Pediatric Wilson Disease Presenting as Acute Liver Failure: An Individual Patient Data Meta-analysis

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ABSTRACT

Objectives: Wilson disease (WD) presenting as acute liver failure (ALF) is rare and typically fatal without liver transplantation (LT). Its rarity has hindered comprehensive studies. We undertook an individual patient data meta-analysis to characterize a cohort of pediatric patients presenting with ALF whose final diagnosis was WD to examine outcomes and identify predictors of poor outcomes.

Methods: Database searches were conducted in PubMed, ScienceDirect, and Google Scholar, restricted to English-language articles published between January 1984 and May 2018. Articles were excluded if pediatric (<18 years old) data were not extractable or if LT was not readily available at reporting institutions. Extracted data included clinical and biochemical characteristics, genotype, treatment, and outcome.

Results: Data were available on 249 subjects from 52 articles, plus 7 additional subjects identified from our institution's WD database (N = 256). Females represented 69% (n = 170/245). Median age at presentation was 13.4 years (n = 204, range 4.0–17.9). Of the total 256 subjects, 87% underwent LT, 11% achieved spontaneous recovery and 2% died before LT. International normalized ratio >2.0 at presentation was a predictor of LT/death (odds ratio 7.6, 95% confidence interval 1.5–28), with a trend observed for hepatic encephalopathy (HE) (odds ratio 4.18, 95% confidence interval 0.99–18). Arithmetic diagnostic scores proved inferior in the pediatric age-bracket compared to adults.

Conclusions: This large international pediatric cohort has permitted an individual patient data analysis of WD presenting as ALF. Notably, 11% of subjects achieved spontaneous survival; the rest required LT. Coagulopathy (international normalized ratio >2:0) and HE at presentation heralded poor outcomes. Further prospective studies may identify additional early predictors of outcomes.

Key Words: apheresis, chelation therapy, children, liver transplantation, spontaneous recovery

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What Is Known

- Wilson disease presenting as acute liver failure is rare and typically fatal without emergency liver transplantation.

What Is New

- Of the total 256 pediatric subjects in this individual patient data meta-analysis, 11% achieved spontaneous recovery. Some type of apheresis was used in nearly half (n = 14/27) of these subjects.
- Identified predictors of death/liver transplantation were coagulopathy (international normalized ratio >2.0) and hepatic encephalopathy at presentation.
- Available arithmetic diagnostic scores proved insensitive in the pediatric age-bracket and cannot be adopted automatically from the adult age-bracket where they were originally developed.

Wilson disease (WD) is an autosomal recessive disorder caused by mutations in the gene *ATP7B*, which encodes an intracellular copper-transporting P-type ATPase (ATP7B) (1,2). Impaired ATP7B function generates adverse effects on hepatocellular metabolism: failure to produce enzymatically active ceruloplasmin and imparied biliary excretion of copper (3). The resulting hepatic copper overload damages the liver and secondarily other organs, notably the brain.

Clinical presentation of WD is highly variable. Acute liver failure (ALF) may be the first manifestation of WD. In general, it is fatal without liver transplantation (LT). Data from the Pediatric Acute Liver Failure (PALF) registry found WD as the etiology in 3% of PALF cases, as in adults (4,5). Many cases of WD presenting as ALF, including those first described, display a highly characteristic constellation of findings (6–10). This ''classic Wilsonian ALF'' (denoted as ALF-WD) is notable for Coombs-negative intravascular hemolysis, relatively low serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and profoundly low serum alkaline phosphatase (ALP).

WD presenting as ALF poses a complex diagnostic challenge when it is clinically indistinguishable from other etiologies of ALF. Clinical evaluation is complicated by the insensitivity of usual diagnostic features of WD in the setting of ALF. Decreased serum ceruloplasmin and/or elevated urinary copper excretion are taken as strongly suggestive of WD; however, they have also been implicated in other etiologies of ALF. Several biochemical diagnostic ratios (typically ratios of ALP to total bilirubin [TB] and/or AST to ALT) with specific cut-off values have been proposed to differentiate WD from other causes of ALF (11–13). Recent studies have produced contradictory results regarding their diagnostic utility, particularly in children (14,15).

