CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

The Overuse of Serum Ceruloplasmin Measurement

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ABSTRACT

BACKGROUND: Wilson disease is rare, found in 3 of 100,000 people (0.03%). Ceruloplasmin is often ordered to evaluate liver enzyme elevations. Because Wilson disease often presents before middle-age, the American Association for the Study of Liver Disease recommends screening patients between the ages of 3 and 55 years with liver abnormalities of uncertain cause. We evaluate guideline adherence and the clinical and economic impact of current clinical use of ceruloplasmin.

METHODS: We reviewed all ceruloplasmin measurements at a clinical laboratory that serves a large primary care network, specialty clinics, and a 600-bed tertiary referral center between January 1, 2003, and December 12, 2011.

RESULTS: Ceruloplasmin was measured 5325 times in 5023 unique patients, resulting in 8 (0.16%) new Wilson disease diagnoses. Ceruloplasmin's positive predictive value was 8.4% (95% confidence interval, 7.7-9.3) and false-positive rate was 98.1% (95% confidence interval, 96.2-99.1). A total of 1109 ceruloplasmin levels (20.8%) were ordered in the 1066 patients aged more than 55 years (none with Wilson disease). A "shotgun" approach to liver disease diagnosis was found: Ceruloplasmin was ordered on the same day as hepatitis B (81.0%), hepatitis C (76.0%), autoimmune hepatitis (75.1%), and hemochromatosis (73.1%). Of 424 positive ceruloplasmin results, 91% were not pursued further.

CONCLUSIONS: Guideline adherence restricts ceruloplasmin use to a population with a higher pre-test probability of Wilson disease: patients with chronic liver disease aged 3 to 55 years who have been tested for common causes of liver disease. The majority of the serum ceruloplasmin was measured in patients not indicated by the guidelines, resulting in poor test performance and wasted healthcare resources. Our data on ceruloplasmin use could serve as a touchstone for broader discussions on rational clinical decision making.
 • The American Journal of Medicine (2013) 126, 926.e1-926.e5

KEYWORDS: Guidelines; Hepatitis; Liver disease; Wilson disease

Wilson disease is a rare autosomal recessive defect of hepatocellular copper disposition prevalent in approximately 3 of 100,000 people (0.03%) that leads to chronic copper accumulation in the liver, brain, and other tissues. Sequelae are varied and include hemolysis, neurodegeneration, and hepatotoxicity.[1-3] The majority of patients with Wilson disease present long before middle age. Patients with Wilson disease with primarily hepatic manifestations present at age 15.5 ± 9.6 years, somewhat younger than those with predominantly neurologic symptoms (20.2 ± 10.8 years).[4] Late-onset Wilson disease—patients who present after the age of 40 years—is exceedingly rare and remains the domain of case reports.[5-14] Although Wilson disease may be rare, liver enzyme elevation is common (7.9% prevalence) and its evaluation often includes testing for Wilson disease.[15] The American Association for the Study of Liver Disease (AASLD) recommends screening for Wilson disease in any individual aged between 3 and 55 years with liver abnormalities of uncertain cause, especially those with comorbid unexplained liver disease and neurologic or neuropsychiatric disorders.[16]

The first step in screening for potential Wilson disease is often serum ceruloplasmin measurement, where a level of ≤20 mg/dL is suggestive of the disease. However, low ceruloplasmin is not specific for Wilson disease; it also can result from malabsorption, malnutrition, and cachexia and therefore requires confirmatory tests.[16,17] Cauza et al[3]

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2013.01.039

looked at the utility of routine ceruloplasmin evaluation for all patients referred for evaluation for liver disease. They found a 5.9% positive predictive value in a population in whom 0.03% (1/2867) had Wilson disease. This low positive predictive value is largely due to the low pre-test probability of the diagnosis. Thus, routine screening of all patients with abnormal liver enzymes for Wilson disease is of limited utility. Certain clinical scenarios naturally increase the likelihood of Wilson disease, for example, the patient with an ultralow alkaline phosphatase coincident with fulminant liver failure or hemolytic anemia.[18] Generally, however, to increase the value of ceruloplasmin testing as a screening test, it should be used in a more selected population, such as the one proposed by AASLD guidelines. On the basis of anecdotal observations, we hypothesized that the actual use of serum ceruloplasmin did not adhere closely to the AASLD guidelines. Herein, we evaluate actual adherence to the AASLD guidelines for screening for Wilson disease and the clinical and economic impact of current clinical practice.

