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Diagnosing a Missed Diagnosis

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The Case

A 57-year old woman was admitted to the hospital with cough, slurred speech, confusion, and disorientation. She was taking modified-release lithium for bipolar disorder. Her medical history was also significant for primary hyperparathyroidism and coronary artery disease. A brain CT on admission showed no evidence of a stroke or intracranial bleed. Her initial serum sodium level was normal at 140 mmol/L, but her serum calcium level was mildly elevated. Her initial serum lithium level was also mildly elevated at 1.5 mmol/L.

The patient's delirium was attributed to hypercalcemia, so she was admitted to the ward and hydrated with intravenous (IV) normal saline. Her lithium was continued. The following day, she remained confused and disoriented. Her hypercalcemia had slightly improved, but her serum sodium had risen to 149 mmol/L. The bedside nurse told the physician that the patient seemed to be going to the bathroom frequently; urine output had not been formally recorded. The physician attributed the rising sodium to the IV fluids and decided to continue aggressive hydration given the lack of improvement in her symptoms. A repeat lithium level was not ordered.

That evening, the nurse found the patient to be comatose and minimally responsive. The patient was urgently transferred to the intensive care unit (ICU), where repeat labs showed a sodium level of 163 mmol/L (normal < 145 mmol/L). She required intubation for airway protection, and a repeat lithium level was markedly elevated at 2.1 mmol/L. After admission to the ICU, her urine output was noted to be 500 cc/hour of extremely dilute urine, consistent with a diagnosis of nephrogenic diabetes insipidus due to lithium toxicity.

The patient was successfully managed in the ICU with 5% dextrose infusion to gradually correct her hypernatremia. Her lithium was held, and she was treated with ibuprofen and diuretics. Her mental status gradually improved and she was able to be extubated on hospital day 3. Fortunately, she did not experience any neurologic sequelae, and she was discharged home on hospital day 7. Her lithium was discontinued and she was started on valproic acid for treatment of her bipolar disorder.

The Commentary

by James B. Reilly, MD, MS, and Christopher Webster, DO

Long-term lithium use for treatment of bipolar or mood disorders is associated with several different types of renal injury. These include nephrogenic diabetes insipidus (NDI), chronic tubulo-intersitial nephropathy, and nephrotic syndrome from minimal change disease or focal segmental glomerulosclerosis.(1) The most common renal toxicity from lithium is acquired NDI, occurring in approximately 40% of patients on chronic lithium.(2) NDI represents the failure of the kidneys to appropriately concentrate the urine in the presence of antidiuretic hormone. Unlike the central form, NDI does not improve with administration of synthetic antidiuretic hormone such as desmopressin. The most common cause of acquired NDI is chronic lithium use, but hypercalcemia, hypokalemia, protein malnutrition, and postobstructive nephropathy may also cause it.(2,3)

Up to 60% of lithium filtered by the kidney is reabsorbed, mainly by the proximal renal tubule but also by the principal cells of the collecting duct, which are responsible for water reabsorption through regulated expression of aquaporin channels.(4) Beyond 8 weeks of exposure, lithium may induce principal cell toxicity, dysregulation of aquaporins, and inability to concentrate urine, leading to NDI.(3) Initially this dysregulation is reversible with removal of the drug, but eventually it may become permanent.(5)

Although mild hypercalcemia may have contributed to her initial delirium, this patient's dilute polyuria in the setting of chronic lithium use and subsequent progressive hypernatremia demonstrates a fairly typical presentation of acquired NDI and lithium toxicity. Patients with diabetes insipidus generally can drink enough water to maintain a normal serum sodium and osmolality. However, once their access to water is restricted, as in this case, hyperosmolarity can quickly develop. Also, because lithium is cleared renally, dehydration from NDI can induce or exacerbate acute kidney injury, creating a vicious cycle of lithium-associated nephrotoxicity and neurotoxicity.