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It is important to characterize WD presenting as ALF in a pediatric population to ensure prompt lifesaving, disease-specific interventions, best utilization of resources, and appropriate screening of first-degree relatives. Because of its rarity, WD presenting as ALF has been difficult to study comprehensively. Current evidence is mainly limited to anecdotal case reports and small cohort studies with adult subjects (≥18 years old). We therefore undertook a meta-analysis of individual patient data (IPD). Our primary objective was to describe the outcome of children and adolescents diagnosed with WD presenting as ALF and identify outcome predictors. In addition, we aimed to evaluate biochemical diagnostic indices, previously proposed as highly informative in adult patients, in this pediatric age-bracket (<18 years old).

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) statement (16).

Search Strategy

Potentially eligible studies were identified in a systematic literature search. We searched Medline via the National Library of Medicine's PubMed electronic database (PubMed), ScienceDirect, and Google Scholar, from January 1, 1984, to May 31, 2018, by using different combinations of the following keywords.

"Fulminant Wilson Disease," "Fulminant Wilson Disease" AND ["Pediatric" OR "Children," OR "Liver Transplant"] "Wilson Disease" AND ["Pediatric" OR "Children," OR "Liver Transplant" OR "Acute Liver Failure"]. Bibliographies of retrieved articles were also examined. Abstracts of identified studies were screened independently by 2 reviewers (S.M.V., M.D.A.). Any disagreements about study eligibility were resolved through discussion.

Our WD database at the Hospital for Sick Children (SickKids) was also reviewed for children diagnosed with WD presenting as ALF. Figure 1 summarizes our study retrieval and selection process.

Eligibility Criteria

Abstracts were retained for full review if the studies were peer-reviewed, published in English between January 1984 and May 2018, and consistent with the following inclusion criteria: subjects were <18 years old; newly diagnosed with ALF as per the study authors' definition of ALF; and identified with a final diagnosis of WD based on a combination of the following features: Kayser-Fleischer rings, serum ceruloplasmin <20 mg/dL, basal urinary copper excretion >40 μg/24 hours, liver copper concentration >250 μg/g dry weight, Leipzig score ≥4 (17), and *ATP7B* genotype consistent with WD. When it was evident that researchers from the same institution reported on the same patient population over time, the article with the largest, best-described cohort was selected. We accepted a study from United Network for Organ Sharing on the basis that urgent listing for LT entailed meeting these criteria for WD (18).

Studies were excluded if IPD were not extractable and not available from the study authors; patients had concomitant acute viral infection (hepatitis A-E) or drug-induced liver injury; LT was not readily available at the respective institution. We adopted this restriction to reflect contemporary medical practice.

Data Extraction

The following data were extracted from each eligible article (by S.M.V. and M.D.A.): author(s); year of publication; country where the study was performed; study design; number of eligible subjects; baseline characteristics of subjects (sex, age at presentation, presence of Kayser-Fleischer rings, Coombs-positive or Coombs-negative anemia, hepatic encephalopathy [HE]); laboratory tests at presentation (international normalized ratio [INR] or prothrombin time [PT]; serum AST, ALT, ALP, TB, ceruloplasmin, and basal 24-hour urinary copper excretion); patient outcome (LT, spontaneous recovery, death before/without LT); graft type (live-donor, deceased, or "not-specified") and *ATP7B* mutations, if available. Clinical data points were reported as binary outcomes, present or absent. The following ratios, ALP to TB and AST to ALT, were noted or calculated.

Additional Data Collection

To retrieve unpublished IPD from eligible articles, we contacted the first and/or senior author of each study via email. If no response was received within 30 days, a second attempt was made, and additional coauthors were contacted. If no response was received after 2 attempts, the data were considered unavailable. Similarly, if the eligibility of a study was unclear, we contacted the study's senior author for further information. If no responses were given after 2 attempts, the study was excluded.

