Changes in Liver Stiffness and Noninvasive Fibrosis Scores in Egyptian Adolescents Successfully Treated with Ledipasvir-Sofosbuvir for Chronic Hepatitis C Virus Infection

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Objective To assess changes in noninvasive liver fibrosis measurements after chronic hepatitis C eradication by direct-acting antivirals in Egyptian adolescents.

Study design Liver stiffness measurement (LSM), by vibration-controlled transient elastography and noninvasive fibrosis scores (Firbosis-4, aspartate aminotransferase-platelet ratio index), was obtained before and 12 months after eradication with ledipasvir-sofosbuvir. The primary outcome was a more than 30% decrease in LSM with resulting fibrosis stage regression for initial fibrosis of F2 or higher and nonprogression of F0-F1, using the Ishak score (F0-F6). The secondary outcome was change in noninvasive fibrosis scores after treatment.

Results Analyzing 85 patients, the median baseline LSM was 5.8 (IQR, 4.2-6.5) and at follow-up 5.1 kPa (IQR, 4-6 kPa) (P = .045); 62 (73%) met the primary outcome, 16 patients (19%) experienced regression, and 46 (54%) nonprogression of LSM. Of 18 with initial fibrosis of F2 0r higher, 13 regressed to F0-F1 and 2 from F6 to F5, 1 unchanged at F3, and 1 increased to F3 and 1 to F4. Among 67 patients with a baseline fibrosis of F0-F1, 62 were unchanged and 5 increased—4 to F2 and 1 to F3. Although 23 (27%) had a more than 30% LSM increase, only 7 (8%), with associated comorbidities (4 β-thalassemia, 3 hepatic steatosis), had increased fibrosis stage. The median baseline FIB-4 and aspartate aminotransferase-platelet ratio index scores were 0.34 (IQR, 0.22-0.47) and 0.35 (0.24-0.57), and at follow-up 0.3 (IQR, 0.22-0.34) and 0.2 (0.18-2.8) (P < .001, <.001), respectively.

Conclusions Chronic hepatitis C eradication by direct-acting antiviral agents in Egyptian adolescents was associated with nonprogression or regression of liver fibrosis, by noninvasive fibrosis measurements, at 12 months after treatment in the majority of cases. *(J Pediatr 2021;231:110-6)*.

Chronic hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease worldwide, with high endemicity in Egypt. According to the Egyptian Ministry of Health and Population Survey between 2008 and 2015, children aged from 1 to 14 years had HCV antibody and HCV RNA in 0.4% and 0.2%, respectively, and adolescents aged 15 to 19 years showed an increase to 1.0% and 0.8%, respectively.[1] The primary HCV genotype in Egypt is 4.

Before April 2017, the standard treatment was pegylated interferon and ribavirin (IFN/RBV) for 24 or 48 weeks with a reported sustained virologic response (SVR) rate of 52% in HCV genotype-4, but this regimen was associated with severe and frequent side effects.[2-4] The US Food and Drug Administration and the European Medicines Agency have approved ledipasvir-sofosbuvir (LED/SOF) fixed-dose combination for chronic HCV genotypes 1 and 4, in patients aged 12 years or older or weighing 77 pounds or more (≥35 kg).[5,6]

Liver fibrosis is the most important prognostic factor in chronic HCV infection.[7] As an alternative to liver biopsy, which has several limitations as sampling error, poor interobserver and intraobserver agreement, and procedural risk of pain and hemorrhage, vibration-controlled transient elastography (VCTE), a US Food and Drug Administration–approved ultrasound-based technique, has become a mainstay of noninvasive liver stiffness measurement (LSM) with accurate, good interobserver

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APRI	Aspartate aminotransferase-platelet ratio index
DAA	Direct-acting antiviral
FIB-4	Fibrosis-4
HCV	Hepatitis C virus
IFN/RBV	Interferon and ribavirin
LSM	Liver stiffness measurement
SVR	Sustained virologic response
LED/SOF	Ledipasvir-sofosbuvir
VCTE	Vibration-controlled transient elastography

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and intraobserver agreement.[8-10] Thus, it is considered a helpful tool for assessment of patients after SVR achievement.[11]

In addition to liver biopsy and VCTE, noninvasive fibrosis scores calculated from serum biomarkers have been developed. The Fibrosis-4 (FIB-4) and aspartate aminotransferase (AST)-platelet ratio index (APRI) scores have been validated for chronic HCV in adults and have acceptable sensitivity and specificity, particularly in advanced fibrosis and cirrhosis.[12]

Studies in adults have shown improvement in liver stiffness 1 year after treatment with direct-acting antiviral (DAA) agents.[11,13,14] We conducted this study to investigate the changes in LSM and noninvasive fibrosis scores among Egyptian adolescents with genotype-4 chronic HCV infection 12 months after successful viral eradication with LED/SOF.