It appears that the treating physician mistakenly attributed the patient's slurred speech and confusion to mild hypercalcemia instead of lithium toxicity, resulting in added harm to the patient, though fortunately it was reversible. The rate of diagnostic errors can vary widely across medical specialties, but it is clear that they are more common and more costly than first thought. Experts estimate an incidence of approximately 10%–20% (6) in internal medicine, and diagnostic errors are associated with greater morbidity, mortality, and malpractice claims than other error types, such as procedural or medication errors.(7) Patient safety experts have recently come to renew their focus on diagnostic errors, supported by new research and as demonstrated by the National Academy of Medicine 2015 report *Improving Diagnosis in Health Care*.(8)

While diagnostic errors can result directly from purely system-based problems (a laboratory error, for example), they are more commonly rooted in cognition.(9) Such errors often elude traditional system-focused methods of identifying and analyzing errors, and, because clinicians often see them as personal failings, they may be more reluctant to report them.

We now have a better understanding of the nature of diagnostic errors. Clinicians make diagnostic decisions using two kinds of mental processes: nonanalytic processing (also called intuitive, or *System 1* reasoning) and analytic processing (also called *System 2* reasoning).(10) As clinicians acquire experience and expertise, they spend less of their time using *System 2* and more of their time in the intuitive System 1 mode, based on pattern recognition. Intuitive processing is a highly efficient, rapid method to cope with the enormous complexity of clinical medicine while maintaining speed and a high level of accuracy. It is grounded in subconsciously applied heuristics (rules of thumb), a type of cognitive bias that tilts the odds of success in the clinician's favor when facing a diagnostic decision. Heuristics are useful but imperfect, and they can lead the clinician down the wrong path when applied inappropriately. Dozens of biases have been described in the medical literature (11); Table 1 lists several prevalent biases with brief definitions.(12)

Although it is unlikely that mild hypercalcemia would lead to diabetes insipidus and delirium in this patient, perhaps it was reasonable to consider it initially. Later, it becomes more apparent that the physician fell victim to biases that led to the error. By focusing solely on the calcium level and failing to consider a broader differential diagnosis, the physician demonstrates an *anchoring bias*. As diabetes insipidus began to manifest itself more obviously, despite improvement in the patient's calcium, a decision to continue to treat hypercalcemia without consideration of lithium toxicity demonstrates *confirmation bias*. This latter term refers to the subconscious tendency of physicians to overemphasize evidence that supports their hypothesis while discounting evidence that may disconfirm it. These biases probably prevented this physician from reconsidering the initial working diagnosis, even as it became more and more apparent that lithium was causing the delirium and the diabetes insipidus that led to hyperosmolar coma. In the end, the final common pathway for all cognitive diagnostic errors is *premature closure* of the diagnostic process—or to put it another way, "once a diagnosis is made, thinking stops," leaving a physician incapable of responding to evolving patient presentations or new data.

Cognitive errors are usually multifactorial, highly subjective, imprecise, and difficult to analyze without understanding the clinician's thought process. In addition, they are impossible to separate from the systems context in which they occur. One study demonstrates that nearly half the time, both cognitive and system factors contribute to a given diagnostic error.(9) They are also very difficult to prevent, given their subconscious nature. Although expanding one's knowledge base and gaining greater clinical experience (expanding the power of pattern recognition in a given individual) should improve diagnostic accuracy, many experts feel that it is probably necessary for clinicians to utilize cognitive aids and other types of debiasing strategies as well, to ensure that System 1 is not used inappropriately. While these strategies have not yet been proven to directly reduce errors in practice, many strategies (including some described in Table 2 [12]) have shown promise in simulated case scenarios, but results have been mixed and all techniques deserve further study.(13) In addition to instruction on the dual process model and metacognition, guided reflection, and other methods of changing thinking habits, system-based improvements have great potential for improving the conditions for optimum diagnosis as well. Knowledge-based checklists and electronic health record–based clinical decision support can be useful, but other applications such as the electronic differential diagnosis generator ISABEL (14) are also being created and utilized by practicing clinicians.

