CLINICAL PRACTICE

*Clinical Practice: Exercises in Clinical Reasoning***A 76-Year-Old Woman with Diaphoresis and Anxiety**

Starr Steinhilber, MD, MPH¹, J. Martin Rodriguez, MD², Carlos A. Estrada, MD, MS^{2,3,4}, and Ryan R. Kraemer, MD^{1,2,3}

¹Tinsley Harrison Internal Medicine Residency Program, The University of Alabama at Birmingham, Birmingham, AL, USA; ²Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA; ³Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA; ⁴Veterans Affairs Quality Scholars Program, Birmingham, AL, USA.

J Gen Intern Med 28(10):1376–80

DOI: 10.1007/s11606-013-2500-7

© Society of General Internal Medicine 2013

In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (**bold**). Additional commentary on the diagnostic reasoning process (*italics*) is integrated throughout the discussion.

Clinical Information. A 76-year-old woman with hypertension and polymyalgia rheumatica presents with episodic diaphoresis and anxiety for 3 months.

Anxiety is a commonly encountered symptom in the ambulatory setting; however, when it presents suddenly in an elderly patient who has no recent stressors, it may be secondary to a new underlying medical condition. There are numerous entities that can lead to anxiety. At this point, I would take a detailed history of the symptoms and circumstances surrounding the episodes.

Diagnostic Reasoning. *The clinician quickly recognizes that without recent major life stressors, the new presentation of anxiety in an elderly person does not fit the more common illness script of generalized anxiety disorder. Illness scripts are the key risk factors, clinical presentations, and pathophysiology that summarize a specific clinical problem.¹ For instance, a clinician's illness script for an acute myocardial infarction might include the acute onset of angina and shortness of breath in a patient with risk factors for coronary artery disease. As a clinician gains knowledge and experience with a particular diagnosis, they refine and expand their illness script for that diagnosis.²*

Once the clinician realizes that he doesn't have one illness script that exactly fits our patient's presentation, he

consciously stops to gather more information instead of making an early differential diagnosis.

Clinical Information. Three months before presentation, she felt very anxious and noticed palpitations while fasting for a routine laboratory evaluation. She was also diaphoretic, had slurred speech, and eventually lost consciousness. Emergency Medical Service personnel found her blood glucose to be 45 mg/dL, and after intravenous administration of dextrose, her symptoms resolved.

Hypoglycemia is an intriguing diagnosis and can certainly cause episodes of anxiety and diaphoresis associated with the adrenergic surge that attempts to raise the blood sugar. The first step in the diagnosis of hypoglycemia is determining whether the patient fulfills Whipple's triad: symptoms of hypoglycemia, documented hypoglycemia, and resolution of symptoms with the administration of glucose. Our patient has all three components. If her other episodes of anxiety and diaphoresis have been similar to the one above, I believe hypoglycemia likely explains her anxiety. Now we must determine the etiology of her hypoglycemia.

We should first determine whether her symptoms occur in the fasting or post-prandial state, as the differential diagnosis varies depending on the circumstances of the hypoglycemia. We should obtain more information regarding recent weight changes or history of diabetes, as early diabetes can present with hypoglycemia. Alcohol abuse or malnutrition can deplete glycogen stores and lead to hypoglycemia. Exogenous insulin or sulfonylurea administration can also cause hypoglycemia. Sepsis and other infections can cause hypoglycemia, but usually not for this duration. Our patient could have a second autoimmune disease such as adrenal insufficiency, which can present with hypoglycemia. Other rarer causes of hypoglycemia include insulinomas, tumors producing insulin-like growth factor (IGF), and insulin-like antibodies. The differential at this point is very broad, and I would like to narrow it by getting some additional history.

Diagnostic Reasoning. *First, the clinician consciously slowed down to make sure the patient fulfilled Whipple's*

Received January 29, 2013

Revised March 18, 2013

Accepted April 19, 2013

Published online June 1, 2013

triad before concluding that the hypoglycemia was to blame for the episodes of anxiety. Then, he quickly moved to an analytical (system 2) approach,³ a slow, deliberate, step-wise process to systematically evaluate a patient. He began generating a differential diagnosis for hypoglycemia and considering whether each diagnosis could fit our patient.

