Comparison of Long-Term Outcome of Patients with Wilson's Disease Presenting with Acute Liver Failure versus Acute-on-Chronic Liver Failure

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Objective: *Wilson's disease (WD) is an inherited disorder of copper metabolism, leading to hepatic and neuropsychiatric manifestations. The long-term outcome of patients with Wilson' disease presenting with acute liver failure (ALF) versus those with acute-on-chronic liver failure (ACLF) has not been well documented. The authors' aimed to compare the clinical presentations and long-term outcome after standard treatments between patients with ALF versus those with ACLF.*

Material and Method: *The authors performed a retrospective review of 39 patients with Wilson's disease, at the King Chulalongkorn Memorial Hospital between January 2003 and December 2011. Primary outcome of the present study was liver complications or deaths from any cause. ACLF was defined as an acute hepatic insult in patients with previously diagnosed or undiagnosed chronic liver disease, whereas ALF was defined as an occurrence in the absence of any pre-existing liver disease.*

Results: *Twenty-two of 39 patients (56.4%) presented predominantly with hepatic symptoms with the mean duration of follow-up of 7.7±8.5 years. Ten of them (45%) presented with ALF, whereas 12 patients (55%) presented with ACLF. Patients with ALF showed a significantly earlier age of onset of presenting symptoms than those with ACLF (15.4±4.5 vs. 28.1±13.0 years; $p<0.05$). The mean baseline of 24-hour urinary copper in patients with ALF was higher than those found in ACLF (1,645±1,406 vs. 441±434 mg/day; $p<0.05$, respectively). Fourteen patients (63.6%) improved with supportive care and chelating agents. No significant difference of clinical improvement was found between patients presented with ALF and ACLF (80% vs. 50%; $p = 0.19$). By using the survival analysis, the mean duration time to liver complications or all cause of death in patients with ALF was significantly longer than those with ACLF (16.2±2.3 years vs. 8.5±3.2 years; $p = 0.012$) as well as higher cumulative percent of free a period from liver complication or death during a 9-year period (80% vs. 21%, $p = 0.012$).*

Conclusion: *Patients with Wilson's disease presenting with acute-on-chronic liver failure manifested symptoms later and had more liver complications than patients with acute liver failure, as well as a lower cumulative free period from liver complication or death.*

Keywords: *Long-term outcome, Wilson's disease, Acute liver failure, Acute-on-chronic liver failure*

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Wilson's disease (WD) is an autosomal recessive inherited disorder of copper excretion, resulting in accumulation of copper in the brain, liver, cornea, and other organs. The prevalence of WD is estimated to be 30 affected individuals per million population in the world[1]. WD has many patterns of clinical presentations that are varied, challenging, and involved hepatic, neurological, psychiatric, and other systems[2]. The clinical presentations of hepatic WD can be highly variable, ranging from asymptomatic with only biochemical abnormalities to liver failure. Most symptoms first appear in the second and third decade of life. There is no single test for the diagnosis of WD. Diagnosis depends primarily on clinical features, biochemical parameters, pathology, molecular testing and the presence of the Kayser-Fleischer ring[2]. Since delayed diagnosis is the principal cause of death in patients with WD, early recognition and appropriate therapy can reduce mortality[3,4]. WD is a progressive disorder, untreated patients may develop

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several complications such as gastrointestinal (liver failure, hepatic encephalopathy, esophageal varices, jaundice), neurologic (disability), psychiatric (depression, suicide) and hematologic (hemolytic crisis) presentation. The clinical outcome of WD has improved markedly following the introduction of various copper chelating agents such as D-penicillamine, trientine hydrochloride, and copper absorption blockers such as zinc salt[5-7]. Liver transplantation has a role in patients who are unresponsive to medical treatment. Under treatment, long-term follow-up found the survival in patient with WD was similar to the disease-free population[7,8]. The overall survival is 91.6%[9]. The main cause of death was due to diagnosis in the advanced stage of disease[4].

