the appropriate therapy, possibly empirically, should be made expeditiously.

Identifying and treating the underlying cause(s) of the encephalopathy is paramount, but supportive and symptomatic therapy should also be considered early, with the important caveat that many of these interventions will (and should) be nonpharmacologic. Finally, attention to the patient’s caregivers and family members is extremely important. Not only are these episodes often frightening for them, but their understanding and help will be critical for the patient’s care in the future. Only through a structured approach to recognize, assess, and manage encephalopathy can clinicians provide the highest quality of care for their patients.

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