Historical Clinicopathological Conference

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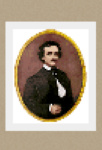

A 40-year-old man with mental status change

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Presentation of Case:

E.P. is a 40-year-old man who was brought to the emergency room in early October for evaluation of lethargy and confusion. He was traveling from Richmond to Philadelphia when he became ill and was found unconscious under the steps of the Baltimore Museum on Baltimore Street in the late afternoon. He was apparently well when he left Richmond at 7 AM. There was no evidence of trauma, and the patient did not smell of alcohol.

History. EP worked as a writer. He had no known allergies, coronary artery disease, diabetes, or other systemic illness, and was taking no medication. He had had cholera three months before the current hospitalization. In addition to a history of depression and possibly of opiate abuse, he had a history of alcohol abuse. However he had abstained from drinking for the past 6 months and there was no reported history of seizures or delirium tremens. The patient smoked tobacco on a regular basis and was sexually active with women. There were no known pathologic work exposures.

Hospital course: EP was admitted to the hospital for observation. He was initially unresponsive and remained so until approximately 3 AM, when he developed tremulousness and delirium and began having visual hallucinations. He was noted to be drenched with perspiration and to have wide variations in his pulse rate. He remained in this state for the next 28 hours. Early in the morning on the third hospital day, he became tranquil.

Results of a physical examination showed a well-developed white male who was calm and appropriate. His skin was warm and diaphoretic. His pulse rate was in the 50s and "thready." Results of a neurologic examination showed the patient was alert, oriented, and appropriate. There was no tremor and he followed commands appropriately.

The patient said he felt "miserable," but denied specific pain. He did complain of mild diffuse abdominal discomfort and headache. He had no recollection of how he had arrived at the hospital or of the events leading up to his illness.

Because of his improving status, he was transferred to the ward room. Here, his physicians attempted to treat him with alcohol, which he vehemently refused to drink. He soon worsened again and by the evening of the third hospital day, his mental status became clouded. He was noted to have shallow, rapid respiration and diffuse weakness. He drank water only with great difficulty. By late evening, he was again delirious, became combative, and required restraint. He remained in this state, calling out for family and friends, until his death on the fourth hospital day.

Differential Diagnosis:
Delirium. Whenever I am faced with a challenging case, I initially try to distill it to its basic features, which in this case I believe to be those of delirium and autonomic variability occurring in a relapsing fashion and resulting ultimately in the patient's death. Delirium is marked by clouded consciousness, impaired memory, impaired cognitive function and perception, and emotional disturbance. It may have a systemic, neurologic, or in rare cases, a psychiatric cause. Psychiatric causes of delirium are generally diagnoses of exclusion. Because delirium almost always reflects a systemic or neurologic cause, I have chosen to concentrate on these etiologies for the purpose of this discussion.

Neurologic causes of delirium are listed in Table 1. We are told the patient had no known history of trauma, and no physical evidence of trauma was noted at the time of examination. Nevertheless, a chronic subdural hematoma from prior trauma could go unrecognized, especially in a patient with a history of prior alcoholism who may have suffered traumatic injury during a period of impaired consciousness. It is unlikely that an epidural expanding hematoma from recent injury would cause this degree of impairment without further lateralizing signs on physical examination. Neoplastic diseases involving the central nervous system (CNS) and vascular malformations may cause changes in processes of thought, emotion, or cognition. In the absence of lateralizing signs on physical examination, I believe it is unlikely that one of these is responsible for the degree of impairment noted in our patient. Epilepsy can certainly cause impaired consciousness and postictal delirium, and may occur in a relapsing or intermittent course. It is unlikely, however, that our patient suffered generalized seizure activity for three days and then spontaneously recovered without further intervention.

Table 1. Neurologic causes of delirium

- Trauma
- Vascular disorders
- Neoplasia
- Epilepsy
- CNS Infections

Primary CNS infectious processes could be responsible for his condition, and I will return to them in greater depth later in the discussion. Systemic causes of delirium are listed in Table 2. Because no clinico-pathologic conference is complete without the mention of porphyria, I list it under the metabolic category. Acute intermittent porphyria may involve delirium, occur in a cyclical course, and be fatal. Patients also may complain of abdominal pain. It is unlikely, however, that our patient had his first episode of acute intermittent porphyria at age 40. There is also no mention of a rash or other skin changes, nor is there any mention of a change in the color of the patient's urine, which may be seen in porphyria. Thus, porphyria appears to be an unlikely etiology.

Table 2. Systemic causes of delirium

- Metabolic
- Endocrine
- Nutritional
- Hematologic
- Infectious
- Toxic

Endocrinopathies, including derangements of glucose, calcium, and sodium homeostasis, can cause delirium, but not usually in a relapsing course without some intervention. For this reason, as well as the fact that these entities are easily identifiable by routine laboratory screening, I will exclude them from the remainder of this discussion. Disorders of the thyroid, adrenal, or pituitary axis could also be responsible, but again do not generally have a relapsing course associated with them in the absence of intervention.

