Exercises in Clinical Reasoning

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A Confusing Interaction

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A 44-year-oldwoman with a history of cerebral palsy, intellectual disability, seizure disorder, and hypothyroidism was brought to the emergency department from her group home for increasing lethargy over the past day. At baseline she was bedbound, nonverbal, and did not follow commands. Her aide reported difficulty feeding her that morning. The patient's family had recently noted abnormal twitching movements and occasional lateral neck movements to the right during eating, which were unlike her usual seizures. Review of systems was otherwise negative. In the emergency department, she was hypothermic (T 95.3°F) and hypotensive (BP 73/54 mmHg) with a heart rate of 80 beats/min.

The combination of hypotension and hypothermia brings to mind several possibilities, including sepsis, myxedema, or a central nervous system disorder affecting the hypothalamic pituitary axis, the area responsible for temperature regulation. The abnormal twitching movements could be a manifestation of her preexisting seizure disorder or possibly myoclonic jerks due to a toxic or metabolic process affecting the brain.

The discussant quickly generates two differential diagnoses: one for hypotension and hypothermia and the other for abnormal twitching movements. This rapid generation of the differential diagnosis is characteristic of non-analytic reasoning or pattern recognition.

The patient had a long-standing history of generalized tonic-clonic seizures occurring twice weekly on average. Three weeks ago she was hospitalized with hypothermia and hypotension, and was treated for a presumed urinary tract infection (UTI) (although cultures were negative). During that hospitalization she experienced an episode of status epilepticus, prompting addition of valproate to her anticonvulsant regimen. At that time, a morning serum cortisol level was 8.5 mcg/dL.

Given her recent hospitalization, UTI or another infection could be responsible for her recurrent hypotension and hypothermia. However the negative urine culture calls into question the previous diagnosis of UTI. Noninfectious causes of hypotension and hypothermia, including adrenal insufficiency or hypothyroidism, are also possible. The serum cortisol level, while in the normal range, does not eliminate adrenal insufficiency from consideration, particularly since the patient is acutely ill (which should elevate cortisol levels). A normal response to adrenocorticotropic hormone (ACTH) administration would be preferred to exclude that diagnosis.

After obtaining further data, the discussant uses analytic reasoning to interpret the normal cortisol level as relatively low in the setting of stress physiology. The cognitive psychology literature has described two types of thinking: non-analytic (i.e., fast, subconscious, intuitive) and analytic (i.e., slow, effortful, conscious). This dual process theory has been used to describe clinical reasoning. Experienced clinicians seamlessly transition between non-analytic and analytic reasoning in making diagnoses. Unfortunately, how clinicians apply and switch between these two modes has not been well characterized.[1]

The patient's medications included divalproex sodium, phenobarbital, levetiracetam, topiramate, and levothyroxine. She is allergic to penicillin, which causes diffuse hives.

She is taking thyroid replacement therapy, but such patients may still become hypothyroid due to nonadherence or poor bioavailability of levothyroxine. The autoimmune polyendocrine syndrome affects multiple glands causing simultaneous hypothyroidism and adrenal insufficiency. Panhypopituitarism is another possibility via decreased production of pituitary trophic hormones. Valproic acid has been added to a regimen of multiple anticonvulsant medications for refractory seizures, suggesting the possibility of an unrecognized central nervous system process. Therefore I would consider performing a lumbar puncture and brain imaging to evaluate for infection or a structural brain abnormality.

Analytic reasoning continues to be the discussant's dominant strategy. Analytic strategies include hypothetico-deductive reasoning, causal reasoning, probabilistic reasoning, and metacognitive reasoning. Clinicians choose a given

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strategy depending on the circumstances and their level of comfort or experience. Here, the discussant employs causal or pathophysiological reasoning to develop a differential diagnosis. Expert physicians often call upon knowledge of disease mechanisms (e.g., pathophysiology) to help expand or confirm their working diagnosis.