An intuitive (system 1) approach is not evident in this section of the clinician's reasoning. System 1 refers to the fast and effortless approach that clinicians employ in familiar situations. In this approach, the clinician easily diagnoses the patient by recognizing key information in the patient presentation that fits an illness script that he/she has for a particular disease. For instance, most clinicians would utilize an intuitive approach to diagnose the following patient with cystitis—a 31-year-old woman with the acute onset of dysuria, urgency, and frequency. In our case, the clinician has not recognized a pattern in the patient presentation that easily gives him the diagnosis.

Clinical Information. She has subsequently had multiple, mild, similar episodes and an increased carbohydrate diet has not improved her symptoms. She has a history of long-standing hypertension, polymyalgia rheumatica, Staghorn calculi, and melanoma in situ resected 13 years prior. She is treated with amlodipine, irbesartan, and prednisone 20 mg daily. No changes in her medications have occurred in over 6 months, and her chronic problems have been stable. She is a former heavy smoker, but quit 30 years ago. She has no alcohol or illicit drug use. Her mother had diabetes mellitus type 2 and congestive heart failure. Her father died from tuberculosis 40 years prior.

It is possible that she got tuberculosis from her father and may have adrenal involvement, or may have autoimmune adrenalitis; however, adrenal insufficiency is an unlikely explanation since she is on greater than 5 mg of prednisone daily. Her episodes occur during fasting, which lowers the probability of nesidioblastosis or dumping syndrome, especially in the absence of a gastric bypass. Both of these processes are more likely to cause post prandial hypoglycemia than fasting hypoglycemia.

Medications can produce hypoglycemia; however, to my knowledge, her medications are not known causes. Her smoking history puts her at risk for malignancy, which is one of the rarer causes of hypoglycemia. Certain tumors can produce insulin (insulinomas) or IGF, although I'm not certain that smoking increases the rates of these tumors. The lack of history of alcohol use or liver disease reduces the chance that depleted glycogen stores are the culprit. The fact that her mother had type 2 diabetes mellitus puts her at risk for diabetes mellitus, and as I mentioned, it can initially present with hypoglycemia.

Diagnostic Reasoning. The clinician followed a systematic approach (system 2) by reviewing each new piece of information and deciding whether it fit into the illness script for each possible diagnosis on his differential. He was looking for clues to quickly move diagnostic possibilities up or down the differential diagnosis. By prioritizing his list of possible diagnoses, the clinician is able to focus his attention on the more likely diagnoses and not expend mental capital on diagnoses that do not fit this patient. This process is important in complex medical cases with a long list of possible diagnoses. Deliberate practice and effectively gathering key information, as compared to gathering large amounts of information, are skills that characterize exceptional diagnosticians and clinical experts.^{4,5}

Clinical Information. Upon review of systems, she reported an unintentional 10 lb weight loss in recent months and dyspnea on exertion for 1 month. She denied dyspnea at rest, fever, chills, or other systemic symptoms. Her appetite was normal. Recently, she started logging her blood glucose values, which ranged from 80–120 mg/dL while feeling well, and ranged between 30–40 mg/dL while symptomatic.

I now have a fair amount of information, and at this point I find it helpful to consolidate the available information. We have an elderly, former smoker with a history of autoimmune disease presenting with 3 months of episodic fasting hypoglycemia, mild unintentional weight loss, and dyspnea on exertion. It is important to note that hypoglycemia is a serious situation, which left untreated, can have detrimental sequelae such as seizures or even death. She should be admitted soon for an inpatient work-up with a 72-hour fast, which can be very helpful in determining the etiology. Insulin and C-peptide levels during symptomatic episodes will help us evaluate for endogenous and exogenous insulin excess. A sulfonylurea screen is important to obtain even without history of sulfonylurea ingestion, since these medications are often taken by mistake. Glucagon administration at the end of a 72-hour fast evaluates for intact glycogen stores.

She should also be evaluated for IGF excess, since fibrous tumors in the chest can produce IGF and cause exertional dyspnea. Going forward, I am interested in more information regarding her dyspnea and her exam, which may give us additional clues to the diagnosis.

Diagnostic Reasoning. The clinician stated at this point he had been given so much information that he thought he might forget a key component if he didn't summarize the case thus far. The clinician is conceptualizing the problem representation—the summary of clinical information described in abstract terms that provides a discriminatory and useful overview of the case.⁶ By summarizing just the

key elements of the case in a concise fashion, the discussant takes a step back from the information and looks at the big picture. Once stated, the clinician quickly realizes the potential danger associated with the diagnosis of recurrent hypoglycemia, while recognizing the most important next step is a supervised 72-hour fast to expedite the diagnostic process. This process also allows the clinician to compare the problem representation with the illness scripts he has for various conditions that cause hypoglycemia.