Methods

This single-center, prospective observational cohort study was conducted at the Gastroenterology, Hepatology and Nutrition Division of Mansoura University Children's Hospital in Mansoura, Egypt.

Study Population

Patients were recruited from April 1, 2018, to March 30, 2019, through the governmental mass HCV screening and treatment program. This program was developed as part of the World Health Organization initiative to eliminate viral hepatitis by 2030. The study included adolescents with chronic HCV, aged from 12 to 18 years or weighing 35 kg or more, IFN naive and experienced, who were treated with LED/SOF and achieved SVR 12. Patients were excluded if they had concomitant hepatitis B infection, HIV infection, schistosomiasis infection, other causes of hepatitis, decompensated cirrhosis, liver transplantation, and difficult or contraindicated VCTE evaluations (body mass index >95th percentile for age and sex), or an implanted medical device.

Study Protocol

All patients were assessed clinically with recording of laboratory investigations and LSM by VCTE at baseline and 12 months after completion of treatment. Clinical data included age, sex, HCV diagnosis, treatment experience, and associated comorbidities. Laboratory investigations included alanine aminotransferase (ALT), AST, albumin, total and direct bilirubin, alkaline phosphatase, international normalized ratio, and creatinine. HCV RNA was measured by quantitative real-time polymerase chain reaction (PCR) on Rotorgene Real time PCR System via kits supplied by Qiagen GmbH (Hoffmann-La Roche AG), which has a lower limit of detection of 15 IU/mL. Assessment of liver fibrosis indices included LSM by VCTE using a FibroScan device (Echosens) by a single trained operator, unaware of patient's data or biomarkers results. Patients fasted for at least 3 hours before VCTE as recommended.[15] LSM was performed from the right hepatic lobe through intercostal spaces in supine position and expressed in kilopascals (kPa). Results were considered reliable if there were at least 10 valid measurements, success rate of more than 60%, and an interquartile range of less than 30% of the median LSM value.[16] The primary outcome was decrease in LSM of more than 30% relative to baseline with the resulting fibrosis stage regression for initial fibrosis of F2 or higher and nonprogression of F0-F1 disease. This threshold was chosen because the VCTE manufacturer allows fluctuations up to 30% of IQR relative to median LSM in a reliable scan, and this threshold has been used in other publications.[11,17,18] In the current study, LSM cut-off values were 4.75, 6.65, 8.25, 13.0, 18.0, and 29.5 kPa to discriminate fibrosis F1 or greater, F2 or greater, F3 or greater, F4 or greater, F5 or greater, and F6, respectively, according to the Ishak score.[19] For noninvasive fibrosis scores, the FIB-4 was calculated as age (years) × AST (U/L)/platelets (10^9/L) × (ALT [U/L]$^{1/2}$) and the APRI as (AST/[AST upper limit of normal])/platelet count (10^9/L) – 100.[20,21] The FIB-4 and APRI cut-off values of greater than 0.13, greater than 0.27, greater than 0.315, and greater than 0.68 were used for predicting mild and advanced fibrosis, respectively.[22] The secondary outcome of interest was changes in noninvasive fibrosis scores after treatment.

Treatment Regimen

Patients received a LED/SOF fixed dose combination (90 mg LED, 400 mg SOF) daily for 12 weeks. SVR 12 was defined as undetectable HCV RNA by PCR at 12 weeks after the completion of treatment.

Ethical Clearance

The study protocol was approved by the Institutional Review Board (IRB-MD/18.02.11) of Mansoura University Faculty of Medicine according to the Declaration of Helsinki. Written informed consents were obtained from the parents/guardians and assents from the adolescents.

Statistical Analyses

The Statistical Package for Social Science (SPSS) program version 21.0 (IBM Corporation) was used for data interpretation. Quantitative data were presented as mean ± SD for parametric data and median (IQR) for nonparametric data. Qualitative data were described as number and percent. Statistical significance of related quantitative data was tested by paired *t* test for parametric data, the Wilcoxon test for nonparametric data, and the Kruskal-Wallis test was used for nonparametric data between independent studied groups. Results were considered significant if the *P* value was .05 or less and highly significant if the *P* value was .001 or less.

