Population screening for Wilson's disease

Wilson's disease, an autosomal recessive disorder, is present in nearly all populations at a prevalence of 1:30,000

persons. Many patients have liver disease, neurologic or psychiatric symptoms, or die because the disease may be recognized only after symptomatic disease develops. Herein lies the imperative for developing an accurate and

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cost-effective test that will permit general screening for this disease.

Historically, Wilson's disease was first recognized by the appearance of

characteristic neurologic symptoms and cirrhosis, and later by the identification of corneal Kayser-Fleischer rings. With the discovery that ceruloplasmin levels were reduced in 95% of patients with Wilson's disease,[1] it became possible to recognize these patients before irreversible disease or death occurred. However, it soon became apparent that this test alone was insufficient to diagnose this disorder because ~20% of heterozygote carriers

for Wilson's disease also have a reduced level of ceruloplasmin.[2] Therefore, the vast majority (~40:1) of asymptomatic patients with a low ceruloplasmin level are heterozygotes and not patients. Other patients with severe hepatic disease or protein-losing states have also been identified with low levels of ceruloplasmin. Rarely, persons that lack ceruloplasmin entirely (aceruloplasminemic) manifest a disorder of iron overload and not copper accumulation.

Among patients with liver disease in which Wilson's disease was considered in the differential diagnosis, screening for reduced serum ceruloplasmin by immunologic methods was found to have a predictive value of only 5.9%.[3] This study of 2876 patients with liver disease identified 17 persons with a low ceruloplasmin level, and 16 of these 17 did not have Wilson's disease, which was confirmed by further testing. This low predictive value of just 5.9% suggested that serum screening by immunologic ceruloplasmin was not effective.

Suzuki et al[4] suggested that the concentration of holoceruloplasmin in the urine of patients with Wilson's disease was lower than in healthy control patients. In the study[5] in this issue of The Journal, urine samples obtained from 41 patients with Wilson's disease and 196 healthy controls were examined for the presence of holoceruloplasmin protein by immunologic methods. In their patients with Wilson's disease, mean levels of urinary holoceruloplasmin were 8.2 + 9.1 ng/mg creatinine (range, 0.1-43.5 ng/mg), with 2 patients noted to be in the high range. Presuming concordance of serum and urinary ceruloplasmin, the detection of 2 patients with relatively elevated urinary holoceruloplasmin is the amount expected because 5% of patients have normal levels of serum ceruloplasmin. The mean holoceruloplasmin values for different age controls was variable (99.3-143.4 ng/mg creatinine). They then screened 48,819 children using this same method and identified 423 patients with values below the third percentile (mean, ~8-9

ng/mg creatinine). When a second sample from these same patients with lower values of holoceruloplasmin was analyzed, only 41 had values below the third percentile. They continued to investigate this group and found only two with low urinary and serum holoceruloplasmin and low serum copper and high urinary copper concentrations. These persons were subsequently proved to have Wilson's disease by evidence of 2 distinct disease specific mutations in each patient (compound heterozygotes).

On the surface, the authors' identification of 2 patients from those screened seems to correspond with the number of patients expected to be found among this number of patients tested. However, more careful consideration of what was not presented in this study suggests that there are significant limits to the overall utility of their methods. In general, the design of a screening test requires careful consideration of the accuracy of the tests in predicting the presence or absence of disease. Unfortunately, we learn little from the current study in this regard, and what we do learn is not supportive. Neither the accuracy of their testing nor its true predictive value are given or can be calculated from the data provided. Specifically, we do not know the precision and accuracy of determinations for a given patient. If as presented, only ~10% of those identified with low urine holoceruloplasmin were found to have similarly low values on repeat testing, the precision and accuracy of individual measurements are questionable. Furthermore, the lack of data on the phenotype of the remaining patients that did not undergo secondary testing for Wilson's disease makes it impossible to determine the sensitivity or specificity of their testing. These analyses in particular help determine the cutoff values of a test used to obtain a useful predictive value for a given test. We must also assume that the presence of two patients with a higher level of urinary ceruloplasmin, overlapping with levels found

in normal control patients, among their group of patients with Wilson's disease, suggests the inability to identify that minority of patients with normal levels of urinary holoceruloplasmin and presumably normal serum ceruloplasmin.