Clinical Information. On physical exam, her temperature is 98.5 F, blood pressure 120/52 mmHg, pulse 76 beats per minute, respirations 23 per minute, and weight 160 lbs. The exam is remarkable only for decreased breath sounds and dullness to percussion in the right lower lung field, and two-plus pitting edema on both legs up to the knees.

Her initial laboratory data includes a sodium of 141 mEq/L, potassium 3.5 mEq/L, creatinine 0.4 mg/dL, glucose 65 mg/dL, and hematocrit 33 %. White blood cells and platelets were normal. Urinalysis, liver function tests, TSH, cortisol, and calcium were unremarkable. A chest radiograph showed mild cardiomegaly, mild emphysematous changes, and blunting of the right costophrenic angle.

The most remarkable findings are her respiratory rate, decreased breath sounds, and dullness to percussion. Her pulmonary findings could represent a pleural effusion, mass, or other parenchymal abnormality. The lung findings are likely significant and an important clue to her final diagnosis. Her pitting edema is also notable, but I'm not sure how it fits in at this time. Her general laboratory data doesn't help me narrow down my differential other than ruling out hypothyroidism, which did not fit clinically. She does have mild anemia; however, it is too nonspecific to be helpful at this point.

Diagnostic Reasoning. The human brain can only handle limited amounts of information at any given time. The clinician temporarily abandons the main problem—hypoglycemia—to allow cognitive space to focus on the new information. He again goes through the mentally taxing process of analyzing each new piece of information to refine his differential diagnosis.

Clinical Information. A sulfonylurea screen was negative. She was hospitalized and placed on a continuous glucose infusion. Her glucose level fell to 51 mg/dL, insulin level was 6.7 mIU/ml (normal 6.0 to 27.0 mIU/ml), and C-peptide was 1.1 ng/mL (normal 0.9 – 6.9 ng/mL). She experienced the same symptoms as during her previous episodes; they resolved with an increase in glucose administration.

Although a formal 72-hour fast was not performed, these results are very helpful diagnostically. Watching her experience the same symptoms she described in the HPI confirms our working diagnosis of hypoglycemia. When hypoglycemic, her insulin level is at the lower end of the normal range for serum insulin values. The C-peptide shows us that the insulin is being made by the patient and is not from an exogenous source. Classically, insulinomas have an elevated insulin level; however, they can also present with an inappropriately “normal” insulin level in the setting of hypoglycemia. A simultaneously suppressed beta-hydroxybutyrate level would further suggest an insulinoma. The negative sulfonylurea screen rules out sulfonylurea intake.

Lung tumors producing IGF would be a way to tie everything together with her dyspnea, physical exam, imaging findings, and hypoglycemia with fasting, although I would expect her insulin level to be more suppressed if she had a tumor producing an insulin-like growth factor. I would need to consult an endocrinologist or the literature to see what insulin levels are expected in patients with IGF producing tumors. In addition, I would like more advanced imaging of her chest and an echocardiogram to evaluate her cardiac function in light of her lower extremity pitting edema.

Diagnostic Reasoning. Illness scripts facilitate the access of more complex information from memory. Comparing and contrasting illness scripts is a strategy to narrow, expand, or mentally re-arrange the diagnostic options; in this case, sulfonylurea use, insulinoma, or tumor-related.

The clinician is able to fit all of the patient's key characteristics except for her insulin level into his illness script for an IGF-producing tumor. Instead of abandoning the diagnosis of IGF-producing tumor, the clinician questions the accuracy of his illness script and recognizes the importance of looking for an expert opinion or referencing the literature to refine his illness script. He is still utilizing an analytical approach to diagnose the patient, but understands that an endocrinologist very familiar with hypoglycemia could potentially employ a system 1 approach to more easily arrive at the diagnosis.

Clinical Information. A computed tomographic exam of the chest showed a 14×12 cm homogeneous, non-enhancing, pleural based mass in the right lower hemithorax, Fig. 1.

She has a very large chest mass that can explain her dyspnea. At this point, I would do a literature search on lung tumors and hypoglycemia. I would consider an IGF-producing tumor or other causes of paraneoplastic hypoglycemia. My next diagnostic step would be a CT-guided biopsy of the mass, as it is peripheral and should be easily accessible. If a tumor is confirmed, she may require surgical excision.