Results

Patient Characteristics

The study started with 100 patients who met the inclusion criteria, but 15 were lost to follow-up after SVR 12 and before the second LSM. Thus, the study population included 85

patients (58 males). Ages ranged from 11 to 18 years (mean, 14.6 ± 1.9 years). Three patients were less than 12 years of age but weighed more than 35 kg.

Thirty-two patients (38%) were diagnosed by HCV surveillance owing to the presence of risk factors such as previous blood transfusion or elevated liver enzymes in oncology patients, and 53 (62%) were discovered by screening through national screening campaigns or owing to the presence of infected family members.

Sixteen patients (19%) received previous IFN/RBV treatment, but none had received prior DAA therapy. Thirty-three patients (39%) had associated comorbidities including β-thalassemia in 9 (11%), hemophilia in 4 (5%), previously treated leukemia/lymphoma in 10 (12%), and a history of solid organ malignancies in 3 (4%). Other comorbidities included epilepsy in 2 (2%), nephrotic syndrome in 2 (2%), diabetes and hypothyroidism in 2 (2%), and asthma in 1 (1%).

The baseline and 12 months post-treatment laboratory and LSM data are summarized in Table I.

Before Treatment

ALT and AST were elevated above the upper limit of normal (30 IU/mL) in 58 (68%) and 59 (69%) patients, respectively. Hypoalbuminemia was detected only in 1 patient with proteinuria owing to nephrotic syndrome. Hyperbilirubinemia was detected in 11 patients (13%) with associated comorbidities as β-thalassemia and previously treated malignancy. The coagulation profile and creatinine level were normal in all patients. The median baseline LSM was 5.8 kPa (IQR, 4.2-6.5 kPa) with a minimum of 3.2 kPa and a maximum of 33.8 kPa. Sixty-seven patients had a baseline LSM consistent with fibrosis stage F0-F1 and 18 correlated with F2 or higher (12 were F2, 4 were F3, and 2 were F6). Liver biopsy was done only in 2 patients with LSM correlated with cirrhosis to confirm it. Comorbid conditions were detected in 25 of the 67 patients with F0-F1 and 8 of the 18 with F2 or higher. The median baseline FIB-4 score was 0.34 (range, 0.12-3.47; IQR, 0.22-0.47) and the median baseline APRI score 0.35 was (range, 0-4; IQR, 0.24-0.57).

Table I. Baseline and 12 months post-treatment laboratory and liver stiffness data

Items	Before treatment	After treatment	*P* value
Liver and renal function tests			
ALT, U/mL	39 (29-67)	21 (18-29)	<.001
AST, U/mL	39 (27-55)	23 (20-28)	<.001
Albumin, g/dL	4.5 (4.3-5)	4.7 (4.4-4.9)	.877
Total bilirubin, mg/dL	0.7 (0.6-0.9)	0.7 (0.6-1)	.482
Direct bilirubin, mg/dL	0.1 (0.1-0.1)	0.1 (0.1-0.1)	.036
Alkaline phosphatase, U/L	258 (184-407)	187 (124.5-270)	<.001
International normalized ratio	1 (1-1.1)	1 (1-1)	.101
Creatinine, mg/dL	0.8 (0.7-0.9)	0.7 (0.6-0.8)	.131
Fibrosis indices			
FIB-4	0.34 (0.22-0.47)	0.3 (0.22-0.34)	<.001
APRI	0.35 (0.24-0.57)	0.2 (0.18-2.8)	<.001
Liver stiffness, Kpa	5.8 (4.2-6.5)	5.1 (4-6)	.045

Data are expressed as median (IQR) and the Wilcoxon test was used for comparisons.

After Treatment

There were statistically significant decrease in the serum ALT, AST, alkaline phosphatase, and direct bilirubin levels with follow-up. Overall, liver fibrosis by noninvasive measurements, such as LSM, FIb-4, and APRI, indicated nonprogression or regression at 12 months after treatment. The LSM had a median of 5.1 kPa (range, 3.5-23.3 kPa; IQR, 4-6 kPa) ($P = .045$), and the median percentage change of LSM was −4.8% (range, −55.7% to 83.3%; IQR, −25.1% to 34.8%). The median FIB-4 at follow-up was 0.3 (range, 0.1-1.2; IQR, 0.22-0.34) ($P < .001$) and the median APRI score was 0.2 (range, 0.1-1.1; IQR, 0.18-2.8) ($P < .001$).

