Wilson disease

(FEBRUARY 2016)

TO THE EDITOR: We read the IM Board Review article by Hanouneh et al in the February issue of the *Journal* with great interest.[1] The authors described an interesting case of a young woman presenting with what initially seemed to be jaundice of acute onset, with rapid progression to acute encephalopathy and worsening liver failure. The patient was eventually diagnosed with fulminant Wilson disease and, thankfully, underwent successful liver transplant. We thank the authors for their in-depth review of the common causes of acute liver failure, the general approach to management, and the tailored treatment of Wilson disease in such settings.

However, we believe that several aspects merit further attention. First, on initial presentation and investigation, it would have been important to consider cholestatic hepatobiliary pathologic processes (eg, choledocholithiasis, cholangitis, primary biliary cirrhosis, primary sclerosing cholangitis), given the characteristic liver panel results.

Second, the authors rightly pointed out that hemolytic anemia is common in patients with acute liver failure secondary to Wilson disease. However, it is important to keep in mind that additional testing should include Coombs testing (typically negative in Wilson disease) and examination of the peripheral smear to exclude other etiologies, since such conditions as thrombotic thrombocytopenic purpura may present with multiorgan failure as well.[2]

Third, the authors report that Kayser-Fleischer rings are pathognomonic for Wilson disease. However, many reports in peer-reviewed medical journals suggest that this may not be the case and the overall clinical picture should be considered.[3]

Fourth, while the authors focus their attention on liver transplant, several other treatments deserve mentioning. We agree that liver transplant is considered the only lifesaving treatment. But in certain situations, molecular absorbent recirculation systems and hemodialysis may provide temporary support while awaiting transportation to a liver transplant center or actual liver transplant.[4]

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REFERENCES

1. **Hanouneh MA, Garber A, Tavill AS, Zein NN, Hanouneh IA**. A tale of two sisters with liver disease. Cleve Clin J Med 2016; 83:109–115.
2. **Nguyen TC, Cruz MA, Carcillo JA**. Thrombocytopenia-associated multiple organ failure and acute kidney injury. Crit Care Clin 2015; 31:661–674.
3. **Frommer D, Morris J, Sherlock S, Abrams J, Newman S**. Kayser-Fleischer-like rings in patients without Wilson's disease. Gastroenterology 1977; 72:1331–1335.
4. **Hamlyn AN, Gollan JL, Douglas AP, Sherlock S**. Fulminant Wilson's disease with haemolysis and renal failure: copper studies and assessment of dialysis regimens. Br Med J 1977; 2:660–663.

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IN REPLY: We thank Dr. Mirrakhimov and colleagues for bringing important questions to our attention.

In terms of the differential diagnosis of cholestatic liver injury, we agree that pathologic processes such choledocholithiasis, cholangitis, primary biliary cirrhosis, and primary sclerosing cholangitis should be generally considered. However, in the case we described, the patient had no abdominal pain or fever, which makes choledocholithiasis or cholangitis very unlikely. Primary biliary cirrhosis and primary sclerosing cholangitis can cause chronic liver disease but should not be considered in the differential diagnosis of acute liver injury (acute hepatitis), such as in the case we described.

We agree that the hemolytic anemia typically seen in patients with Wilson disease is Coombs-negative, and that Coombs testing and a peripheral smear should be performed. Both were negative in our patient.

We also agree with Dr. Mirrakhimov and colleagues that Kayser-Fleischer rings are not necessarily specific for Wilson disease and can be seen in patients with other

forms of cholestatic liver disease such as primary biliary cirrhosis. However, Kayser-Fleischer rings are pathognomonic for acute liver failure from Wilson disease. In other words, when Kayser-Fleischer rings are seen in a patient with acute liver failure, the diagnosis is Wilson disease until proven otherwise.

We discussed on page 112 of our article other treatments such as plasmapheresis as adjunctive therapy to bridge patients with acute liver failure secondary to Wilson disease to transplant. However, liver transplant is still the only definitive and potentially curative treatment.

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Cognitive bias and diagnostic error

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TO THE EDITOR: I appreciated the article on cognitive biases and diagnostic error by Mull et al in the November 2015 issue.[1] They presented an excellent description of the pitfalls of diagnosis as reflected in a case of a patient misdiagnosed with heart failure who ultimately died of pulmonary tuberculosis complicated by pulmonary embolism (the latter possibly from using the wrong form of heparin). To the points they raised, I would like to add a few of my own about diagnosis in general and heart failure in particular.

First, any initial diagnosis not confirmed objectively within the first 24 hours should be questioned, and other possibilities should be investigated. I have found this to be essential for every day's stay in the hospital and for every outpatient visit. The authors mention checklists as part of the solution to the problem of misdiagnosis, and I would suggest that confirmation of initial diagnoses be built into these checklists.