Data Integrity

To establish data integrity, 2 authors (S.M.V., M.D.A.) first extracted the data independently and each compiled a personal database. Then they conferred to reconcile the 2 databases, thus ensuring accuracy of the data. Any discrepancies were checked against the publication and/or data received from the study authors. The resulting merged database served as the definitive dataset for analysis.

Statistical Analysis

Continuous variables were summarized as medians (interquartile range [IQR] or range) and categorical variables as frequencies (proportions). To examine outcome predictors, a 1-stage IPD meta-analysis was performed whereby a generalized linear mixed model with random effects was used to account for clustering by study. Estimation was performed by penalized quasi-likelihood, as preferred (19). Models with a random intercept only (rather than random intercept and random slope) had the best fit and were therefore used. Univariate and multivariable associations were examined. Sensitivity analyses excluding studies that included only transplanted patients were performed. For all statistical tests, a P value <0.05 was considered statistically significant. Mixed effects analyses were performed with SAS University Edition. All other analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, IL) version 25 for Mac.

RESULTS

Study Identification and Selection

Our search strategy yielded 4898 articles. After removal of duplicates and abstract screening, 198 full-text articles were selected for further evaluation. After full-text review, 79 articles were determined eligible or potentially eligible for inclusion, and additional aggregate IPD was requested from 60 articles. We received some or all requested unpublished IPD from the authors of 33 articles. A total of 52 articles were included in our IPD meta-analysis: 24 case reports, 15 case series, and 13 cohort studies. Data from eligible subjects were extracted from these articles or were