Changes in Fibrosis Stages

The primary outcome was detected in 62 patients (73%); 16 (19%) had regression and 46 (54%) had nonprogression of LSM relative to baseline (Table II). Although 23 patients (27%) had a more than 30% LSM increase, this finding was indicative of increased fibrosis stage in only 7 patients (8%). Although in comparing LSM changes with baseline, there was a statistically significant difference between the regressed, stationary, and progressed groups ($P < .001$). Thus, patients with higher baseline LSM were more likely to have regression after treatment (Figure 1).

Of the 67 patients with baseline LSM consistent with F0-F1, 62 were unchanged and 5 had a higher fibrosis stage—4 from F0-F1 to F2 and 1 from F0-F1 to F3. Of the 18 patients with initial fibrosis of F2 or higher, 13 had post-treatment stage of less than F2; 11 from F2 to F0-F1 and 2 from F3 to F0-F1. The remaining 5 patients showed regression from F6 to F5 in 2, unchanged F3 in 1, increase from F2 to F3 in 1, and increase from F3 to F4 in 1. Therefore, 23 patients had significant fibrosis changes from 1 stage to another with (mean, −1.8 ± 3.9; $P = .036$; Figure 2).

Overall, there were 7 patients with an increased fibrosis stage after treatment. All had associated comorbidities: 4 had transfusion-dependent β-thalassemia major with inadequate control of iron overload–related complications and high serum ferritin levels. The other 3 were obese with S3 hepatic steatosis by a controlled attenuation parameter score as assessed by VCTE (299-320-340 decibels/meter). There was a significant negative correlation between LSM regression and associated comorbidities ($P = .036$).

Table II. Association between baseline liver stiffness, changes, and percentage changes before and 12 months after treatment

Liver stiffness changes	No. (%)	Baseline liver stiffness (kPa)	Percentage changes
Regressed	16 (19)	7.7 (6.6-8.4)	−35.9 (−41.1 to −31.7)
Stationary	46 (54)	5.9 (4.6-6.5)	−9 (−21.2 to 15.7)
Progressed	23 (27)	3.9 (3.6-4.4)	47.2 (41.9 to 15.7)
Total	85 (100)	*P* < .001	−4.8 (−25.1 to 34.8)

Data are expressed as median (IQR) and the Kruskal-Wallis test was used for comparisons.

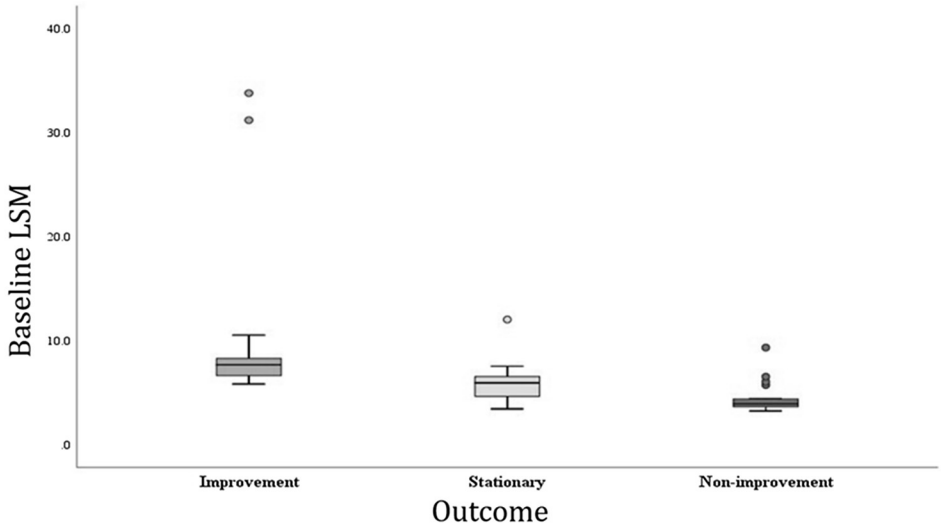

Figure 1. Baseline liver stiffness in relation to the outcome.

Discussion

Chronic HCV eradication as assessed by SVR is the aim of HCV treatment, but the main goal is a decrease in the mortality and morbidity associated with liver fibrosis.[23] Liver biopsy remains the gold standard for the assessment of fibrosis regression, but serial biopsies carry a risk of complications. Therefore, they are not used in the routine management of patients receiving DAA.[24] Instead, they have been gradually replaced in clinical practice by noninvasive techniques, such as VCTE and serum biomarker scores to assess LSM.[25]

Although LSM showed long-term improvement after SVR achievement by IFN/RBV regimens, the experience with successful DAA treatment and long-term clinical outcomes is still accumulating.[18,26,27] Most published articles studied fibrosis changes in the DAA therapy era among adults with chronic HCV, but not among children and adolescents. This study adds to the current literature as one of the few prospective cohorts studying LSM changes by VCTE, FIB-4, and APRI among Egyptian adolescents before and 12 months after successful treatment with LED/SOF.