Figure 1. Computed tomographic scan of the thorax with contrast, coronal view, showing a 14×12 cm homogeneous non-enhancing mass in the right lower hemithorax that originates from the pleura.

Diagnostic Reasoning. *The diagnostic and management path is now clear and directed to the lung mass. The clinician has only one illness script that fits this patient's presentation, but acknowledges the limitations of his knowledge and considers the possibility of a disease for which he does not have an illness script.*

Clinical Information. An excisional biopsy of the pleural mass showed spindle cells, keratin negative, with findings consistent with a solitary fibrous tumor of the pleura, previously referred to as benign mesothelioma. The IGF-I level was 59 ng/mL (normal range 54–205 ng/mL), IGF-II level was 1,400 ng/mL (normal less than 1,248 ng/mL). After surgical resection, the patient's hypoglycemic episodes resolved.

DISCUSSION

Diagnostic errors are an increasingly recognized source of medical errors.⁷ To make diagnoses, clinicians employ two different modes of thinking. The system 1 (intuitive) mode of thinking utilizes heuristics (mental short cuts) to help clinicians diagnose patients when they present with familiar illness scripts. Its fast processing enables the clinician to work efficiently, but its use of heuristics can occasionally lead to diagnostic errors.⁸ System 2 (analytical) checks and balances system 1, but is time consuming and mentally taxing. The interplay between system 1 and system 2 is

often subconscious. When a clinical pattern does not fit a known illness script, the clinician moves from system 1 to system 2 clinical reasoning. Expert clinicians are especially adept at instinctively knowing when to move from system to system.

Metacognition is one tool to improve a clinician's diagnostic skills. Metacognition refers to the act of analyzing one's own thought processes—thinking about thinking.^{9–12} When a clinician utilizes system 1 to quickly diagnose a patient, they can then consciously decide to employ system 2 to review the case for diagnostic errors. When a clinician misses a diagnosis or misdiagnoses a patient, metacognition can help them understand where their cognitive process erred. Metacognition allows us to learn from both our diagnostic errors and successes in order to hone our diagnostic skills. Through metacognition, we can become better at “slowing down when you should”^{13,14} which is a hallmark of the expert clinician.

Recent studies examined the attributes of successful ward attending rounds from the perspective of trainees.^{15,16} The attending behavior that trainees valued most was “sharing of the attending's thought process.” Trainees often marvel at expert clinicians who effortlessly diagnose patients on the wards or in morning report. Through metacognition and being explicit in the discussion of their thought processes, clinician educators can help their trainees improve their cognitive and clinical skills.

Sole reliance in one's own self-assessment—a hallmark of metacognition—has its limitations though; an individual who is unskilled and unaware would be unable to engage in a meaningful process. As metacognitive abilities vary among individuals,¹⁷ monitoring of errors also varies.¹⁸

Metacognition is a powerful tool to both improve a clinician's clinical reasoning and to teach clinical reasoning to trainees. A review of strategies to promote metacognition in science education is available elsewhere.¹⁹

CLINICAL TEACHING POINTS

1. Whipple's Triad for the diagnosis of hypoglycemia includes symptoms and/or signs of hypoglycemia, documented hypoglycemia, and resolution of symptoms and/or signs with the administration of glucose.²⁰
2. Hypoglycemia has a wide differential diagnosis, including medications, factitious hyperinsulinemia, inherited metabolic diseases, critical illness, infection, alcohol use, nesidioblastosis (islet cell hypertrophy), insulin producing tumors, and insulin-like growth factor producing tumors among others.
3. A 72-hour fasting plasma glucose test is the most reliable diagnostic test for fasting hypoglycemia and can differentiate diseases of over-production, such as insulinoma, from impaired hepatic glycogen mobilization or other causes of hypoglycemia.

4. Insulin-like growth factors are proteins similar to insulin that, when present in large quantities, can act on insulin receptors causing hypoglycemia. They can be secreted from mesenchymal tumors in the lung, gastrointestinal system, and others.^{21,22}
5. Solitary fibrous tumors of the pleura produce IGF-2 and can result in Doege-Potter Syndrome—paraneoplastic hypoglycemia in association with solitary fibrous tumors. Complete surgical excision of the fibrous tumor improves hypoglycemia.²³

Acknowledgements: We thank Dr. Robert M. Centor for providing suggestions on prior versions of this manuscript.