CLINICAL SIGNIFICANCE

- Frequently, ceruloplasmin is measured in patients aged more than 55 years, a population with a low pre-test probability of Wilson disease.
- Usually, ceruloplasmin is tested at the same time as common causes of liver disease—the "shotgun" approach to liver disease.
- Following Wilson disease guidelines from the American Association for the Study of Liver Disease would limit the use of ceruloplasmin and improve its clinical impact.

PATIENTS AND METHODS

We conducted a retrospective review of patient records of serum ceruloplasmin sent to the Beth Israel Deaconess Medical Center clinical laboratory between January 1, 2003, and December 12, 2011. The clinical laboratory of the Beth Israel Deaconess Medical Center serves outpatient clinics, including a large primary care network, specialty clinics (eg, hepatology, neurology), and a 600-bed tertiary referral center in the greater Boston area and eastern Massachusetts. Given that the laboratory serves a large network of primary care centers and their specialty referral clinics, laboratory follow-up can be considered complete. The time period was chosen to include the maximum data available. The study was approved by the institutional review board.

For each ceruloplasmin order, we recorded the age and sex of the patient at the time of the order, together with the value of the most recent alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, urine, and serum copper. In accordance with published external guidelines,[16] we used 20 mg/dL as the lower end of the reference interval in our study and treated values $\leq$20 mg/dL as potentially positive for Wilson disease. We excluded any patients who already carried a diagnosis of Wilson disease at the time of ceruloplasmin testing.

A diagnosis of Wilson disease was determined on the basis of the results of confirmatory testing (urine and hepatic copper, ophthalmologic examinations) and medical record documentation. We thoroughly reviewed the charts of all patients who had any of the following:

- a positive ceruloplasmin,
- urine copper measurement performed,
- serum copper measurement performed, and
- hepatic copper measurement performed.

Chart review was performed looking for mention of a clinical diagnosis of Wilson disease, based on firm evidence confirmatory tests. Also according to guidelines, positive urine copper was considered >40 μg/L in a 24-hour collection and a positive hepatic copper was considered >50 μg/g dry weight in a liver biopsy.[16] Accordingly, a false-positive ceruloplasmin was defined as a level of $\leq$20 mg/dL with a negative urine copper or hepatic copper measurement. (Note we use "false positive" strictly in reference to Wilson disease, not to suggest laboratory error.)

For each ceruloplasmin ordered, we assessed whether there was simultaneous testing for hepatitis B (surface antigen, surface antibody, core antibodies, viral load), hepatitis C (antibody or viral load), autoimmune hepatitis (anti-nuclear antibody, anti-smooth muscle antibody, immunoglobulin G), hemochromatosis (iron binding capacity, mutation screen), alpha-1 antitrypsin deficiency (alpha-1 antitrypsin levels and phenotype), cytomegalovirus (immunoglobulin assays and viral load), and Epstein−Barr virus (immunoglobulin assay). Hepatitis B infection was defined as positive surface antigen, viral load, or isolated core immunoglobulin-M. Hepatitis C infection was defined as a positive antibody or viral load.

All data were kept on a firewall-secured server or password-protected Microsoft Excel file (Microsoft Corp, Redmond, Wash). Data were extracted from Beth Israel Deaconess Medical Center data warehouses using Python 2.7.3 (Enthought Python distribution 7.3-1) and analyzed using Python and JMP SAS 8 (SAS Institute Inc, Cary, NC). Descriptive statistics included mean and standard deviation for normal distributions and for median and range for non-normal distributions (eg, distributions in which the standard deviation exceeded the mean). Means were compared using the Student *t* test. Medians were compared using Wilcoxon rank-sums. Proportions were compared using the Fisher exact method. Post-test probabilities were determined using Bayes' theorem.