Our study demonstrated that SVR 12 achievement by DAA treatment among Egyptian adolescents with genotype-4 HCV was associated with nonprogression or regression of LSM compared with baseline values. The overall percentage change of LSM has a median of −4.8% kPa (IQR, −25.1% to 34.8%). Previous studies reported similar findings in Egyptian adults and adults with different genotypes.[28-33] In support of the

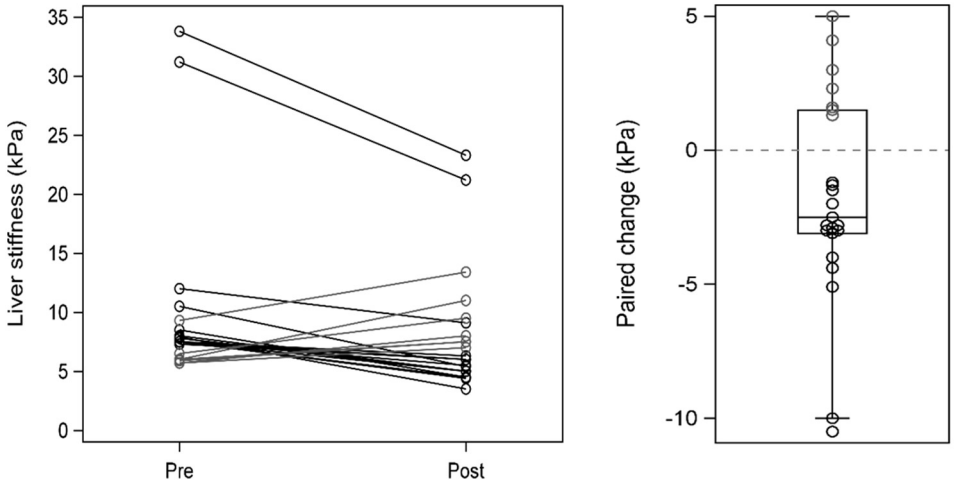

Figure 2. LSM changes of 23 patients with significant fibrosis changes.

LSM findings, noninvasive fibrosis scores (FIB-4 and APRI) showed a significant decrease, which was also reported by other studies.[13,14,34]

The lower LSM and noninvasive fibrosis scores among children, compared with the adults, can be explained by the nature of slowly progressive fibrotic disease of chronic HCV infection in childhood.[35,36] Various LSM cut-offs have been presented by various investigators representing different liver fibrosis stages. Lee et al detected a significant correlation between LSM and Metavir score in children with chronic liver diseases, but only for discriminating advanced liver fibrosis stages (>8.6 for F3 and >11.5 for F4).[37] Fitzpatrick et al reported LSM cut-offs of 6.1, 6.9, 7.5, and 14.1 kPa in discriminating F1 or greater, F2 or greater, F3 or greater, and F4 in pediatric patients with chronic liver diseases using Metavir score.[38] Behairy et al reported similar results with cut-offs of 4.75, 6.65, 8.25, 13.0, 18.0, and 29.5 kPa to discriminate fibrosis of F1 or greater, F2 or greater, F3 or greater, F4 or greater, F5 or greater, and F6, respectively, using the Ishak score.[19] We used the latter cut-off points because this study included 50 Egyptian children with chronic HCV infection. Thus, it has the largest number of patients with chronic HCV, compared with others, and with the same genotype-4 as our study.[19] By the Ishak score, fibrosis can be classified into mild (F1), moderate (F2-F3), and severe fibrosis or cirrhosis (F4-F6).[39]

Although fibrosis regression with the IFN/RBV regimen can be explained by the antifibrotic effect of IFN, this is not applicable to DAA therapy.[40] It is mainly related to HCV cure, which is a composite indicator of liver fibrosis and causative agent of liver injury and inflammation.[41] An elevated baseline aminotransferase levels reflecting hepatocyte necroinflammation, have improved with SVR achievement and could account for some of LSM regression. This finding is supported by the work of Deterding et al, who reported that ALT decreases when viral replication is blocked and this may even continue once treatment is stopped.[42]

