BENDING THE VALUE CURVE

Is That Normal? A Case of Diagnostic Error Due to Misinterpretation of Laboratory Findings

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CASE PRESENTATION

A 2-month-old boy born at 37-weeks' gestational age with no chronic medical conditions presented to the emergency department with jaundice and poor weight gain. The patient was born appropriate for gestational age, weighing 3.83 kg, and developed mild jaundice several days after birth but did not require any phototherapy. He was exclusively breastfed. He had additionally been having several episodes per day of small-volume nonbloody, nonbilious emesis daily since he was 1 week old. He had daily stools that were yellow and soft. At 5 weeks of life, the patient became jaundiced, at which time his pediatrician ordered laboratories that were notable for elevated alanine transaminase (ALT) of 59 U/L and aspartate transaminase (AST) of 158 U/L, total bilirubin of 10.4 mg/dL, direct bilirubin of 0.35 mg/dL, hemoglobin of 9.6 g/dL, reticulocyte count of 1.7%, and normal thyroid study results. In response to the laboratory abnormalities, the pediatrician referred him to an adult gastroenterologist for additional evaluation. During the appointment, at 7 weeks old, he weighed 4.58 kg (15 g/day of weight gain since birth). The gastroenterologist obtained a right upper quadrant ultrasound, which was normal, and laboratory values notable for negative hepatitis serology results, stable AST and ALT, and bilirubin with a normal gamma-glutamyl transferase, creatine kinase, and electrolytes. An α-fetoprotein (AFP) level was 3870 ng/mL (laboratory reference range of 0.6–28.3 ng/mL).

Because of concern for malignancy based on the elevated AFP, outpatient oncology was consulted, and the patient was referred for a computed tomography (CT) scan of the chest, abdomen, and pelvis, which was unremarkable. In the week after his CT scan, the patient was noted to have difficulty waking for feeds overnight and was increasingly fussy, prompting presentation to the emergency department.

At the time of his presentation, the patient weighed 4.75 kg (fourth percentile) with mild scleral icterus but no jaundice and an otherwise unremarkable examination. Repeat laboratories were largely unchanged from previous studies, with an AFP of 2990 ng/mL. The patient was admitted to the general pediatric service for management and evaluation of malnutrition with elevated AFP.

After admission, a strict feeding regimen of expressed breast milk and formula with a volume minimum to achieve 108 kcal/kg per day was initiated. Gastrointestinal (GI) and metabolism teams were consulted and recommended cytomegalovirus, plasma amino acids, urine organic acids, urine-reducing substances, and a cholestasis panel, all results of which returned normal. After further literature review by the pediatric hospital medicine team, the AFP

www.hospitalpediatrics.org
DOI:https://doi.org/10.1542/hpeds.2020-005520

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Dr Herchline drafted the initial manuscript; Drs Rasooly and Bonafide reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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was determined to be normal for the patient's age. The patient fed appropriately during the remainder of his 5-day admission and achieved an average weight gain of 57 g/day. The patient's malnutrition was attributed to inadequate intake. His AST, ALT, and bilirubin values trended downward, although they were still mildly elevated at the time of discharge. Repeat AFP on the day of discharge was 2940 ng/mL. After discussion with all consultants, the patient's abnormalities of bilirubin, ALT, and AST were attributed to malnutrition due to inadequate intake.

After discharge, the patient was managed closely by the GI and metabolism teams, during which time he demonstrated appropriate weight gain and development. His AFP was 30.8 ng/mL at 11 months of age, at which point the GI team concluded follow-up.

INFANT MALNUTRITION AND THE LIVER

Infant malnutrition is a common pediatric indication for hospital admission.[1,2] Although the majority of cases stem from inadequate caloric intake resulting from biological or environmental factors that inhibit appropriate intake, a small proportion of patients have underlying life-threatening systemic disease.[3] Despite a broad differential of potential causes, the etiology of most cases of infant malnutrition can be diagnosed via history and physical examination, including observation of feeding.[4] Laboratory evaluation has historically yielded poor results in identifying organic etiologies of infant malnutrition, although the true incidence of organic causes of infant malnutrition is still unknown.[5,6]

Our patient demonstrated jaundice and insufficient weight gain. His extensive diagnostic evaluation for jaundice did not include addressing his nutritional status. After initiation of an adequate feeding regimen, our patient demonstrated sustained weight gain as well as normalization of laboratory markers, including AST, ALT, and bilirubin. Given the known relationship between protein deficiency and hepatic dysfunction, we suggest that the improvement in laboratory markers was possibly because of optimization of nutrition because no other interventions were employed during the course of the patient's hospitalization.[7,8] This case highlights the need for the development of best practices for the evaluation and management of children presenting with acute malnutrition.

WHAT ABOUT THE AFP?