In the case of a presumptive diagnosis of an acute exacerbation of heart failure treated empirically with diuretics, the diagnosis should be confirmed by the next day's response to the diuretics, ie, increased urine output, a lower respiratory rate, and a fall in the pro-B-type natriuretic peptide level. Moreover, a change in the radiographic appearance should be seen, and respiratory and pulmonary function should improve after the first 24 hours on oxygen supplementation plus diuretics. Daily patient weights are also critical in determining response to a diuretic, and are rarely done accurately. I order weights and review them daily for patients like this.

Second, it is good to look at things yourself, including the patient, medication lists, laboratory values, and radiographic films. The attending physician should look at the radiographs together with a senior radiologist. Seeing no improvement or change on the second hospital day, or seeing signs incompatible with heart failure, one could order computed tomography of the chest and begin to entertain pulmonary diagnoses.

Even vital signs can be questionable. For example, in the case presented here, with a temperature of 99°F, a heart rate of 105, and a pulse oxygenation saturation of 89%, a respiratory rate of 24 seems unbelievably low. In my experience, the respiratory rate is recorded erroneously most of the time unless it is recorded electronically or checked at the bedside by the physician using a timepiece with a sweep second-hand.

Additionally, I have found that ordering several days' laboratory tests (eg, complete blood cell counts, chemistry panels) in advance, in many cases, risks missing important findings and wastes time, energy, and the patient's blood. I have learned to evaluate each

patient daily and to order the most pertinent laboratory tests. With electronic medical records, I can check laboratory results as soon as they are available.

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REFERENCES
1. **Mull N, Reilly JB, Myers JS**. An elderly woman with 'heart failure': cognitive biases and diagnostic error. Cleve Clin J Med 2015; 82:745–753.

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IN REPLY: We thank Dr. Field for his insights and personal observations related to diagnosis and biases that contribute to diagnostic errors.

Dr. Field's comment about the importance of revisiting one's initial working diagnosis is consistent with our proposed diagnostic time out. A diagnostic time out can incorporate a short checklist and aid in debiasing clinicians when findings do not fit the case presentation, such as lack of response to diuretic therapy. Being mindful of slowing down and not necessarily rushing to judgment is another important component.[1] Of note, the residents in our case did revisit their initial working diagnosis, as suggested by Dr. Field. Questions from learners have great potential to serve as debiasing instruments and should always be encouraged. Those who do not work with students can do the same by speaking with nurses or other members of the healthcare team, who offer observations that busy physicians might miss.

Our case highlights the problem that we lack objective criteria to diagnose symptomatic heart failure. While B-type natriuretic factor (BNP) has a strong negative predictive value, serial BNP measurements have not been established to be helpful in the management of heart failure.[2] Although certain findings on chest radiography have strong positive and negative likelihood associations, the role of serial chest radiographs is less clear.[3] Thus, heart failure remains a clinical diagnosis in current practice.

As Dr. Field points out, the accuracy and performance characteristics of diagnostic testing, such as the respiratory rate, need to be considered in conjunction with debiasing strategies to achieve higher diagnostic accuracy. Multiple factors can contribute to low-performing or misinterpreted diagnostic tests, and inaccurate vital signs have been shown to be similarly prone to potential error.[4]

Finally, we wholeheartedly agree with Dr. Field's comment on unnecessary testing. High-value care is appropriate care. Using Bayesian reasoning to guide testing, monitoring the treatment course appropriately, and eliminating waste is highly likely to improve both value and diagnostic accuracy. Automated, ritual ordering of daily tests can indicate that thinking has been shut off, leaving clinicians susceptible to premature closure of the diagnostic process as well as the potential for "incidentalomas" to distract them from the right diagnosis, all the while leading to low-value care such as wasteful spending, patient dissatisfaction, and hospital-acquired anemia.[5] We believe that deciding on a daily basis what the next day's tests will be can be another powerful debiasing habit, one with benefits beyond diagnosis.

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REFERENCES
1. **Schiff GD**. Minimizing diagnostic error: the importance of follow-up and feedback. Am J Med 2008; 121(suppl):S38–S42.
2. **Yancy CW, Jessup M, Bozkurt B, et al**. 2013 ACCF/AHA guideline for the management of heart failure. Circulation 2013; 128:e240–e327.
3. **Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT**. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA 2005; 294:1944–1956.
4. **Philip KE, Pack E, Cambiano V, Rollmann H, Weil S, O'Beirne J**. The accuracy of respiratory rate assessment by doctors in a London teaching hospital: a cross-sectional study. J Clin Monit Comput 2015; 29:455–460.
5. **Koch CG, Li L, Sun Z, et al**. Hospital-acquired anemia: prevalence, outcomes, and healthcare implications. J Hosp Med 2013; 8:506–512.

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