Several nutritional causes of delirium are worth mentioning given our patient's history of alcoholism. Superior hemorrhagic polioencephalitis (Wernicke syndrome) and alcohol amnestic disorder (Korsakoff psychosis) are due to thiamine deficiency and may result in delirium, dementia, and death. The former, however, is generally associated with ocular motor signs (usually bilateral sixth nerve palsy) and is generally progressive rather than relapsing. Thus, Wernicke syndrome is an unlikely cause of our patient's death. Pellagra (niacin deficiency) also occurs in alcoholics with chronic poor nutritional intake. It is characterized by progressive dementia, diarrhea, dermatitis, and ultimately death. Given the relapsing, acute course of our patient's illness and the lack of associated dermatologic findings, I will exclude this as a possibility.

Hematologic causes of delirium include leukemic infiltration of the CNS and hyperviscosity syndromes such as Waldenstrom macroglobulinemia. Neither is generally associated with a relapsing course or with autonomic variability. In addition, in hyperviscosity syndromes, examination of the retinas may show vessels that have a characteristic "sausage link" appearance, which is not mentioned in our patient.

Toxic causes of delirium are worth mentioning, given our patient's proclivity for alcohol and drugs. Alcohol withdrawal is characterized by tremors, autonomic hyperactivity, delirium, and seizures. In chronic alcoholics, symptoms usually begin within 5 to 10 hours of a decrease in serum alcohol levels, peak in intensity at 24 to 48 hours, and improve by the fourth or fifth day. If withdrawal is appropriately treated, it is rarely lethal. We are told that our patient had abstained from alcohol for the past six months, and that he did not smell of alcohol at the time of admission. In addition, it is unusual for patients suffering from alcohol withdrawal to become acutely ill, recover for a brief time, then worsen and die. For these reasons, although it is an attractive possibility, I will exclude alcohol withdrawal.

We are told that our patient may have used opiates, and so opiate withdrawal must be considered. Withdrawal from opiates generally begins 36 to 72 hours after discontinuation of the drug. It is an acute syndrome lasting 5 to 8 days and characterized by nausea, lacrimation, profuse sweating, "goose flesh," and yawning. It is generally not characterized by a relapsing course and it is associated with a persistent increase in sympathetic tone (elevated temperature and increased heart rate and blood pressure) rather than a variable sympathetic tone.

Finally, I would like to discuss infectious processes that involve the CNS. Although any infectious process accompanied by high fever, hypotension, or the other characteristics of sepsis may cause delirium, I have tried to focus on agents that are also associated with a relapsing course and autonomic variability.

Borrelia recurrentis is a louse or tick borne spirochetal disease associated with an acute febrile illness that may have CNS involvement and that has a relapsing course. However, "relapsing fever," as it is often called, is also associated with hepatomegaly, splenomegaly, jaundice, and prominent respiratory symptoms, none of which our patient had. In addition, the afebrile period between bouts averages 7 to 9 days, much longer than the lucid period our patient experienced.

Yellow fever is an acute severe febrile illness caused by an arbovirus transmitted via the mosquito Aedes aegyptii. It lasts approximately 3 days in its initial phase, followed by a remission lasting hours to days, and finally by recurrence of symptoms marked by neurotropic signs, coma, and death in 10% to 60% of patients. More than 50% of patients develop Faget's sign (inappropriate bradycardia, generally in the 50 to 60 range with a full pulse). However, yellow fever is also associated with icterus, severe musculoskeletal pain, nausea, vomiting, and gingival bleeding. In addition, neurotropic signs are generally absent until the final phases, and high fever is an unmistakable characteristic of the disease. Today, it is unheard of, for a person traveling from Richmond to Philadelphia, and residing on the eastern seaboard, to acquire yellow fever without more exotic travel. In the mid to late 1800s, however, yellow fever was a scourge along the eastern seaboard. In the late 1800s, Philadelphia had one of the most severe epidemics of yellow fever recorded, with more than 24,000 inhabitants affected and almost 4000 deaths. Almost everyone who remained in the city contracted the disease, and one in six patients with yellow fever died.

Although it may seem preposterous, I mention malaria as a possibility, particularly because we are told that our patient had recently contracted cholera. Malaria coexists with cholera in some parts of the world, and since our patient's travel history is unknown, we should explore this possibility. Of the four species of Plasmodium that are human pathogens, only P. falciparum is lethal. It may be contracted in some cholera-endemic areas and may produce recurrent or relapsing symptoms based on the cyclical release of parasites. Patients may appear well between episodes. There may be delirium in response to high fever, CNS involvement with the plasmodium, or secondary to hypoglycemia, which is not infrequent. However, there is a marked fever and tachycaradia, and I do not believe these features would have been missed. In addition, there is an incubation period of only one to two weeks, which is incompatible with the exposure to cholera (if we assume travel to an endemic area).

