copper content was significantly higher in WD children than in the control group (Table 1).

We assessed the receiver operating characteristic curve to evaluate the diagnostic values of liver copper content. The area under the receiver operating characteristic curve was 0.919 (95% confidence interval 0.847-0.990). According to the cutoff levels used in the scoring system for WD diagnosis,[2] liver content >50 and >250 μg/g dry weight had sensitivity and specificity of 92.9% and 72.3%, 64.3% and 98.4%, respectively. The most useful single cutoff value in our study was 120 μg/g dry weight, with sensitivity and specificity of 82.1% and 91.0%, respectively. Liver concentration was <250 μg/g dry weight in eight WD children. Two of eight WD children had liver copper content <50 μg/g dry weight. Both children, aged 12 years and 4.5 years, were investigated for liver copper content because of positive family history. Livers weighing 3.19 and 1.4 g were used to measure the liver concentration, with 7 and 38 μg/g dry weight as a result, respectively.

Our data show that estimation of liver copper was reliable in children with WD even when the liver biopsy sample size was <1 mg. Our method is much simpler and could avoid having to do more than one liver biopsy pass, thus making it arguably safer.

Palittiya Sintusek, M.D., M.Sc.[1,2]
Anil Dhawan, M.B.B.S., M.D., F.R.C.P.C.H.[1]
[1]Paediatric Liver, GI and Nutrition Centre
King's College Hospital
London, United Kingdom
[2]Division of Paediatric GI and Hepatology
Faculty of Medicine
King Chulalongkorn Memorial Hospital
Chulalongkorn University
Bangkok, Thailand

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REPLY:

We sincerely appreciate the comments and questions raised by Sintusek and Dhawan regarding our article.[1] Based on our findings, we recommended that an entire core of liver biopsy sample with more than 1 mg dry weight should be used for hepatic copper determination. However, the coefficient of variation (CV) of the hepatic copper measurement was not significantly different between subgroups classified by dry weight of the liver, although there was a trend. Sintusek and Dhawan questioned the rationality of our recommendation and present data showing that estimation of liver copper is reliable in children with Wilson's disease (WD) even when the liver biopsy sample size is less than 1 mg.

The copper concentration in the liver of a normal human newborn contains roughly 6-8 times that of an adult, and this concentration falls to the adult value, approximately 30 μg/g of dry tissue, within 6 months and varies little throughout life.[2] However, the amount of liver copper in WD patients after birth does not fall to the normal range, but gradually increases because of the WD gene mutation. Therefore, if the liver copper concentration in an untreated WD patient is not elevated, the most likely cause is laboratory error, including sampling error and/or measurement error.

It is well accepted that the distribution of copper in the liver is inhomogeneous and that the accuracy of liver copper measurement is improved with an adequately sized specimen.[3] The tissue obtained with biopsy needle is only 1.0∼3.5 mg dry weight. In clinical practice, liver copper content is usually determined with a part of a needle biopsy specimen. This practice may occasionally result in a false result. Indeed, nondiagnostic hepatic copper levels in patients with confirmed WD have been reported by many investigators in the past two to three decades. Among 28 patients with genetically confirmed WD, as reported by Sintusek and Dhawan, liver copper concentration was below 250 μg/g dry weight in 8 patients. These data demonstrate that estimation of liver copper is not reliable using their method.

In our study, we observed a trend where larger liver biopsy specimens resulted in smaller CV of the copper measurement. Although the *P* value was not less than that required for statistical significance, we believe that the size of the liver biopsy specimen has important influence on the precise determination of the copper content, based on "Do not reject null

hypothesis" rather than "Accept null hypothesis." More important, the sensitivity of hepatic copper level for the diagnosis of WD at the conventional cut-off value of 250 μg/g dry weight was as high as 94.4% with our method. Although not a head-to-head comparison, the sensitivity of our method was higher than that reported by Ferenci et al., which determined sensitivity using part of a needle biopsy specimen (83.3%).[4]

Xu Yang, M.D.[1]
Xiao-peng Tang, M.D.[1]
Yong-hong Zhang, M.D.[1]
Kai-zhong Luo, M.D.[1]
Yong-fang Jiang, M.D.[1]
Hong-yu Luo, M.D.[1]
Jian-hua Lei, M.D.[1]
Wen-long Wang, M.D.[1]
Ming-ming Li, M.D.[1]
Han-chun Chen, Ph.D.[2]
Shi-lin Deng, B.A.[3]
Li-ying Lai, M.D.[1]
Jun Liang, M.D.[1]
Min Zhang, M.D.[1]
Yi Tian, M.D.[1]
Yun Xu, M.D.[1]
[1]Liver Disease Research Center
the Second Xiangya Hospital
Central South University
Changsha, China
[2]Department of Biochemistry
School of Life Sciences
Central South University
Changsha, China
[3]Research Laboratory of Spectral and Chemical Analysis Center of Modern Analysis and Testing
Central South University
Changsha, China

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High von Willebrand Factor Antigen Levels and Procoagulant Imbalance May Be Involved in Both Increasing Severity of Cirrhosis and Portal Vein Thrombosis

TO THE EDITOR:

We read with interest the article by Nery et al.[1] on the causes and consequences of portal vein thrombosis (PVT) in patients with cirrhosis. The authors demonstrated that advanced cirrhosis is associated with a higher risk of developing PVT but is not causatively related to PVT. Their results are consistent with those of Villa et al.[2], who concluded that the progression of cirrhosis and PVT are two separate sequelae of coagulation system activation, considering that both can be prevented by anticoagulant treatment. Consequently, we investigated whether certain hemostatic factors are independently related to both increasing severity of cirrhosis and subsequent development of PVT.

A total of 102 patients with cirrhosis (men, n = 81; women, n = 21; mean age, 56.6 ± 7 years; alcoholic/viral/other etiology, n = 71/18/13; Child-Pugh score, 9 ± 3; Model for End Stage Liver Disease [MELD] score, 12 ± 6) distributed equally for each Child-Pugh class (A/B/C, n = 34/34/34) were followed up for a mean period of 27.2 months (range, 6-53 months).