LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Huffman and Dr. Stern discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Assessment of the Awake but Unresponsive Patient

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The sight of an apparently awake but unresponsive patient challenges the clinical skills of all practitioners. Diagnostic and therapeutic strategies may not be readily obvious, and the clinician may be unsure of what to do next. Debate frequently arises regarding the medical, psychiatric, or neurologic etiologies of the unresponsiveness, and it may be difficult to determine appropriate interventions.

Have you ever wondered how to distinguish among the many possible causes of unresponsiveness? Are you uncertain about which diagnostic tools and treatments to use in the care of these perplexing patients? How can you determine if a patient's lack of interaction is due to a medical cause or a psychiatric illness? The following case and ensuing discussion highlight diagnostic considerations and strategies for care of the unresponsive patient.

Case Presentation

Emergency medical technicians (EMTs) found Ms. H, a 55-year-old woman with a history of hypertension, coronary artery disease, and depression, lying motionless on the couch in her apartment. Her neighbors had called the police because she had neither left her house nor answered her door for 6 days. Upon arriving at her home, EMTs discovered that Ms. H was minimally responsive; her vital signs were normal except for a pulse of 100 beats/min. She withdrew to noxious stimuli but did not otherwise show purposeful movement. After her arrival in the emergency room, further examination revealed that her pupils were equal and reactive to light; examination of the heart, lungs, abdomen, and extremities was unremarkable. Serum and urine toxicologic screening test results were normal. The chest x-ray, electrocardiogram (ECG), complete blood count, serum chemistries, urinalysis, and liver function test results were also unremarkable. A computerized tomographic scan of the head revealed abnormalities in the left frontal lobe consistent with cerebral infarction.

Ms. H was admitted to the neurology service for evaluation and workup of her mental status change and possible cerebrovascular accident. Despite having essentially normal vital signs and a "nonfocal" neurologic examination (she spontaneously moved all 4 extremities on occasion), she remained unresponsive to voice, light touch, and other stimuli. However, at most times, she seemed awake and possibly aware of her surroundings. Interview of the family revealed that Ms. H had appeared depressed the preceding 2 weeks and that she had never had similar episodes of depression or unresponsiveness. Psychiatry was consulted to evaluate "psychogenic causes of unresponsiveness."

How Should One Approach the Care of a Minimally Responsive Patient?

No matter how likely a psychiatric cause for unresponsiveness may seem, the life-threatening causes of stupor and coma must be considered

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first. The basic tenets of emergency care (establishment of airway, confirmation and support of breathing, and maintenance of circulation) should be followed. If there is any indication of trauma, the cervical spine should be immobilized. Administration of thiamine, glucose, and naloxone should be strongly considered as rapid empiric treatments for the unresponsive patient.

One should then consider a broad differential diagnosis of stupor and coma that includes (but is not limited to) the following:

- Central nervous system (CNS) events: e.g., intracranial hemorrhage, epidural or subdural hemorrhage, acute ischemia, CNS infection, atonic seizures or partial complex seizures, brain abscess, and brainstem lesions.
- Toxic ingestion: e.g., of alcohol, benzodiazepines, barbiturates, opioids, or prescribed medications, as well as carbon monoxide poisoning.
- Endocrine dysfunction: e.g., diabetic ketoacidosis, nonketotic hyperosmolar coma, hypoglycemia, hypothyroidism, and Addison's disease.
- Infectious disease: e.g., meningitis, encephalitis, and systemic sepsis.
- Respiratory malfunction: e.g., hypoxia or hypercarbia that results from acute or chronic respiratory or musculoskeletal disease.
- Cardiovascular events: e.g., myocardial infarction, aortic dissection, ruptured abdominal aortic aneurysm, and hypertensive encephalopathy.
- Hepatic and renal dysfunction: e.g., hepatic encephalopathy and uremia.
- Hypovolemia: e.g., secondary to severe dehydration or bleeding.
- Other causes: e.g., Wernicke's encephalopathy, hyperthermia, and hypothermia.
- Neuropsychiatric causes: e.g., severe depression, conversion disorder, catatonia, abulia or apathy (from frontal lobe dysfunction), and "locked-in" syndrome.