Liver failure is one of the most common presentations in hepatic WD, which have many clinical aspects, outcomes and can develop as acute liver failure (ALF: in the absence of any pre-existing liver disease) or acute-on-chronic liver failure (ACLF: an acute deterioration of known or unknown chronic liver disease). According to the new definition from the consensus recommendation of the Asian Pacific Association for the Study of the liver[10] (APASL) on acute-on-chronic liver failure (ACLF), identification of patients presenting with liver failure is more clarified. There have been different outcomes between patients who presented with ALF and ACLF. Patient with ACLF have high mortality rate. The 30- and 90-days mortality rate were 50% and 63%, respectively. In general, multisystem organ failure is the primary cause of death in ACLF[11], whereas the leading causes of death in ALF are cerebral edema and sepsis[12]. The clinical presentation and long-term outcome of patients with WD presenting with ALF versus those with ACLF have not been well documented. The present study aimed to compare the clinical presentation and long-term outcome after various treatments between patients with ALF versus those with ACLF.

Material and Method

Between January 2003 and December 2011, 39 patients were diagnosed with WD at the King Chulalongkorn Memorial Hospital (KCMH). The clinical, biochemical, histological, and radiological data of 39 patients were reviewed retrospectively. The diagnosis was confirmed by clinical presentations, presence of Kayser-Fleischer rings on slit lamp examination, family history, biochemical testing, increase serum copper (≥25 mcg/dL), low serum ceruloplasmin (<20 mg/dL), increase 24-hour urinary copper excretion (>100 mcg/day), and liver biopsy with excluding other causes of liver disease. Twenty-two of 39 patients were presented with hepatic manifestation[2]. Based on the definition from APASL[10] and American Association for the Study of Liver Diseases[13] (AASLD) consensus recommendations, all of these patients were classified as ALF or ACLF groups. The criteria for diagnosis of ACLF is acute hepatic insult manifesting as jaundice and coagulopathy, complicated within four weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. Chronic liver failure was diagnosed by imaging or liver biopsy. ALF has been defined by AASLD consensus recommendation' 2005[13] that includes evidence of coagulation abnormality, usually an INR ≥ 1.5, and any degree of encephalopathy in a patient without preexisting cirrhosis and with an illness of <26 weeks duration.

Long-term outcomes were evaluated focusly on treatment response, time to the recovery of liver synthetic function, development of liver complication, and death from any cause. The treatment response was evaluated by the improvement/normalization of liver function tests (i.e. aminotransferases) or the disappearance of signs of liver failure such as hyper-bilirubinaemia, hypoalbuminaemia, coagulopathy, or ascites. Complications of liver disease included development of decompensated cirrhosis, esophageal varices, ascites, jaundice, or encephalopathy.

Statistical analysis

Means (± standard deviation, SD), median, range and frequency (%) were used to describe demographic data. The t-test and the Mann-Whitney Rank Sum Test were used for mean or median comparison. Chi-square and Fisher's exact test were used for comparison between proportions (categorical data). The analysis of survivals was performed using the Kaplan-Meier method. A p-value of ≤0.05 was required for statistical significance. All statistical analyses were performed using SPSS (version 15.0; SPSS, Chicago, IL, USA). The present study was approved by the ethic committee of KCMH.

Results

Twenty-two of 39 patients (12 women and 10 men) were diagnosed with WD and initially presented predominantly with hepatic symptoms, which nine (23.1%) showed neuropsychiatric symptoms, eight (20.5%) were asymptomatic. The demographic and

Table 1. Clinical characteristics and laboratory parameters 22 patients with Wilson's disease: acute liver failure vs. acute-on-chronic liver failure