There was a significant negative correlation between LSM regression and associated comorbidities, act as a contributing factor of liver fibrosis, such as hemosiderosis in β-thalassemia or chemotherapy hepatotoxic effects in patients with malignancy. This finding may explain why those patients had increased LSM after treatment, whereas patients without associated comorbidities could be explained by VCTE decreased reproducibility in patients with increased body mass index, hepatic steatosis, and lower degrees of liver fibrosis.[43] This result has also been observed in adult studies.[44]

The baseline LSM by VCTE is an independent factor that predicts fibrosis improvement in our patients. It is noteworthy that patients with higher pretreatment LSM showed more regression than those with lower values. This finding is in agreement with previous studies that detected the best improvement in LSM occurred in patients who were stage F4 with mean percent of −25% vs −8% in F0-F3.[28,30,41] In contrast, Vukobrat-Bijedic et al reported that significant fibrosis improvement was higher in patients with mild-to-moderate fibrosis stages (F1/F2/F3) than advanced fibrosis stage (F4), but this could be attributed to their smaller sample size (40 patients) and different genotype (genotype-1).[33]

Noninvasive fibrosis scores (FIB-4 and APRI) have been used to predict advanced fibrosis in adults. However, several studies have shown that they are not appropriate for children, and there is an urgent need to validate and introduce new cut-off values for pediatrics.[45-47] The used cut-off values were chosen based on the study including a cohort of 166 Egyptian children with chronic HCV.[22] In this study, the area under the receiver operating characteristic curve for the FIB-4 and APRI for mild fibrosis were 0.66 and 0.74, and for advanced fibrosis were 0.82 and 0.8, respectively; thus, they are more specific to predict advanced fibrosis better than mild fibrosis. Similar results were obtained by other published values for HCV-infected Egyptian children.[48,49]

The main limitation of our study was the lack of histologic evidence to confirm the exact extent of fibrosis changes, which can be overestimated by VCTE.[50] FIB-4 and APRI new cut-off values are needed to be validated in pediatrics. Also, there was inadequate statistical power to detect independent factors associated with LSM improvement owing to the large proportion of patients with a low baseline LSM. A larger sample size with longer follow-up periods will be required to identify predictors of regression in the era of DAA and if it continues beyond 1 year.

In summary, successful treatment and achievement of SVR among Egyptian adolescents with genotype-4 chronic HCV infection via DAA therapy is associated with nonprogression or regression of liver fibrosis, by VCTE and FIB 4 and APRI. Earlier treatment is urgent before permanent liver damage occurs. Otherwise, the maximum benefit of anti-HCV treatment will be missed. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Wilson's Disease Remains a Great Masquerader

Slovis TH, Dubois RS, Rodgerson DO, Silverman A. The varied manifestations of Wilson's disease. Pediatr 1971;78:578-74.

A century after the initial description of "hepatolenticular degeneration," Wilson's disease remains a rare entity with variable manifestations requiring a high index of suspicion for diagnosis. The authors described this inherited disorder of copper metabolism owing to an undetermined genetic defect. They illustrate the clinical findings in various Wilsonian phenotypes—acute and chronic liver disease, fulminant liver failure with hemolytic crisis, neuropsychiatric disorder, as well as asymptomatic siblings.

In 1993, the genetic defect in *ATP7B* was identified. The resultant mutant protein leads to decreased excretion of copper in bile and accumulation in the liver with subsequent copper release into the bloodstream and deposition in other organs.[1] Contemporary diagnostic algorithms have been developed incorporating clinical measures described by the authors—low ceruloplasmin level, increased urine copper, pathognomonic Kayser-Fleischer rings, and hepatic iron quantification on biopsy as the gold standard. More than 500 *ATP7B* mutations have been identified, and genetic testing has improved the diagnostic process, particularly for asymptomatic relatives.

Therapeutic options have expanded and include the chelating agents D-penicillamine and trientine, as well as zinc blockade of enteral copper absorption. One described patient was the first described recipient of a liver transplant for Wilson's disease. Currently, liver transplantation is a well-established treatment for end-stage liver disease and fulminant liver failure, with almost 900 transplants performed in the US for Wilson's disease over the last 30 years.[2] It is the only chronic disease granted the highest priority (status 1A) on the waitlist for those with fulminant failure, because transplantation remains the sole life-saving option for these patients. Emerging technologies, such as gene therapy, aimed at correcting the *ATP7B* mutation, may change the landscape of Wilson's disease.[3] Most important for favorable outcomes in these patients is early recognition of varied presentations, just as described 50 years ago.

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