In the case of Ms. H, some, but not all, of these potential causes of stupor were evaluated. The primary treatment team might have considered checking thyroid function, arterial blood gas, cardiac enzymes, and carboxyhemoglobin level, as well as a human immunodeficiency virus (HIV) test. A lumbar puncture (LP) could have been considered (despite the lack of fever or nuchal rigidity), especially if the patient was immunocompromised.

Given that Ms. H's symptoms thus far involved primarily the CNS, more extensive evaluation of the brain was necessary. A magnetic resonance imaging (MRI) scan, to evaluate more effectively the possibility of acute cortical stroke (and to evaluate for brainstem lesions), would have been an important investigation. An electroencephalogram (EEG) would also have been helpful.

Are There Specific Neurologic Syndromes or Symptoms That Should Be Considered When a Person Appears Awake but Is Unresponsive?

The following 4 neurologic syndromes are associated with an apparently awake but unresponsive patient:

1. Locked-in syndrome. This syndrome results from bilateral pontine lesions and destruction of the pontine motor tracts. Afflicted individuals are mute and paralyzed but generally appear alert and have preserved intellectual function. Upward gaze and eye blinking are preserved. Ms. H, with a lack of alertness and an ability to move all of her extremities, did not appear to have this syndrome.

2. Isolated frontal lobe damage. This can result in apathy, abulia (loss of motivation), and a substantial increase in latency of response to questions. Importantly, this damage may result from head trauma or from congenital causes that would not produce grossly visible abnormalities on brain imaging. Patients with frontal lobe dysfunction may present in different ways—with disinhibition, apathy, poor organizing and planning (i.e., executive dysfunction), or any combination of these. In the case of Ms. H, a slow and careful interview would have allowed the physician to determine whether the patient's apparent inability to respond was the result of frontal lobe malfunction or whether more global cerebral dysfunction was present.

3. Akinetic mutism. One specific frontal lobe syndrome is akinetic mutism, which is caused by unilateral or bilateral lesions of the superior mesial region of the frontal lobe. In akinetic mutism, a patient makes no attempt to communicate, either by gesture or verbally, and maintains a noncommunicative facial expression. The patient's movements are limited to tracking with the eyes and to arm and body movements that are used to perform certain tasks, such as eating. Otherwise, the patient is unable to move or speak. In contrast to patients with aphasia, patients with akinetic mutism do not attempt to communicate and do not become frustrated with their limited ability to communicate; instead, such patients do not attempt to respond to questions or other stimuli and appear unconcerned about their unresponsive state. Given her awake but uncommunicative state, a paucity of attempts to communicate, and no frustration at being unable to respond, Ms. H may have manifested akinetic mutism. A careful interview and observation of her ability to track with the eyes and to perform some motor behaviors would have suggested or refuted this diagnosis.

4. Isolated global aphasia. In contrast to patients who have so-called fluent or nonfluent aphasia, in which some

comprehension or fluency may be preserved, patients with isolated global aphasia are unable to communicate verbally or to comprehend spoken language. These lesions usually result from large ischemic or hemorrhagic events in the left frontal, temporal, and parietal areas of the brain. In most cases of global aphasia, a host of other cerebral functions are abnormal. However, in rare cases of isolated aphasia, language is disrupted while other cerebral functions remain intact. With this condition, a patient may appear to be unresponsive, as such a patient does not follow commands and is unable to communicate verbally. However, if the aphasia is isolated, the patient can be alert, able to communicate nonverbally, and able to perform meaningful tasks; therefore, such an individual is not truly unresponsive. In the case of Ms. H, she was neither alert nor able to perform complex activities consistently. While she may have had an aphasia, it was not an isolated aphasia, as her illness had affected her level of consciousness and other cerebral domains.

It should be emphasized that a patient with diffuse cerebral damage may have an aphasia or frontal lobe dysfunction; however, in such a case, the frontal dysfunction or aphasia is only a part of a greater syndrome of cerebral dysfunction that has led to unresponsiveness.

What Psychiatric or Neuropsychiatric Conditions Should Be Considered in a Patient Who Is Unresponsive but Appears Awake?