The initial examination showed a woman lying in bed in no acute distress. Her initial vital signs were: T 95.4°F, BP 70/50 mmHg, and heart rate 80 beats per minute. Her body mass index (BMI) was 24.5. After fluid administration, her vital signs were: BP 115/60 mmHg, heart rate 75 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 100 % while breathing room air. She opened her eyes but blinked frequently, limiting the fundoscopic examination. Her pupils were equal, round and reactive to light and accommodation. Conjugate gaze and oculocephalic and corneal reflexes were intact. There was no nystagmus. Facial movements were symmetric and tongue was midline. Baseline repetitive oral movements were present. She had new multifocal myoclonus at rest, not triggered by stimuli. There was increased tone in the proximal upper extremities and decreased tone in the lower extremities. Reflexes were symmetric and 2+ in the biceps, triceps and brachioradialis; 1+ in the knees, and absent at the ankles. Plantar responses were extensor bilaterally. She withdrew all four extremities to noxious stimuli. Cardiac, pulmonary and abdominal examinations were normal. There were no meningeal signs. A chronic indwelling bladder catheter was present.

The examination confirms hypothermia and hypotension. She does not have tachycardia, the normal response to systemic hypotension, implying either autonomic neuropathy or another condition affecting the chronotropic activity of the heart, such as hypothyroidism or a drug side effect. The diffuse myoclonus is nonspecific and associated with various metabolic or toxic encephalopathies. The cranial nerves appear intact and there are no lateralizing neurologic signs. The Babinski signs suggest an upper motor neuron lesion, but could be due to her baseline cerebral palsy. I remain concerned about an infectious process such as encephalitis, which could be affecting autonomic control centers in the brainstem. Lumbar puncture would be indicated to evaluate for meningoencephalitis.

The discussion highlights the iterative nature of clinical reasoning, whereby the discussant incorporates the new findings into his diagnostic thinking. Once again, causal reasoning is the predominant approach as he tries to explain unusual pathophysiological findings (e.g., hypotension without tachycardia). In analyzing such a case, the clinician may decide to apply Occam's razor (i.e., one disease explains the entire clinical presentation) or Hickham's dictum (i.e., a patient can have as many diseases as s/he pleases). This type of decision is an example of metacognition, or "thinking about thinking." Metacognition can be a form of analytic reasoning if the physician consciously wonders, "Should I try to combine all these findings into a unifying diagnosis?"

Laboratory values were significant for: sodium 141 mEq/dL, potassium 3.2 mEq/dL, chloride 109 mEq/dL, bicarbonate 26 mEq/dL, BUN 2 mg/dL, creatinine 0.42 mg/dL, glucose 90 mg/dL, albumin 2.9 g/dL, WBC count 4,800 cells/μL, hemoglobin 9.5 g/dL, MCV 97.3 fl, hematocrit 29 %, platelets 369,000 cells/μL and lactate 1.1 mEq/L. Thyroid stimulating hormone (TSH) was 2.8 μIU/mL (0.34-4.94 μIU/mL) and total T4 6.9 μg/dL (4.5-10.9 μg/dL). Urinalysis was cloudy with 8 WBCs/hpf and trace positive leukocyte esterase. Urine and blood cultures were subsequently negative.

CXR showed low lung volumes with bibasilar atelectasis and was unchanged from prior studies. Unenhanced computed tomography (CT) of the head showed a congenital brain abnormality unchanged from previous studies.

Lumbar puncture showed clear, colorless fluid with the following characteristics: protein 82 mg/dl (15–45 mg/dl), glucose 84 mg/dl (38-85 mg/dl), 13 red blood cells, 20 white blood cells with 89 % lymphocytes and 11 % macrophages.

Cerebrospinal fluid (CSF) gram stain and bacterial cultures were subsequently negative, as were tests for herpes simplex, varicella, cytomegalovirus, and Epstein-Barr viral infection.

The normal serum TSH and T4 levels eliminate the possibility of hypothyroidism. The absence of hyperkalemia and metabolic acidosis, classic electrolyte abnormalities of Addison's disease, does not rule out adrenal insufficiency because aldosterone production may be adequate to maintain potassium and acid–base homeostasis. She has mild pyuria with multiple negative urine cultures, or sterile pyuria, which is most likely caused by her indwelling catheter.