Variables	Acute liver failure (ALF, n = 10)	Acute-on-chronic liver failure (ACLF, n= 12)	p-value
Male, n (%)	5 (50.0)	5 (41.7)	0.69
Age (years), mean±SD, range	23.8±6.7 (16-36)	31.0±12.9 (13-55)	<0.05*
Age at onset(years), mean±SD, range	15.4±4.5 (9-25)	28.1±13.0 (8-53)	<0.05*
KF ring, n (%)	7 (70.0)	5 (41.7)	0.26
Onset of symptom to diagnosis (days), mean±SD, range	33.0±17.0 (15-60)	158.0±156.0 (130-450)	0.59
Time from diagnosis to last follow-up (years), mean±SD, range	6.4±5.8 (0.2-19)	8.8±8.3 (0.6-26)	<0.05*
Number of patients with follow-up ≥ 5 years, n (%)	5 (50.0)	8 (66.7)	0.37
INR, mean±SD	3.6±1.7	2.5±1.2	0.45
Total bilirubin at presentation, mean±SD (mg/dL)	15.5±16.2	2.3±1.1	0.03*
Serum ceruloplasmin, mean±SD (mg/dl)	8.1±3.9	6.2±4.9	<0.05*
Serum copper	9.5±23.6	0.5±0.2	0.16
24-h Urine copper, mean±SD (mcg/day)	1,645.0±1,406.0	441.6±433.9	<0.05*
Treatment with medication, n (%)	10 (100)	12 (100)	-

* Unpaired t-test

clinical characteristics are presented in Table 1. The mean duration of follow-up calculated from the onset of the diagnosis of WD to death or lost to follow-up until December 30, 2011, for patients alive, was 7.7±8.5 years with range of 2.5 months to 26 years. Patients with ALF showed a significantly (15.4±4.5 vs. 28.1±13.0 years; $p<0.05$) earlier age of onset of presenting symptoms than those with ACLF. Time from first presentation to diagnosis was longer in patients with ACLF (mean 158.2±156.5 days) than those with ALF (mean 33.0±17.0 days) without significant difference between both groups.

The predominant presentations were jaundice, edema, and ascites. The K-F ring was found in 70% of the patients with ALF and 41.7% in ACLF. Patients with ACLF were associated with lower serum ceruloplasmin ($p<0.05$) and lower 24-hours urine copper ($p<0.05$). Table 2 has shown the imaging or liver pathology used to diagnosis chronic liver disease in ACLF. None of these patients with ACLF had chronic liver stigmata on physical examination.

All patients were treated with D-penicillamine, zinc salts or combined drugs and were monitored for serum ceruloplasmin, serum copper, 24-hours urine copper during follow-up. One patient had liver transplantation due to acute liver failure.

Table 3 shows the clinical outcomes at the end of follow-up. During the follow-up period, six patients were lost to follow-up, one patient with ALF died of gram-negative septicemia, whereas all patients in ACLF are alive. Ten patients developed liver complications (Table 4); jaundice was the most common complication (18.2%). After treatment, eight patients with ALF (80%) and six patients (50%) with ACLF had improved liver function tests ($p = 0.19$). Mean time from initial presentation to liver complication was significant longer in ALF group (16.2±2.3 years) than ACLF group (8.5±3.2 years, $p = 0.012$) The cumulative percent of free period from liver complication or death during the 9-year period in patients with ALF group (80%) was significant better than ACLF group (21%, $p = 0.012$, Fig. 1).

Table 2. Tools for diagnosis in ACLF (n = 12)

Tools for diagnosis	n (%)
Clinical signs of chronic liver disease	0
Imaging suggestion for chronic liver disease	10 (83.3)
Ultrasound	7 (58.3)
Computed tomography scan	2 (16.7)
Magnetic resonance imaging	1 (8.3)
Liver biopsy: chronic hepatitis	2 (16.7)
Fibrosis stage 2	1 (8.3)
Fibrosis stage 3	1 (8.3)

Discussion

The present study emphasizes on WD patients with hepatic manifestations. This is the first study to

Table 3. Clinical outcomes at the end of follow-up of 22 patients of Wilson's disease with hepatic presentation