Catatonia. Catatonia is a syndrome typically manifest by motor abnormalities and unresponsiveness. It may be caused by psychiatric, neurologic, or general medical disorders. Muscular rigidity, immobility, waxy flexibility, echopraxia or echolalia (in which the patient repeats the motions or speech of another), mutism, staring, and stereotyped movements can be present. A patient may be unresponsive to voice, to command, or to deep stimulation; vital signs may be normal, though the pulse is frequently elevated.

The most common psychiatric cause of catatonia is mood disorders; however, schizophrenia may also result in catatonia. Medical causes of catatonia (which include subdural hematoma, HIV encephalopathy, renal disease, progressive multifocal leukoencephalopathy, and other neurologic and medical disorders) produce a catatonic syndrome that is indistinguishable from one that is caused by psychiatric illness. This has led many to believe that catatonia is best considered a symptom of medical and neuropsychiatric disease, rather than a specific disorder with a single cause.

Ms. H did not clearly manifest symptoms of catatonia; no rigidity, waxy flexibility, echolalia, or echopraxia were noted. However, given that Ms. H was reported to have depressive symptoms for a week prior to her admission for unresponsiveness, one could consider that she might be having catatonia as a result of her depression, with symptoms of mutism and staring. The physician should perform a careful neurologic examination to confirm or deny the existence of findings consistent with catatonia. If catatonia appeared to be present, a trial of intravenous benzodiazepines would be indicated.

Severe depression. Severe depression may lead to an inability or an unwillingness to respond to environmental stimuli. Affected persons may not eat, drink, talk, or respond as a result of severe depression; depression can at times be difficult to distinguish from other causes of stupor. Depression that is manifest by decreased interactions and by unresponsiveness may be especially common in the demented elderly, in whom such symptoms may be the only way to distinguish a depressive recurrence. A careful interview with Ms. H and observation of her responses in the presence of emotionally charged stimuli (e.g., the entrance of family members) can help to make this diagnosis.

Conversion disorder. Conversion disorder refers to a syndrome of neurologic symptoms that is judged to be the result of (unconscious) emotional factors. In conversion disorder, sudden or progressive emotional distress may lead to the development of symptoms that resemble neurologic disease. Symptoms of conversion disorder can include unresponsiveness and apparent coma. There is typically an emotional precipitant just prior to the onset of neurologic symptoms, and there is often a history of similar presentations or the presence of sudden or severe physical symptoms in times of great emotional distress. No clear emotional precipitant was noted in the case of Ms. H, though it would be useful to determine what had happened to generate her depressive symptoms 2 weeks prior to her admission.

Malingering. While technically not a neuropsychiatric syndrome, malingering can also present as a decrease in responsivity. Malingering is defined as the intentional creation of physical symptoms for secondary gain. Therefore, to diagnose malingering, one must establish some benefit (e.g., housing, disability payments, or escape from police) for the production of symptoms. Malingering can be identified through (1) inconsistencies in behavior (identified by monitoring the patient when he or she is unaware of being observed), (2) the patient's avoidance of noxious stimuli, and (3) evidence of malingering obtained through historical information provided by external sources.

How Should the Evaluation of This Patient Proceed to Distinguish Between Medical, Neurologic, and Psychiatric Causes of Unresponsiveness?

Although a "psychogenic cause" for her unresponsiveness is being postulated, all potential causes of Ms. H's abnormal mental status should be considered. One should

confirm that a complete work-up of the potential medical and neurologic causes of stupor and coma has been completed. In addition, it is important to gather information to determine the psychiatric history, recent psychosocial stressors, and other factors that are suggestive of psychiatric illness as a cause of the presentation.

When meeting with the patient, the physician should complete the relevant portions of the neurologic examination (including examination of pupillary response, muscle tone, reflexes, and frontal release signs). Response to stimulation, from light touch to deeper stimuli, should be assessed. The use of a cotton swab placed in the nostril is a noxious but nonpainful stimulus that can elicit a response. A mental status examination should also be completed. The physician should speak to the patient to assess any response to voice or to specific content areas. Notice of changes in vital signs when emotionally charged topics are broached can indicate that the patient comprehends what is being said, even if the patient fails to respond.