AFP is a protein synthesized in the yolk sac and liver of the fetus beginning at ~6 weeks' gestational age. It represents an important tumor marker in several oncologic processes and may also be elevated in other disease processes, including infantile hemangiomas and Beckwith-Wiedemann syndrome.[9–11] However, in several studies, researchers indicate that serum AFP levels fall rapidly in infancy, beginning at an average of ~50 000 ng/mL at term birth (with a wide normal range encompassing values exceeding 100 000 ng/mL) to <10 000 ng/mL by 1 month of age, <1000 ng/mL by 3 months, <100 ng/mL by 6 months, and normal adult levels by 9 months.[12–15] Additionally, AFP levels are often higher in premature and low birth weight infants.[16] Although our patient's AFP level was greater than the reference range for our laboratory (0.6–28.3 ng/mL), it was not abnormal when put in the context of reported median levels and half-life for infants. Given this wide range of normal values in infants, use of AFP as a diagnostic tool has the potential to mislead clinicians and may ultimately result in a cascade effect.[17] In our patient, misinterpretation of the AFP level led to urgent consultation with subspecialists as well as additional laboratories and imaging with radiation exposure. Providers, including experts, can be susceptible to overconsultation and casting a broader net than appropriate, particularly in cases for which there is diagnostic uncertainty. Furthermore, the patient's family likely experienced increased anxiety when an oncologic etiology of the patient's AFP level was discussed. Multiple providers, including those on the admitting team, failed to question the reference range provided for AFP and assumed the patient's level was pathologic. Only several days into the admission did the team identify the misinterpretation after performing a literature review on normal AFP values by age.

EVALUATING THE ETIOLOGY OF DIAGNOSTIC ERROR

Diagnostic error, the failure to establish or communicate an accurate, timely explanation of a patient's symptom, is an important domain of patient safety and quality improvement.[18] In this case, the patient underwent significant diagnostic evaluation because of misinterpreted laboratory values and experienced a delay in explaining and addressing his nutritional status. Additionally, the psychological harm imposed on new parents who were erroneously told their infant required urgent oncologic evaluation should not be understated. Applying the Modified Diagnostic Error and Evaluation Research taxonomy, a tool that maps errors to aspects of the diagnostic process, to this case highlights the opportunities for improvement in the stages of "Testing" and "Hypothesis Generation"[19] (Supplemental Table 1). Specifically, within the domain of testing, results were misinterpreted, and incorrect tests were ordered (domains 4D and 4I). With regard to hypothesis generation, there was delay in considering the correct diagnosis, suboptimal weighing and prioritization of differential diagnoses, and too much weight given to a lower-probability diagnosis (5A–C).

In considering systems opportunities for improvement in testing, misinterpretation of the AFP contributed to both the unnecessary CT imaging and delay in identification and management of the patient's inadequate intake. In general, pediatric laboratory data must be interpreted in light of age-based norms.[20,21] Neonatal thyroid stimulating hormone and plasma creatinine are familiar examples in which values vary greatly on the basis of age with markedly elevated levels seen in neonates.[22,23] It is not feasible for clinicians to know the specific age-based reference range for every laboratory study, particularly uncommon ones. Potential opportunities for improvement include changes to the way uncertain or variable reference ranges are

flagged in laboratory reporting systems and implementation of electronic health record decision support to facilitate accurate and timely interpretation of tests that are ordered infrequently or whose reference ranges may vary on the basis of age. Although providers should remain vigilant about age-specific normal values for infrequently ordered laboratories, harnessing the electronic health record to include age-specific normal values for infrequently ordered laboratories represents a way to mitigate diagnostic errors across practice settings. Implementing this type of change would benefit both providers in community and academic settings. Additionally, it will be imperative to leverage existing and future data to continue to develop more nuanced reference ranges for laboratory tests that vary on the basis of age.[24]

This case reveals opportunities to improve processes associated with hypothesis generation, a crucial element of the diagnostic process and one subject to cognitive bias, including diagnostic momentum, base-rate neglect, and anchoring, which was evident in this particular case.[25] Infant malnutrition due to inadequate intake and resulting in slight aberrations of metabolic laboratory values is far more common than intrinsic liver pathology or oncologic processes. Formalizing and standardizing opportunities for clinicians to articulate and reflect on their reasoning may be one way to overcome cognitive bias.[26] Fostering communication norms in which clinicians explicitly discuss with patients and colleagues what they know, what they are uncertain about, and what they expect to learn from diagnostic evaluation is another important step in promoting diagnostic excellence.

LESSONS LEARNED

In this case, we discuss system and clinician opportunities to improve diagnosis. We also provide clinical pearls on the relationship between infant malnutrition and liver dysfunction as well as the clinical utility of AFP. The family in our case experienced increased costs, increased harms, and incalculable stress during the patient's illness course. This example reminds us that to provide optimal patient care, clinicians and systems must be improved to promote accurate, timely interpretation of all laboratory and imaging studies.

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