We do learn from the data shown in this study that there was some increase in the urinary copper excretion in those 2 patients (cases A and B) that had Wilson's disease, raising the question as to whether this test alone would have been equally efficacious as a screening test. Although the results are given in ng/mg creatinine and not absolute values for the copper excretion, it is clear that at least one of these patients had a value for basal urinary copper excretion that did not differ in statistical significance from the normal range. These data are consistent with our own experience and another report of patients with hepatic presentation of Wilson's disease,[7] where basal urinary copper excretion has been found to be below the typical cutoff value of 100 μg/24 hours found in most neurologically symptomatic patients with Wilson's disease. The use of a penicillamine challenge to increase the specificity of urinary copper excretion in the diagnosis of Wilson's disease in pediatric patients has previously been proposed for patients with liver disease.[6] In this study by Owada et al,[5] after a penicillamine challenge of 800 mg/day, urinary copper excretion increased in both cases A and B; however, the excretion in case A did not reach levels of >1600 μg per 24 hours reported in patients with Wilson's disease.[6] The interpretation of this value must be tempered by the fact that the authors report the use of 800 mg of the drug and give no further information as to how it was administered during the 24-hour urine collection. This is important because the amount of copper excretion is dose-dependent. The lack of standardization of this test among different studies hinders the direct comparison of reported data.

Despite the limitations mentioned, the identification of patients with

Wilson's disease before the development of disease is a laudable goal. The 2 patients identified in this study would have likely gone undetected for years before becoming symptomatic. Other genetic diseases are routinely screened for in neonates and during infancy, some with lower prevalence rates compared with Wilson's disease; however, the testing for most of these disorders is not as complex as Wilson's disease where no single clinical or lab finding establishes the diagnosis.[2,7] Cost-benefit analysis and the predictive value of the available testing often helps to decide whether to screen for a particular disease. However, it is difficult to factor in costs of lifelong treatment and follow-up if the diagnosis is positive, and, importantly, the negative cost and the effect of false-positive screens on nonaffected patients.[8] The possibility that specific populations with signs of liver disease may have a higher prevalence of Wilson's disease (in reference 3, the frequency was 5.5/1000 vs 1/30,000 in the general population) has to be considered. Screening of these patients and others with neuropsychiatric symptoms with serum ceruloplasmin, liver biochemistry and coagulation profile, ophthalmologic examinations, urinary copper excretion, and when appropriate, liver biopsy and copper quantitation, should vastly increase the cost-effectiveness of testing for this disorder. The use of a combination of tests will help reduce false-positive results. Testing for Wilson's disease by molecular genetic analysis is currently impractical for general screening purposes in most ethnically diverse populations given the numerous disease specific mutations already identified and the high frequency of compound heterozygosity among patients. The development of better methods for molecular genetic screening is likely to provide the solution for population screening and the de novo diagnosis of Wilson's disease in suspected patients. For now, in light of current limitations of genetic testing for this disorder, the gold standard for establishing a diagnosis of Wilson's disease remains the combination of a low serum ceruloplasmin and the presence of corneal Kayser-Fleischer rings or elevated hepatic copper, and appropriate histologic features on liver biopsy specimens. Because Kayser-Fleischer rings are often absent in many pediatric patients, a liver biopsy with histologic evaluation and copper quantitation is frequently necessary. However, routine use of a liver biopsy as follow-up for a single nonspecific screening test is not recommended, and the tests described previously must still be performed. In conclusion, screening for Wilson's disease by determination of immunologic ceruloplasmin, whether from serum or urine, does not have an adequate predictive value to recommend its use for general population screening.

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