	Acute liver failure (ALF, n = 10)	Acute-on-chronic liver failure (ACLF, n = 12)	p-value
Improved, n (%)	8 (80)	6 (50.0)	0.19
Liver transplantation, n (%)	1 (10)	0	0.36
Died, n (%)	1 (10)	0	0.36
Lost to follow-up, n (%)	1 (10)	5 (41.7)	0.16
Development of liver complication during long-term treatment	1 (10)	9 (75.0)	<0.05*
Time to liver complication (years), mean±SD	16.2±2.3	8.5±3.2	0.012**
Percent survival of liver complication in a 9 years period	80	21	-

* Fisher's exact test
** Unpaired t-test

Table 4. Clinical outcomes of 22 patients with WD - ALF and ACLF

Case	Age (year)	Gender	ALF or ACLF	Presenting symptom	Liver complication	Time to recovery of liver function (months)	Follow-up (years)
Presenting with acute liver failure							
1.	19	Female	ALF	Jaundice, hepatic encephalopathy	No	1.0	0.2
2.	21	Male	ALF	Jaundice	No	1.0	4.0
3.	20	Male	ALF	Jaundice, ascites	No	1.0	6.4
4.	22	Male	ALF	Jaundice	Yes (hepatic encephalopathy)	0.5	13.0
5.	16	Male	ALF	Jaundice, ascites	No	0.5	2.5
6.	36	Male	ALF	Jaundice	No	1.0	10.8
7.	19	Female	ALF	Jaundice	No	1.0	2.0
8.	22	Female	ALF	Jaundice, ascites	No	1.0	5.8
9.	32	Female	ALF	Jaundice	No	1.0	18.8
10.	31	Female	ALF	Jaundice	No	1.0	18.7
Presenting with acute-on-chronic liver failure							
1.	13	Female	ACLF	Jaundice, ascites	Yes (hepatic encephalopathy)	1.0	5.0
2.	14	Male	ACLF	Ascites	Yes (cirrhosis)	1.0	5.7
3.	37	Female	ACLF	Jaundice	Yes (cirrhosis)	N/A	14.2
4.	37	Female	ACLF	Jaundice, ascites	No	1.0	26.0
5.	55	Male	ACLF	Ascites	Yes (esophageal varices)	1.0	0.6
6.	23	Female	ACLF	Jaundice	No	0.5	8.3
7.	25	Male	ACLF	Jaundice, splenomegaly, ascites	No	1.0	11.0
8.	40	Male	ACLF	Jaundice	Yes (hepatic encephalopathy)	0.5	4.3
9.	26	Male	ACLF	Esophageal varice bleeding, splenomegaly	Yes (jaundice)	1.0	4.2
10.	23	Female	ACLF	Ascites	Yes (jaundice)	1.0	10.0
11.	31	Female	ACLF	Jaundice, splenomegaly	Yes (jaundice)	1.0	1.0
12.	48	Female	ACLF	Ascites	Yes (jaundice)	N/A	13.2

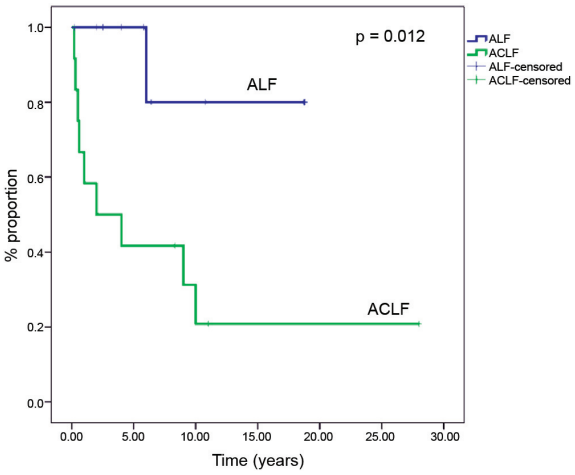

Fig. 1 Kaplan-Meier estimates of proportion of free of liver complication or death since diagnosis of patients with Wilson's disease: ALF vs. ACLF.

compare long-term outcome of treatment in WD patients with initial ALF with ACLF manifestations. One objective of our analysis was long-term follow-up with regard to the course of hepatic symptoms while under treatment. The main finding of the present study was patients with WD presenting with ACLF had more liver complications and lower cumulative free period from liver complication while under treatment. During the nine years of observational period, one patient (4.5%) died and 45.5% developed liver complications.