It is noteworthy that although cholera is not now endemic to the mid-Atlantic area of the United States, in 1866 approximately 50,000 Americans died of cholera. New York, which had more than 2000 fatalities, created the first municipal board of health in the United States in response to the crisis.

We are told that our patient was brought to the hospital in October, which is interesting given that several viral encephalitides are more common in the autumn. The most notable in our area is eastern equine encephalitis (EEE). Like its relatives (western equine encephalitis, St. Louis encephalitis, and Venezuelan encephalitis), however, EEE is a progressive disease from which patients either recover or, more commonly, die. The relapsing course noted in our patient would be extremely atypical.

Another viral encephalitis that bears mentioning is rabies. Rabies encephalitis is marked by the acute onset of confusion, hallucinations, combativeness, muscle spasms and seizures, all of which may occur in episodic fashion. Between episodes, patients may be calm and lucid. They may exhibit marked autonomic variability with periods of tachycardia and bradycardia, profuse sweating, lacrimation, and salivation. The disease is almost always lethal; median survival from the onset of overt symptoms is four days.

Rabies may be contracted when saliva of an infected animal is directly inoculated into an open wound, usually associated with the bite of a rabid animal. Other means of virus transference have been recorded (e.g., transplantation of infected corneal material), but are rare. Our patient had no reported history of such animal exposure, and at first that factor may make rabies seem unlikely. In 1994, however, of 6 reported cases of human rabies in the United States, epidemiologic investigation failed to identify a clear history of animal exposure in 3. From 1977 to 1994, clear evidence for animal exposure was documented in only 9 of 33 cases of human rabies (27%) in the United States. The difficulty may be due in part to the fact that rabies may have a long incubation period (up to or more than one year), depending on the size and location of the inoculum.

Human rabies may be preceded by a nonspecific prodrome characterized by generalized malaise and paresthesias or dysesthesias at the site of the inoculation. The severity and frequency of the prodrome is variable, and it is possible that patients may not even notice the symptoms.

We are told that during our patient's hospitalization, he adamantly refused alcohol and drank water only with "great difficulty." Patients with rabies characteristically develop intense, involuntary oropharyngeal and laryngeal spasms that may be provoked by attempts at drinking (hydrophobia), the sound of water (sonophobia), or stimuli as seemingly harmless as a breeze of air (aerophobia). The increased salivation and the concomitant difficulty in swallowing may lead to the "foaming at the mouth" so often mentioned.

Clinical diagnosis. In Virginia and Maryland, human rabies is fortunately rare. In Maryland, only 2 cases of human rabies have been documented since 1945, both of which were associated with bat exposures (Maryland Department of Health and Mental Hygiene, personal communication). If the information presented in the protocol is factual, I believe our patient died from rabies and that his initial exposure was distant and forgotten.
Discussion:

When I first read the protocol, I was perplexed by the conspicuous lack of laboratory and radiographic investigation. I found it unusual that the physicians should attempt to treat a patient with alcohol. I was concerned that I could not find a Baltimore Museum on Baltimore Street. I also found it unlikely that in 1995, a patient would be admitted to the hospital "for observation." Beginning to suspect that our case was not a recent one, I started to search for a more historical perspective.

On September 28, 1849, a 40-year-old American writer named Edgar Poe journeyed by steamer from Richmond to Baltimore, where he disembarked the following day. He was on his way to Philadelphia, probably to finalize some business before his upcoming wedding. He was neither seen nor heard of for five more days, until October 3, when he was found semiconscious, sprawled across a broad plank laid across two barrels outside Ryan's Saloon on Lombard Street. He was said to be wearing another man's clothes, an item of information that has never been explained. He was taken to Washington College Hospital (now Church Hospital), where he was admitted under the care of Dr. J.J. Moran. Delirium and tremors preceded a coma, from which he emerged on the second day of hospitalization. He was said to be calm and lucid before lapsing again into combativeness and a coma. He died October 7, 1849. He was buried in the Presbyterian cemetery at Fayette and Greene streets on October 9, and now rests within the shadow of the Baltimore VA Medical Center.

Addendum:

To the best of our knowledge, this historical case is presented as factually as possible and the writer in question is indeed Edgar Allan Poe. Although it is well known that Poe had a certain fondness for drink, it is also postulated that he was extremely sensitive to and intolerant of alcohol. Whether alcohol contributed to his death may never be known, but we congratulate Dr. Benitez on a new theory regarding its etiology.

It is interesting to note that Edgar Allan Poe loved household pets, especially cats, at a time when routine animal inoculation against rabies was not available.

JOSEPH COSTA, MD:

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Reference

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Final diagnosis