Cerebrospinal fluid (CSF) examination shows a mild lymphocytic pleocytosis with elevated protein, suggesting aseptic meningitis. Recent seizure activity may cause similar CSF findings; however, in light of her encephalopathy and myoclonus, a subacute or chronic meningoencephalitis should still be considered. The common viral infections including herpes simplex have been excluded, but West Nile and human immunodeficiency virus should also be checked. Other possibilities include neurosyphilis, tuberculosis, sarcoidosis, autoimmune disorders such as paraneoplastic or limbic encephalitis, and drug-induced or chemical meningitis. Although CT of the head without contrast is unremarkable, a contrast-enhanced CT or magnetic resonance imaging (MRI) would be more sensitive for detecting inflammatory processes affecting the brain. An electroencephalogram (EEG) might be helpful to further evaluate the myoclonic movements and determine whether they reflect ongoing seizure activity.

The discussant demonstrates classic hypothetico-deductive reasoning. A previously considered hypothesis (e.g., hypothyroidism) has now been rejected by the evidence; so he presents a new hypothesis (e.g.,. adrenal insufficiency), reviews the relevant findings, and determines that further information is required before he can decide for or against it (i.e., deduction).

The patient was resuscitated with intravenous fluids, warmed with blankets, and administered intravenous aztreonam and vancomycin. Continuous EEG monitoring showed an abnormal background (consistent with prior studies) and occasional seizures with tonic posturing. The myoclonus continued but did not correlate with EEG activity. The patient was administered intravenous valproic acid 1.5 g twice daily with additional loading doses to achieve therapeutic levels; however, her lethargy, altered mentation and myoclonus worsened. She developed refractory hypotension requiring vasopressor support in the intensive care unit. A morning serum cortisol level was 4 mcg/dL.

Empiric antimicrobial therapy is reasonable, although I do not believe a systemic bacterial infection explains the overall clinical picture. Cortisol levels are typically highest in the morning, and a level less than 3.0 is considered diagnostic of adrenal insufficiency. However, with stress or critical illness I would expect values greater than 10–15 mcg/dl. So I suspect she has adrenal insufficiency, although an ACTH stimulation test would be required to establish the diagnosis. EEG shows seizure activity and her myoclonus remains, again suggesting the possibility of meningoencephalitis. Interestingly, extrapulmonary tuberculosis could also explain adrenal insufficiency, aseptic meningitis, and sterile pyuria.

Concern for a toxic or metabolic encephalopathy prompted a serum ammonia level to be drawn, which was elevated at 135 mg/dL (normal less than 60 mg/dL).

Marked hyperammonemia is most commonly associated with hepatic encephalopathy due to liver failure. The patient has no clinical evidence of liver disease, although it would be prudent to measure her hepatic enzymes and prothrombin time to assess for occult liver dysfunction. Another consideration would be one of the urea cycle enzyme deficiencies, rare disorders affecting children which cause developmental delay and severe hyperammonemia. While metabolic disorders may cause encephalopathy, myoclonus and seizures, they are quite unusual and do not explain CSF pleocytosis. An additional possibility is a drug-induced encephalopathy, which might also explain aseptic or chemical meningitis, especially since the patient required escalating doses of valproic acid. I would obtain a valproate drug level and perform an ACTH-stimulation test, again a more reliable indicator of adrenal function.

The discussant uses non-analytic reasoning to link hyperammonemia and liver failure (e.g., hepatic encephalopathy), and then switches to analytic reasoning in concluding this diagnosis is unlikely. He then lists alternative conditions that may cause this laboratory finding. Probabilistic reasoning (e.g., "When you hear hoofbeats, think of horses, not zebras") is highlighted as he describes urea cycle enzyme deficiencies as being unusual and instead considers a medication-related side effect.

Hepatic enzymes and liver function tests were normal, including an INR of 1.1. Initial valproate (VPA) level was 21.6 but increased to 47.5 mcg/mL (50–100 mcg/mL) after the additional loading doses. Results of a 4 pm ACTH stimulation test were: 0 min 3.5 mcg/dL; 60 min 20 mcg/dL. ACTH level was 13 pg/mL (6–50 pg/mL).