From a previous study, Taly et al[14] followed-up 225 patients with WD for a mean period of 46 months, and found improvement in 176 patients (78.2%), no improvement in 20 patients (8.9%) and 23 patients (8.1%) died while under treatment. However, these patients were mainly presented with neurologic symptoms (69.1%). U Merle et al[15], retrospectively analyzed 163 patients with WD and found three patients (1.8%) died during 17-year period of observation. Additionally, 79% of patients with initial hepatic manifestation improved their liver function test. The present findings showed that only WD patients with ALF presentation had similar rate of improvement of liver function test (80%), but these decreased in ACLF group. One patient (4.5%) died with gram-negative bacterial sepsis, which was less than the previous studies[4,6]. Czlonkowska et al studied the causes of death in a consecutive series of 164 patients with WD with all presented symptoms diagnosed over an 11-year period. Twenty patients (12%) died during the observation period[4]. Another study with 300 patients with WD, the survival after 10 years was 22.3%[3]. The causes of death in patients with WD were predominantly related to hepatic failure[4,16].

It remains unclear why serum ceruloplasmin and 24-hour urinary copper excretion were low in patients with ACLF. One possible explanation could be related to the lower bilirubin level at presentation, since there is evidence that the serum copper and ceruloplasmin level in WD was correlated with hepatic function[17]. Moreover, serum ceruloplasmin was one of the acute phase proteins that are found at a higher level in ALF patients.

Patients with ACLF showed a considerably later onset of symptoms and suffered a longer delay before definite diagnosis when compared to those with ALF. Therefore, awareness and looking for evidence of chronic liver diseases at presentation, especially by imaging study or liver biopsy, in patients with WD is crucial because ACLF patients suffer worse long-term outcomes and prognosis. Long-term treatment with medication is required for WD. The current therapeutic options include copper chelating agents, D-penicillamine, trientine, and Zinc, which decreased copper absorption via intestinal tract. Liver transplantation can be considered another therapeutic option for WD patients presented with ALF or decompensated liver disease that is unresponsive to medical therapy[2]. Unfortunately, liver transplantation could be offered to only one patient, as the transplantation program was not well organized at the time.

The present study has several limitations, the data was collected retrospectively from medical records and thus some information in was incomplete. The number of patients diagnosed with hepatic WD was small due to various reasons and patient's data record was not accessible in the past. The present study in natural history of the disease outcomes need longer follow-up period to ensure detection of events. Nine patients (41%) were followed for less than five years and five patients from ACLF group were lost to follow-up for more than one year from the last visit to date at the end of the present study.

In summary, there is a difference between WD presenting with acute-on-chronic liver failure and acute liver failure. Patients with acute-on-chronic liver failure manifested later and had a worse clinical outcome including liver complications or death.

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Potential conflicts of interest

None.