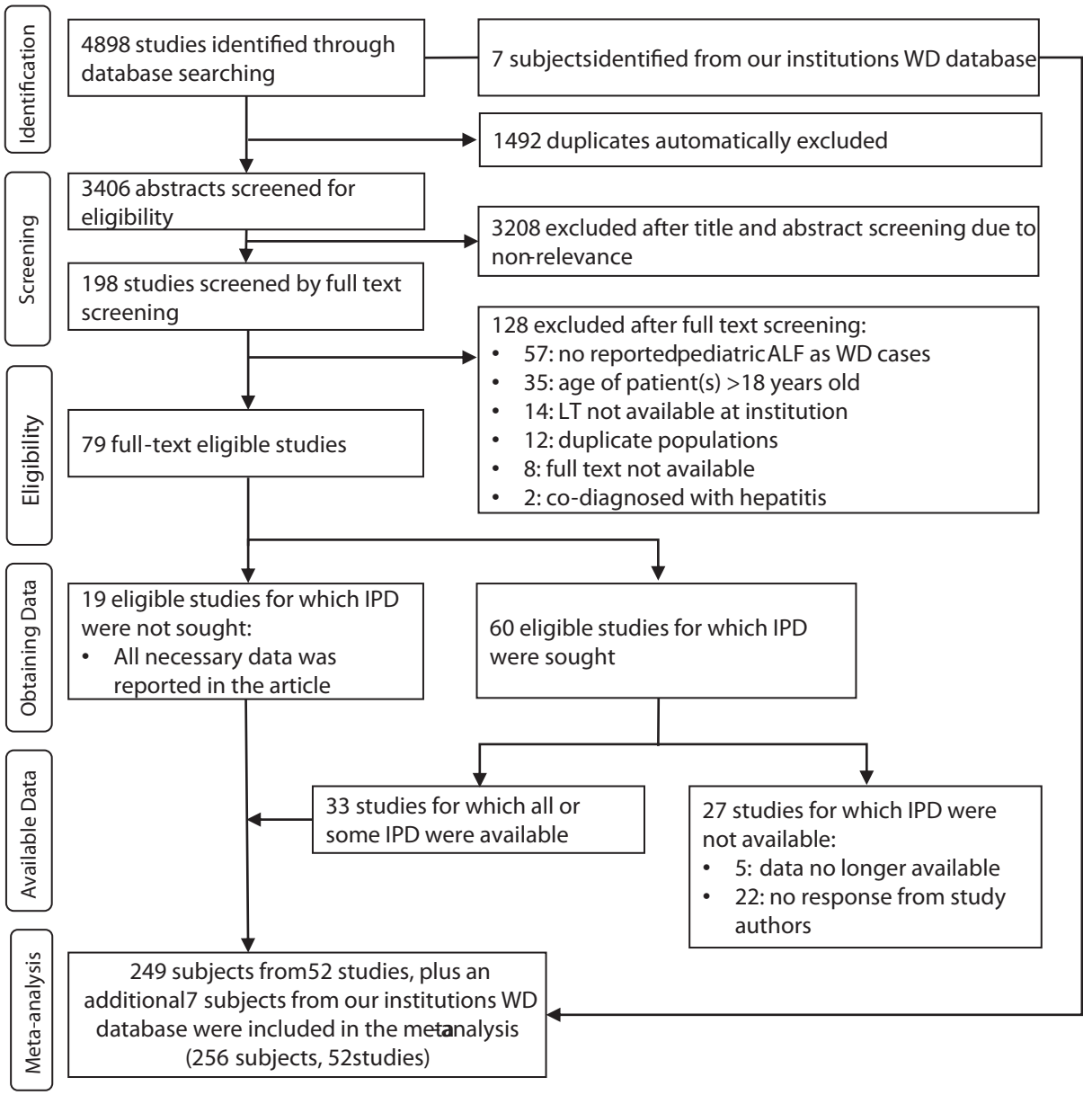

FIGURE 1. Outline of selection of studies for analysis. PubMed, ScienceDirect, and Google Scholar were searched for English-language articles published between January 1, 1984 and May 31, 2018, by using different combinations of keywords as indicated in ''Methods.'' This flow diagram illustrates the retrieval and selection process for identifying studies to generate our individual patient meta-analysis (249 subjects). An additional 7 subjects were identified from the SickKids WD database (N = 256).

provided by the study authors. An additional 7 eligible subjects were identified from the WD database we maintain at SickKids. Our final definitive dataset comprised 256 subjects. The detailed steps of the systematic literature search are depicted in Figure 1.

Characteristics of Included Studies

All included studies were retrospective. The majority were conducted in Asia (34%), followed by Europe (27%), North America (25%), Middle East (6%), South America (4%), and Australia (4%). Study cohorts ranged in size from 1 to 41 subjects. Ninety percent of the studies included were published in or after 2000. A summary of included studies is presented in Supplemental Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B837*).

Characteristics of Included Subjects

Clinical and biochemical features of the definitive dataset are summarized in Table 1. Females represented 69% (n = 170/245, female: male ratio = 2:1) of all subjects. The median age at presentation for the entire cohort was 13.4 years (n = 204, range 4–17.9). Where both age and sex data were available, 13% were prepubertal girls (ages 4–9), 27% were peripubertal girls (ages 10–13), and the majority (60%) were postpubertal. HE was reported in

TABLE 1. Clinical and biochemical features of the definitive dataset stratified by outcome