Her normal hepatic enzyme panel and coagulation studies eliminate the possibility of hepatic encephalopathy. VPA levels are below the therapeutic range, but many anticonvulsants are highly protein-bound so serum levels may underestimate the therapeutic or toxic effects. In particular, VPA may cause a clinical syndrome of encephalopathy with hyperammonemia.

The ACTH stimulation test would be considered normal because the patient's stimulated cortisol exceeds 18 mcg/dl; however, in critically ill patients, the diagnostic criteria for adrenal insufficiency are not well defined. The markedly low baseline cortisol and brisk response (implying intact adrenocortical function) suggests central or secondary adrenal insufficiency. ACTH levels are in the lower normal range; however, in a patient with symptomatic hypotension, one would expect elevated levels. Therefore, relative adrenal insufficiency may also be contributing to her illness.

This patient developed encephalopathy, myoclonus, hyperammonemia, and probable adrenal insufficiency after commencement and escalation of VPA therapy. The most likely single explanation would be valproate-related hyperammonemic encephalopathy (VHE), although I am unaware that VPA causes adrenal insufficiency. I would discontinue VPA and thoroughly review the side effects of VPA by consulting an on-line resource or clinical pharmacist.

The discussant arrives at a final diagnosis by considering the patient's risk factors and excluding other diagnostic possibilities through a combination of hypothetico-deductive, causal, and probabilistic reasoning.

Blood amino acid levels demonstrated mildly elevated glutamine and arginine concentrations, likely reflecting valproate-induced decreased ammonia flux through the urea cycle. Urine organic acid levels were normal, making a urea cycle enzyme deficiency unlikely.

The VPA was discontinued and levocarnitine was begun for presumed valproate-associated hyperammonemic encephalopathy (VHE). The patient's mental status, blood pressure and body temperature improved and the myoclonic jerks resolved over the next day. Forty-eight hours later, the serum ammonia level was normal and EEG showed a decrease in high amplitude delta waves, suggesting improved encephalopathy.

DISCUSSION

Dual process theory is well described in cognitive psychology, typically focusing on non-analytic reasoning such as pattern recognition and heuristics or biases. However, analytic reasoning plays a major role in diagnostic reasoning, particularly in complex cases. This case demonstrates several analytic

techniques, including causal reasoning, hypothetico-deductive reasoning, probabilistic reasoning, and metacognition, each playing a key role in making the diagnosis. Several studies have demonstrated improved diagnostic accuracy when analytic reasoning and non-analytic reasoning are combined.[2,3] It behooves individual clinicians to develop flexibility in their analytic approaches by "practicing" the various clinical reasoning strategies.[2]

This patient presented a diagnostic dilemma, given the limited history and presence of two seemingly unrelated syndromes (encephalopathy and hypotension with hypothermia). Development of myoclonus and lethargy in the context of a recently added anti-epileptic medication were key clues to the etiology of the patient's metabolic encephalopathy. VPA, phenobarbital, and topiramate each inhibit reuptake of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the brain, and thus may cause hypothermia and hypotension.[4,5] GABA also inhibits corticotropin-releasing hormone release, which may explain this patient's central adrenal insufficiency.[6–8]

This case reminds clinicians to perform a thorough medication review and to use an analytical checklist that includes adverse medication effects. Medication-related toxicities may occur in the setting of sub-therapeutic drug levels due to complex drug–drug interactions.

Clinical Teaching Points

1. Valproate-associated hyperammonemic encephalopathy (VHE) is characterized by confusion, lethargy, and myoclonus or increased seizure frequency.
2. VHE occurs in patients with normal liver function and therapeutic or even subtherapeutic VPA levels.[9] Risk is heightened in patients taking VPA in combination with other anticonvulsants, particularly phenobarbital and topiramate.[10–12]
3. The pathophysiology of VHE remains speculative. VPA inhibits carbamoyl phosphate synthetase activity, and thus impairs urea cycle function, which is responsible for ammonia elimination from the body. Supplementation with levocarnitine enhances urea cycle activity and is often used to treat VHE.[13]

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