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ผลของการรักษาในระยะยาวของผู้ป่วยโรควิลสันที่มาด้วยภาวะตับวายเฉียบพลันเทียบกับภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง

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วัตถุประสงค์: *โรควิลสันเป็นโรคทางพันธุกรรมที่มีความผิดปกติทางเมตาบอลิซึมของทองแดงจนทำให้เกิดความผิดปกติทั้งทางตับและระบบประสาท ก่อนหน้านี้ยังไม่เคยมีรายงานการศึกษาถึงผลการรักษาในระยะยาวของผู้ป่วยโรควิลสันที่มาด้วยภาวะตับวายเฉียบพลันเทียบกับภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง จึงเป็นที่มาของการศึกษานี้เพื่อที่จะเปรียบเทียบอาการอาการแสดง และผลการรักษาในระยะยาวของผู้ป่วยโรควิลสันที่มาด้วยภาวะตับวายเฉียบลันเทียบกับภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังในผู้ป่วยโรควิลสัน ทั้งสิ้น 39 ราย ที่มารับการตรวจรักษาที่โรงพยาบาลจุฬาลงกรณ์ในช่วงเดือน มกราคม พ.ศ. 2546 ถึงเดือน ธันวาคม พ.ศ. 2554 โดยวัตถุประสงค์หลักคือ ภาวะแทรกซ้อนของโรคตับหรือการเสียชีวิต ภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรังหมายถึงการเกิดภาวะแทรกซ้อนเฉียบพลันของโรคตับในผู้ป่วยที่มีโรคตับเรื้อรังซึ่งอาจจะได้รับการวินิจฉัยมาก่อนหรือไม่ก็ได้ ขณะที่ภาวะตับวายเฉียบพลันหมายถึงการเกิดภาวะแทรกซ้อนของโรคตับในผู้ป่วยที่ไม่มีโรคตับเรื้อรัง*

ผลการศึกษา: *จากผู้ป่วยทั้งหมด 39 ราย มีผู้ป่วย 22 ราย (ร้อยละ 56.4) ที่มาด้วยอาการของโรคตับ โดยมีค่าเฉลี่ยของการตรวจติดตามที่ 7.7±8.5 ปี ผู้ป่วย 10 ราย (ร้อยละ 45) มาด้วยภาวะตับวายเฉียบพลัน ขณะที่ 12 ราย (ร้อยละ 55) มาด้วยภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง ผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันเริ่มมีอาการที่อายุน้อยกว่ากลุ่มผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง (15.4±4.5 เทียบกับ 28.1±13.0 ปี; ค่าพี <0.05) ค่าเฉลี่ยของทองแดงในปัสสาวะที่เก็บ 24 ชั่วโมง ในผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันสูงกว่าผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง (1,645±1,406 เทียบกับ 441±434 ไมโครกรัม/วัน, ค่าพี <0.05) ผู้ป่วย 14 ราย (ร้อยละ 63.6) ดีขึ้นด้วยยาแต่ไม่แตกต่างกันในผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลัน และผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรัง (ร้อยละ 80 เทียบกับ ร้อยละ 50; ค่าพี = 0.19) เมื่อใช้การวิเคราะห์การอยู่รอด พบว่าเวลาเฉลี่ยของการเกิดภาวะแทรกซ้อนของโรคตับหรือการตายในผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันจะยาวนานกว่าผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลันแทรกซ้อนภาวะโรคตับเรื้อรัง (16.2±2.3 เทียบกับ 8.5±3.2 ปี; ค่าพี = 0.012) เช่นเดียวกับมีเปอร์เซ็นต์สะสมของการปลอดจากการเกิดภาวะแทรกซ้อนทางตับหรือการตายที่สูงกว่าในช่วงที่ศึกษา 9 ปี (ร้อยละ 80 เทียบกับ ร้อยละ 21, ค่าพี = 0.012)*

สรุป: *ผู้ป่วยโรควิลสันที่มาด้วยภาวะตับวายเฉียบพลันแทรกซ้อนบนภาวะโรคตับเรื้อรังจะแสดงอาการที่ช้ากว่า มีภาวะแทรกซ้อนทางตับมากกว่า และมีเปอร์เซ็นต์สะสมของการปลอดจากภาวะแทรกซ้อนทางตับหรือตายที่น้อยกว่าผู้ป่วยที่มาด้วยภาวะตับวายเฉียบพลัน*