In addition, the use of unexpected humor, rapid movement toward the patient, or an action that implies a noxious stimulus will be reintroduced can result in a voluntary response from a patient who had seemed unresponsive; such reactions suggest that the unresponsiveness is at least, in part, voluntary. Observation of the patient's response to family members and to other visitors is also useful, as is the initial response to the physician's arrival.

Of utmost importance is information from external sources. Nursing staff see the patient all day and night and may be able to report inconsistencies, patterns of behavior, or a waxing and waning course that may be consistent with delirium, depression, or malingering. Family members and friends can describe the patient's medical and psychiatric health prior to unresponsivity. They also may be able to describe whether the patient had prior episodes and to report a cause of such episodes.

Along with neurologic examination, mental status examination, and use of external collateral information, diagnostic testing should be performed to complete the physician's evaluation. When attempting to determine the etiology of a patient's unresponsiveness, the usual diagnostic tests—bloodwork (including serum and urine toxicologic screens), ECGs, and radiographic tests—are tremendously important. When there is diagnostic uncertainty, it is useful to evaluate the CNS as methodically as possible. One can perform an LP to culture and perform other diagnostic tests on the cerebrospinal fluid, and one can image the brain (preferably with MRI to obtain as accurate and detailed sense of the brain's structure as possible). An EEG can be tremendously helpful in this clinical situation. EEG patterns can be used to differentiate between a number of potential causes of unresponsiveness, including the following:

Recurrent spiking. Nonconvulsive status epilepticus is a cause of altered mental status and unresponsiveness that is often overlooked. Such patients may have prolonged periods of unresponsiveness or may manifest periods of intermittent alertness interspersed with stupor. An EEG can help to diagnose unremitting complex partial or atonic seizures that are causing lethargy, stupor, or coma.

Focal hypoactivity. Focal neurologic events can lead to focal hypoactivity on the EEG. Ischemic events and other causes of localized damage are among the events that can cause unresponsiveness and lead to areas of hypoactivity on the EEG.

Diffuse slowing. Global cortical dysfunction (with diffuse slowing) is seen in the majority of cases of unresponsiveness. Toxic, metabolic, infectious, and endocrine causes of unresponsiveness all tend to create generalized slowing on the EEG without focal hypoactivity or spiking.

Normal EEG. A normal EEG conveys normal electrical activity within the cerebral cortex. This absence of an electrical abnormality throughout the brain suggests either localized brainstem abnormalities (with no effects on cerebral electrical function) or, more commonly, psychiatric causes of unresponsiveness (such as depression, malingering, or conversion disorder).

In the case of Ms. H, additional physical and neurologic examination revealed no further abnormalities. A brain MRI revealed a small area of subacute infarction in the left frontal lobe but no other abnormalities. An EEG showed focal slowing in the area of infarction but was otherwise normal. Further conversation with family and friends revealed that Ms. H had been in her usual state of health recently, but, beginning approximately 2 weeks before, stopped speaking and interacting with them. She would wave others away, and her family and friends assumed that Ms. H simply did not feel like being with them and left her alone.

Given this data, the working hypothesis was that Ms. H was manifesting a severe depression after a left frontal stroke. A trial of psychostimulants was started (methylphenidate, 5 mg in the morning), and the dose was increased over the next 2 days (to 15 mg/day) after she had no response to 5 or 10 mg/day. Over the next 48 hours, Ms. H gradually became more alert and interactive. She was able to follow a number of commands and appeared to comprehend verbal information. However, she was unable to repeat information, and her speech was limited to 1- to 2-word sentences; these symptoms were consistent with a Broca's aphasia resulting from her stroke in the left frontal lobe. Over the next 6 weeks, Ms. H recovered well from her stroke and from her depression; she manifested only minor motor and speech abnormalities, and her mood had become euthymic.

In summary, by (1) performing a bedside examination of the patient to determine an individual's mental status and neurologic deficits, (2) obtaining important historical information about the patient from external sources, and (3) utilizing appropriate diagnostic testing, the physician can systematically approach the case of an unresponsive patient to gain a better sense of the etiology of these difficult-to-diagnose patients.

Drug names: methylphenidate (Ritalin, Metadate, and others), naloxone (Suboxone, Narcan, and others).

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