Demographics	All	Transplanted	Spontaneous recovery	Death without LT
n	256	223 (87%)	27 (11%)	6 (2%)
Female, %	69% (n = 170/245)	67% (n = 142/212)	85%	83%
Age at presentation, mdn (IQR)	13.4 (IQR 10.0–16.0) (n = 204)	13.0 (IQR 10.0–15.9) (n = 171)	15.0 (IQR 10.6–17.0)	15.5 (IQR 10.9–16.3)
Clinical Characteristics				
Kayser–Fleischer rings	74% (n = 118/159)	74% (n = 95/129)	74% (n = 20/25)	67% (n = 3/5)
Coombs-negative anemia	92% (n = 115/125)	90% (n = 92/102)	100% (n = 22/22)	100% (n = 1/1)
Hepatic encephalopathy	78% (n = 170/219)	80% (n = 152/189)	54% (n = 14/26)	100% (n = 4/4)
Laboratory characteristics				
INR	3.3 (IQR 2.5–4.6) (n = 127)	3.8 (IQR 2.6–5.5) (n = 107)	1.9 (IQR 1.7–2.3) (n = 19)	3.6 (IQR NA) (n = 2)
PT, %	20% (IQR 13.0–33.8) (n = 66)	19% (IQR 12.8–28.0) (n = 58)	39.5% (IQR 32.8–72.0) (n = 8)	NA
PT, sec	26.0 (IQR 20.5–34.0) (n = 55)	25.1 (IQR 20.3–32.5) (n = 45)	33.3 (IQR 29.0–41.8) (n = 7)	19.4 (IQR NA) (n = 3)
AST:ALT, U/L	2.3 (IQR 1.5–5.5) (n = 146)	2.2 (IQR 1.5–6.1) (n = 123)	3.4 (IQR 1.1–4.0) (n = 20)	5.5 (IQR NA) (n = 3)
ALP:TB, U/L	1.7 (IQR 0.6–6.2) (n = 114)	1.7 (IQR 0.6–4.4) (n = 98)	3.9 (IQR 0.7–9.1) (n = 12)	0.54 (IQR NA) (n = 3)
Ceruloplasmin, mg/dL	11.0 (IQR 6.7–16.0) (n = 160)	11.0 (IQR 6.7–16.0) (n = 135)	10.7 (IQR 6.8–16.0) (n = 19)	12.2 (IQR 7.8–17.2) (n = 5)
24-Hour basal urinary copper, μg/day	3133.0 (IQR 912.3–6712.8) (n = 124)	3087.5 (IQR 744.0–7042.0) (n = 99)	2787.0 (IQR 1066.8–6737.0) (n = 21)	3400.0 (IQR NA) (n = 3)
Diagnostic indices				
>4.0 AST:ALT*	34% (n = 49/146)	34% (n = 42/123)	25% (n = 5/20)	66.8 (n = 3/5)
>2.2 AST:ALT†	52% (n = 76/146)	50% (n = 62/123)	60% (n = 12/20)	66.8 (n = 3/5)
<2.0 ALP:TB*	55% (n = 63/114)	56% (n = 55/99)	50% (n = 6/12)	66.8 (n = 3/5)
<4.0 ALP:TB†	71% (n = 81/114)	74% (n = 73/99)	50% (n = 6/12)	66.8 (n = 3/5)
AP:TB ratio < 4 +AST:ALT ratio>2.2†	49% (n = 45/92)	49% (n = 38/77)	42% (n = 5/12)	66.8 (n = 3/5)

INR = international normalized ratio; IQR = interquartile range; LT = liver transplantation; TB = total bilirubin.
*Berman et al.
†Korman et al.

78% (n = 170/219) of subjects at the time of clinical presentation. The median INR at presentation was 3.3 (n = 127, IQR 2.5–4.6). Of the 256 subjects included in our definitive dataset, we were able to evaluate the PALF-definition in 139 subjects; Coagulopathy (PT >20 seconds or INR >2.0) without HE, OR, presence of coagulopathy (PT >15 seconds or INR>1.5) with HE. Of these 139 subjects, 91% (n = 126) met the PALF criteria.

Features of classic Wilsonian ALF were evaluable in approximately half of the subjects. Coombs-negative hemolytic anemia was found in 92% (n = 115/125); the median 24-hour urinary copper excretion was 3133 μg (IQR 912.3–6713.8) (n = 124). At presentation, Kayser-Fleischer rings were found in 74% (n = 118/159).

Diagnostic Ratios

The diagnostic sensitivity of currently available biochemical ratios, developed for distinguishing WD presenting as ALF from other etiologies of ALF, was evaluated. Utilizing the criteria proposed by Berman and colleagues, we found ratios of AP/TB <2.0 and AST/ALT >4.0 yielded a sensitivity of only 55% (n = 63/114) and 34% (n = 49/146), respectively. We examined the sensitivity of the amended ratios proposed by Korman et al: the ratios ALP/TB <4.0 and AST/ALT >2.2 yielded only a slightly higher sensitivity of 71% (n = 81/114) and 52% (n = 76/146), respectively. When these ''Korman'' ratios were combined, the sensitivity was 49% (n = 45/92).