Take-Home Points

- Chronic lithium use is associated with renal toxicity, most commonly nephrogenic diabetes insipidus. Any condition that reduces a patient's access to free water can unmask nephrogenic diabetes

insipidus and lead to a severe hyperosmolarity syndrome.
- Diagnostic errors are highly prevalent, complex, costly, and difficult to prevent. They frequently result from cognitive biases that are well described in the medical literature.
- Raising awareness of the dual modes of thinking, development of cognitive aids, and systems-based interventions to improve conditions for thinking all have potential to reduce diagnostic errors, and they require further study.

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Tables

Table 1. Common Biases and Brief Definitions (Adapted From 12)

Bias	Definition
Affective	Also called *visceral bias*; emotional influences can induce thinking errors, including the feelings physicians have about their patients, both positive or negative
Anchoring	Narrow focus on a single feature in a patient's presentation to support a diagnostic hypothesis, even if other concurrent features or subsequent information refutes the hypothesis
Availability	The tendency to think that things that come to mind immediately are more likely or more common
Blind obedience	Inappropriate deference to the recommendations of authority, either by direct superiors or by expert consultants, even in the absence of a sound rationale
Confirmation	The tendency to search for evidence to support an initial diagnostic impression, and the tendency not to search for, or even to ignore, evidence that refutes it
Diagnostic momentum	The tendency of a diagnostic label to become propagated by multiple intermediaries (patients, physicians, nurses, other team members) over time; what might have begun as a possible "working diagnosis" becomes "definite"
Framing effect	The susceptibility of diagnosticians to be disproportionately influenced by how a problem is described, by whom it is described, or even the environment where an encounter takes place
Hindsight bias	Knowing the outcome of an event influences the perception and memory of what actually might have occurred; in analyzing diagnostic errors, this can compromise learning by creating illusions of the participants' cognitive abilities, with potential for both underestimation and overestimation of what the participants knew (or could have known)
Overconfidence	The tendency to think one knows more than one does, especially in physicians who might place faith in opinions without gathering the necessary supporting evidence
Premature closure	Making a diagnosis before it has been fully verified

Table 2. Possible Techniques to Avoid Diagnostic Errors (Adapted From 12)

- Improving data collection
- Building and strengthening repository of illness scripts (mental prototypes of disease states)
  - Promote knowledge of atypical presentations of disease
  - Symptom-based Reading
  - Case reports (e.g., *NEJM* series)
  - Flash card review to build clinical knowledge base
- Raising awareness of dual processing cognition
  - Reduce personal stigma of cognitive errors
  - Facilitate adoption of other techniques
- Metacognition: "thinking about your thinking"
  - Cognitive forcing strategies
    - Structured reflection
    - "Two-pass" diagnostic approach (generating diagnosis from System 1, using System 2 to double-check)
  - Know one's favored biases
  - Acknowledge emotions
    - Due to external demands
    - Due to internal stresses
    - Stemming from patient interactions (counter-transference)
- Fostering better intuition
  - Bayesian reasoning
  - Progressive problem solving
    - Avoiding routinization of work by creating cognitive challenges that are not required at the time (e.g., planning alternative diagnosis/treatment plan should the initial plan prove ineffective or incorrect)
  - Giving feedback
  - Simulation
- Reducing reliance on memory
  - Checklists
  - Mnemonics
  - Clinical references (e.g., UpToDate)
  - Differential diagnosis tools
  - Clinical decision support (e.g., through EHR)
- Systems thinking
  - Understanding how systems affect thinking
  - Recognizing and compensating for system flaws
  - Openness to discussing error
  - Analysis of errors
    - Due to external demands
    - "Cognitive autopsy" (chart-stimulated recall and narrative writing)
    - Root cause analysis (e.g., Fishbone diagram)
    - Morbidity and mortality conference

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