Conflict of Interest: The authors declare that they do not have a conflict of interest.

Disclaimer: The opinions expressed in this article are those of the authors alone and do not reflect the views of the Department of Veterans Affairs.

Corresponding Author: Ryan R. Kraemer, MD; Department of Medicine, The University of Alabama at Birmingham, 720 Faculty Office Tower 510 20th Street, Birmingham, AL 35294-3407, USA (e-mail: rkraemer@uab.edu).

REFERENCES

1. Charlin B, Boshuizen HP, Custers EJ, Feltovisch PJ. Scripts and clinical reasoning. *Med Educ.* 2007;41:1178–1184.
2. Schmidt HG, Rikers RM. How expertise develops in medicine: knowledge encapsulation and illness script formation. *Med Educ.* 2007;41:1133–1139.
3. Croskerry P. A universal model of diagnostic reasoning. *Acad Med.* 2009;84:1022–1028.
4. Mylopoulos M, Lohfeld L, Norman GR, Dhaliwal G, Eva KW. Renowned physicians' perceptions of expert diagnostic practice. *Acad Med.* 2012;87:1413–1417.
5. Ericsson KA. An expert-performance perspective of research on medical expertise: the study of clinical performance. *Med Educ.* 2007;41:1124–1130.
6. Bowen JL. Educational strategies to promote clinical diagnostic reasoning. *N Engl J Med.* 2006;355:2217–2225.
7. Redelmeier DA. The cognitive psychology of missed diagnoses. *Ann Intern Med.* 2005;142:115–120.
8. Croskerry P. Achieving quality in clinical decision making: cognitive strategies and detection of bias. *Acad Emerg Med.* 2002;9:1184–1204.
9. Flavell JH. Metacognition and cognitive monitoring: a new area of psychological inquiry. *Am Psychol.* 1979;34:906–911.
10. Fleming SM, Dolan RJ, Frith CD. Metacognition: computation, biology and function. *Philos Trans R Soc Lon B Biol Sci.* 2012;367:1280–1286.
11. Elstein AS. Thinking about diagnostic thinking: a 30-year perspective. *Adv Health Sci Educ.* 2009;14:7–18.
12. Schoen DA. The reflective practitioner: how professionals think in action. New York, NY: Basic Books; 1983.
13. Moulton CE, Regehr G, Mylopoulos M, MacRae HM. Slowing down when you should: a new model of expert judgment. *Acad Med.* 2007;82(10 Suppl):S109–S116.
14. Moulton CE, Regehr G, Lingard L, Merritt C, MacRae HM. Slowing down when you should: initiators and influences of the transition from the routine to the effortful. *J Gastrointest Surg.* 2010;14:1019–1026.
15. Roy B, Castiglioni A, Kraemer RR, Salanitro AH, Willett LL, Shewchuk RM, Qu H, Heudebert G, Centor RM. Using cognitive mapping to define key domains for successful attending rounds. *J Gen Intern Med.* 2012;27:1492–1498.
16. Castiglioni A, Shewchuk RM, Willett LL, Heudebert GR, Centor RM. A pilot study using nominal group technique to assess residents' perceptions of successful attending rounds. *J Gen Intern Med.* 2008;23:1060–1065.
17. Fletcher L, Carruthers P. Metacognition and reasoning. *Philos Trans R Soc Lon B Biol Sci.* 2012;367:1366–1378.
18. Yeung N, Summerfield C. Metacognition in human decision-making: confidence and error monitoring. *Philos Trans R Soc Lon B Biol Sci.* 2012;367:1310–1321.
19. Tanner KD. Promoting student metacognition. *CBE—Life Sci Educ.* 2012;11:113–120.
20. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94:709–728.
21. Guettier JM, Gorden P. Hypoglycemia. *Endocrinol Metab Clin North Am.* 2006;35:753–766.
22. Steigen SE, Schaeffer DF, West RB, Nielsen TO. Expression of insulin-like growth factor 2 in mesenchymal neoplasms. *Mod Pathol.* 2009;22:914–921.
23. Kalebi AY, Hale MJ, Wong ML, Hoffman T, Murray J. Surgically cured hypoglycemia secondary to pleural solitary fibrous tumour: case report and update review on the Doege-Potter syndrome. *J Cardiothorac Surg.* 2009;4:45. doi:10.1186/1749-8090-4-45.