Outcomes and Predictors

In the definitive dataset (N = 256), 87% (n = 223) of subjects underwent LT, 11% (n = 27) achieved spontaneous recovery and 2% (n = 6) died before/without LT. To assess the risk of bias in the definitive dataset, we performed a sensitivity analysis excluding studies that used LT as an inclusion criterion (n = 83), the proportions experiencing LT, death, and spontaneous recovery were 61% (n = 51), 7% (n = 6), and 31% (n = 26), respectively.

INR >2.0 was identified as a significant predictor of LT or death (vs spontaneous recovery); patients with INR >2.0 at presentation had >7 times higher odds of LT/death (odds ratio [OR] 7.6, 95% confidence interval [CI] 1.5–38, $P = 0.014$). There was a trend toward increased risk in patients with HE at presentation (OR 4.2, 95% CI 0.99–18, $P = 0.052$). No significant association was observed between the outcome of LT/death and any of the other patient/disease characteristics. In a multivariable analysis including INR and HE, only INR remained significantly associated with poor outcome (adjusted OR for INR 7.4, 95% CI 1.4–38, $P = 0.017$; adjusted OR for HE 1.3, 95% CI 0.20–9.0, $P = 0.76$). Sensitivity analyses excluding studies that included only patients undergoing LT yielded similar findings (unadjusted OR for INR >2.0 7.1, 95% CI 1.4–35, $P = 0.018$; unadjusted OR for HE 3.3, 95% CI 0.76–15, $P = 0.11$). Models were adjusted for the effect of publication bias.

To address possible selection bias, we examined the outcomes of all subjects who were removed from our study cohort because LT was not available at their institution. Fourteen studies reporting on 96 subjects fit this exclusion criterion. In 13 of these articles, 77% of subjects died (n = 27) and 23% (n = 8) achieved spontaneous recovery. If these subjects were included in our study cohort, the rate of mortality and spontaneous recovery would increase to 10% and 12%, respectively. In the 14th article, 54% (n = 33) of subjects died and 46% (n = 28) achieved spontaneous recovery. These findings suggest a problem in disease definition.

Spontaneous Recovery

D-penicillamine was the most commonly used chelating agent in this subset of subjects (37%, n = 10/27). Temporally

dispersed trientine and zinc (19%, n = 5/27) and 2,3-dimercapto-1-propanesulfonic acid (18.5%, n = 5/27) were less often employed. Subjects who achieved spontaneous recovery received supportive medical treatment including chelation and possibly apheresis; specifically, apheresis was used in 48% (n = 13/27). Among apheresis systems, plasmapheresis was most often used (n = 12/13).

Genetic Characteristics

Complete genotype data were available in 46 subjects, and a single allele sufficient for analysis was reported in 1 subject (n = 47, 18% of total cohort). Homozygotes accounted for approximately one-third (n = 17). Among homozygotes, 6 of 17 had H1069Q. Among the 30 heterozygotes, 12 of 30 had 1 H1069Q allele. In 4 of these 12 subjects, H1069Q was paired with a mutation involving a deletion. Four compound heterozygotes had 1 allele with R778L, and 1 had an allele displaying R778G. Twenty-five subjects had exclusively missense mutations; 10 of 25 were homozygotes. Eight subjects had mutations identified as truncating, and an additional 9 subjects had at least 1 allele with a deletion; 1 had both a deletion and a truncating mutation. Five of these 10 had an allele featuring a deletion paired with H1069Q (n = 4) or R778L (n = 1). In the younger children (4–<11 years old), 5 of 12 were homozygotes; in addition, 5 displayed at least 1 allele with truncation or deletion.

DISCUSSION

In this IPD meta-analysis, we describe a large cohort of children and adolescents diagnosed with WD following presentation characterized as ALF. Female preponderance, a well-recognized feature of classic Wilsonian ALF (20,21), is clearly demonstrated. We took this finding as methodological validation. Notably, 11% of subjects achieved spontaneous recovery, whereas all remaining subjects underwent LT or died. Coagulopathy (INR >2.0) and HE at presentation were associated with poor outcome. We found that simple arithmetic ratios based on routine liver function tests, previously proposed as highly effective for distinguishing WD from other etiologies of ALF, had limited sensitivity in the pediatric age-bracket.

Of the 256 subjects identified here, twice as many females as males presented with WD as ALF. This supports the suggestion that estrogen may play a role in the etiopathogenesis of ALF in WD (21). Contrariwise, identifying reports of WD presenting as ALF in 18 prepubertal girls was somewhat unexpected; a comparable number of boys (n = 19) in that age group was reported. These findings may point to a complex mechanism for the development of ALF in WD, including but not limited to hormonal effects.

Our study found that 11% of children with WD presenting as ALF achieved spontaneous recovery. This finding contrasts the general impression, based on previous reports, that WD presenting as ALF is invariably fatal without LT. Improvements in general clinical management in the intensive care setting may contribute to improved survival. Our findings may be driven by biased reporting of experience with the use of extracorporeal support systems. In this cohort, plasmapheresis combined with D-penicillamine was the most frequently used therapeutic strategy incorporating apheresis that was associated with spontaneous recovery. Other apheresis technologies (in order of frequency) were albumin dialysis with continuous veno-venous hemodialysis, molecular adsorbent recirculating system (MARS), and single pass albumin dialysis. Apheresis was also used as a bridge to LT in several reports.

The relatively high rate of spontaneous recovery may also reflect subtle variations in the disease definition of WD presenting as ALF. When we examined outcomes in a sensitivity analysis restricted to studies in which LT was not an inclusion criterion, as was the case in some of the studies included in our systematic review, we found that 31% achieved spontaneous recovery. The true rate of spontaneous recovery may lie somewhere between 11% and 31%, likely closer to the lower value. It may be difficult to determine this rate by systematic review, due to definitional ambiguities. The research definition of ALF in children and adolescents, as articulated by the PALF consortium, has often been adopted to serve as a clinical definition. Specifically with WD, this definition can be problematic. A pediatric patient with WD could present—as the very first evidence of WD—with severely decompensated cirrhosis, displaying marked intractable coagulopathy but no HE, thus fulfilling the PALF criteria. These patients may respond to intensive medical treatment and avoid LT (22–25). Such may have been the case with one of the excluded articles which employed the PALF definition and reported an extremely high rate of spontaneous recovery (14). Of the 27 subjects in our definitive dataset who achieved spontaneous recovery, only 1 to 2 appear to have decompensated cirrhosis, not ALF. Thus, we believe the unexpectedly high rate of spontaneous recovery (11%) is actual. Importantly, if approximately 10% of these subjects with ALF due to WD achieved spontaneous recovery, that finding does not change the mandate to arrange for LT urgently in such patients. The survival of WD patients after LT is 80% to 90%, almost an order of magnitude higher than this rate of spontaneous recovery (18,26). Moreover, expeditious transfer to a pediatric liver transplant center enhances the likelihood of such favorable outcomes.

A further definitional issue relates to the cumulative experience that WD presenting as ALF has highly characteristic features, which we are calling ''classic Wilsonian ALF'' (ALF-WD). These include acute Coombs-negative intravascular hemolysis, severe coagulopathy, relatively low serum aminotransferases (compared most causes of ALF), strikingly low serum ALP, and prominent hyperbilirubinemia; HE present initially or within days of presentation; basal 24-hour urinary copper excretion generally 10 times greater than that found in most patients with WD (also higher than that in other forms of ALF); and early renal failure (27). Just how classic this presentation of WD really is in children, where it was first reported, has not been examined in detail. The ALF-WD clinical profile was discerned in numerous subjects, approximately half of this cohort; more extensive assessment was limited by incomplete availability of critical data. Importantly, basal 24-urinary copper excretion was extremely elevated. We conclude that many children and adolescents present with typical ALF-WD. This clinical presentation should facilitate diagnosis and prompt consideration for therapies to remove excess copper in the plasma compartment. In the pediatric age-bracket, some children with WD presenting as ALF, however, lack these distinctive features.

One approach to identifying individuals with WD presenting as ALF is calculation of informative ratios of routine laboratory data. The ratios suggested by Berman and colleagues did not find support from other investigators (28). In a more recent study, Korman et al (13) evaluated the diagnostic accuracy of ratios ALP/TB <4.0 and AST/ALT >2.2 for the biochemical diagnosis of WD presenting as ALF. In a cohort of 16 subjects (mean age 25.6 years, range 14–53), they reported high rates of sensitivity and specificity for the individual ratios; combining these 2 ratios provided a diagnostic sensitivity and specificity of 100%. In contrast, in this large meta-analysis, these ratios demonstrated limited sensitivity for early diagnosis of WD presenting as ALF in children and adolescents. It appears that these ratios cannot be adopted automatically from the adult-age bracket. It is possible that

variations in ALP through childhood account for some of the inaccuracy, but subset analysis suggests that this is not the case.

Data regarding *ATP7B* genotype were available in a small but representative subgroup. The proportion of homozygotes (36%) was higher than expected. Truncating mutations and mutations involving deletions were numerous but not predominant. It is difficult to draw any conclusions from these data about an association of certain types of mutation with the ALF presentation of WD.

Our study shows that coagulopathy (INR >2.0) and HE at presentation portend a poor prognosis in pediatric WD presenting as ALF. The median INR in those who did not recover spontaneously was 3.3. HE at presentation was reported in 80% of patients transplanted and in 100% of those who died, whereas only 50% of spontaneous survivors had HE. From early reports onward, patients with ALF-WD were noted to have HE at presentation or shortly thereafter. Here, onset of HE within days of clinical presentation was recorded as ''no encephalopathy''; this delayed pattern was reported in some subjects. In PALF, according to the PALF Study Group, HE has indicated a poor prognosis (29).

In classic Wilsonian ALF, a sudden massive release of copper from the liver leads to exceedingly high levels of nonceruloplasmin-bound copper in the plasma compartment, leading to intravascular hemolysis and excessively high urinary copper excretion (30). Plasma exchange, albumin dialysis with continuous venovenous hemodialysis, and molecular adsorbent recirculating system are strategies that have all been proposed to remove copper from the plasma compartment rapidly and thus control hemolysis and stabilize renal function. Although the numbers are small, some sort of apheresis was used in nearly half of children who achieved spontaneous recovery. Similar findings have been reported by apheresis specialists (31). Although it is by no means a novel approach to treat ALF-WD via plasma exchange or some form of apheresis, at this point a prospective evaluation of the role of apheresis in WD presenting as ALF deserves priority (9).

Inevitably, a study of this sort has limitations. The commitment to inclusiveness entailed accepting a broad range of definitions, of both ALF and WD. Although we concurred with the diagnosis of WD in all cases, we found a very small minority where we judged the diagnosis to be severe end-stage liver disease, not ALF. Despite assembling a very large cohort of subjects and having ample ancillary data supplied to us, for some critical conceptual issues, we had to rely on findings in only approximately half of the subjects. We doubt that reviewing only the English-language literature disadvantaged our findings; we achieved a broad worldwide geographic distribution of reports.

In conclusion, this IPD meta-analysis is a very large and detailed study of outcomes in pediatric WD presenting as ALF. These data demonstrate that the clinical presentation of ALF in pediatric WD has a wide clinical spectrum. The typical profile of classic Wilsonian ALF (ALF-WD) is often, but not always, present. Likewise, arithmetic ratios to aid in diagnosis appear insufficiently sensitive in the pediatric age bracket. Further investigation is needed to identify early predictors of treatment outcomes in pediatric WD presenting as ALF, particularly to identify patients where conservative management with oral chelation and/or apheresis therapy may be a reasonable alternative to LT. Our IPD meta-analysis suggests that such selected cases will be a small minority.

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