Mahmud *et al. Egyptian Liver Journal* (2022) 12:64
https://doi.org/10.1186/s43066-022-00228-6

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Outcome of Wilson's disease in Bangladeshi children: a tertiary center experience

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Abstract

Background: Wilson disease (WD) is an inherited disorder of copper metabolism commonly involving the liver, cornea, and brain. Its incidence is increasing day by day worldwide. Early diagnosis and prompt treatment are the key for best outcome.

Material and methods: A cross-sectional descriptive study was done from January 2014 to December 2019. Sixty children of both genders between 3 and 18 years were diagnosed by clinical and laboratory profile meeting selected criteria.

Results: Mean age was 8.42 ± 2.6 years and male female ratio was 1.5:1. Consanguinity of marriage was found in 38.3% cases. Seventy percent of cases were hepatic, 16.7% were neuropsychiatric, 5.0% were hepatic with neuropsychiatric, and 8.3% cases were manifested asymptomatically. Asymptomatic and hepatic WD were reported between 3 and 10 years and most of the neuropsychiatric and hepatic with neuropsychiatric manifested after 10 years of age. More than 50% cases improved, a little more than 20% children died, 18.4% were unchanged and 6.6% were hepatic added neuropsychiatric manifestations. Most of the asymptomatic (100%) and hepatic (61.9%) cases improved. High mortality was found with 76.9% cases of acute liver failure (ALF), 7.7% case of chronic liver disease (CLD) and 25% cases of CLD with portal hypertension (CLD and PH). Most of the neuropsychiatric cases (90.0%), and approximately two-third (66.6%) of hepatic with neuropsychiatric cases remained unchanged. Neuropsychiatric manifestations were added in 15.4% cases of CLD and 25% cases of CLD with PH patient. The treatment was well tolerated in 66% children without any side effects. Low WBC (6.3%) and platelet count (4.3%), vomiting (6.3%), anorexia (4.3%), loss of taste (4.3%), rash (4.3%), and proteinuria (2.1%) were found in few cases.

Conclusion: Majority of the children were presented with hepatic manifestations. More than half of patients with WD treated by D-penicillamine (DP) were improved. Significant mortality was found in acute liver failure whereas neuropsychiatric presentations had persistent abnormalities. No major side effects of DP was observed in most of the cases. Early diagnosis and prompt treatment were crucial for better outcome.

Keywords: Bangladesh, Child, Wilson's disease, Hepatic presentation, Neurological presentation D-Penicillamine

Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism that reduces the secretion of copper through bile and lessens the absorption into ceruloplasmin resulting in excessive copper accretion in organs, including liver, brain and cornea [1–8]. According to the World Health Organization (WHO), the estimated global prevalence of WD ranges from 1/10,000 to 1/30,000 [9–12]. In India, WD accounts for 7.6–19.7% of pediatric liver diseases in tertiary hepatobiliary centers [9, 13]. A recent study in Bangladesh reported 43.7% cases of WD among 71 pediatric liver disease cases [14]. The clinical manifestation of WD varies greatly depending

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on several factors. Before the age of 10 years, majority of WD patients have hepatic symptoms and a few have neuropsychiatric symptoms; between the ages of 10 and 18 years, patients mostly have hepatic and neuropsychiatric symptoms whereas, after the age of 18 years, most of the patients have neuropsychiatric symptoms and the others suffer from liver diseases [8, 9, 15]. A positive family history or a history of sibling death in a patient with symptoms indicative of WD increases the likelihood of a WD diagnosis. The most common test for WD is a combination of serum ceruloplasmin, KF rings, and 24-h urine copper. Although the analysis of ATP7B mutations is recommended, it is not available in Bangladesh.

The drugs used to treat WD include DP, trientine, ammonium tetrathiomolybdate (TTM), and zinc. Clinical and biochemical improvements usually occur within a year of starting the treatment, while normalization of hepatic synthetic functions might take up to 10 years [16]. Currently, Zn is used to maintain asymptomatic patients with prolonged use of DP or trientine [7, 9, 17]. Trientine (triethylenetetramine-2-hydrochloride) is a chelator that works similarly to DP but has fewer side effects. In Bangladesh, neither Trientine nor Ammonium TTM is available.

In addition to the limited resources for diagnosis and treatment of WD in Bangladesh, there is a lack of comprehensive and reliable statistics on the prevalence and outcome of WD, particularly among the pediatric population of Bangladesh. With these considerations in mind, this study was conducted on Bangladeshi children to assess the response to DP treatment, including side effects, and to determine the outcome by identifying improvement, worsening, mortality, and unchanged behavior using a variety of clinical and biochemical parameters.

Materials and methods

Study design

This study used medical records, from January 2014 to December 2019, of the department of Pediatric Gastroenterology, Hepatology & Nutrition, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh. A total of 60 admitted cases of WD aged 3 to 18 years and of either gender were included. The Ethical Review Committee of Bangladesh Shishu Hospital & Institute (No. Admin/1039/DSH/2021) evaluated and approved the study protocol. Figure 1 details the flow chart of the study:

Clinical presentation

Individual or family histories were collected in detail, especially on a history of consanguinity, sibling death, or the same type of illness. Symptoms (yellow skin, sclera, and urine, anorexia, nausea, right upper quadrant pain, progressive abdominal distension, hematemesis, malena, muscle weakness, weight loss, exhaustion and malaise, declined school performance, saliva drooling, and inability to walk, stand or sit, loss of memory, slurring of speech, behavioral problems, etc.) were documented. A thorough physical examination was done for Jaundice, Kayser Fleischer (KF) ring, sunflower cataract, hepatomegaly, splenomegaly, ascites, edema, wasting of thenar and hypothenar muscle, palmar erythema, clubbing, leuconychia, gynaecomastia, testicular atrophy, engorged superficial abdominal veins, encephalopathy, dysarthria, dystonia, rigidity, tremor, chorea, and abnormal gait.

Laboratory tests

Complete blood count (CBC), serum bilirubin, ALT (alanine transaminase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), prothrombin time (> 3 s of control was considered prolonged), INR (international normalization ratio), serum albumin, slit lamp examination of eyes, serum ceruloplasmin, and 24-h urinary copper concentration with or without penicillamine challenge test were all performed. Hepatic copper measurement (by liver biopsy) and mutation analysis were not performed because testing was not available in Bangladesh. Wilsonian patients' siblings were also studied in the same way. The presence of Kayser-Fleischer (KF) rings, a low blood ceruloplasmin concentration (20 mg/dl), an elevated urine copper content (> 100 gm/day) before or after penicillamine challenge, and/or a low blood ceruloplasmin concentration (20 mg/dl) were all utilized to diagnose WD. Penicillamine challenge tests (PCT) were used in cases when 24-h urine copper levels of 40–100 gm/day or more than 1200 gm/day were regarded to be WD. In doubtful cases, Modified Leipzig Scoring System was applied [9].

The eyes were examined by slit lamp examination from the NIO (National Institute of Opthalmology). Serum ceruloplasmin from BSMMU (Bangabandhu Sheikh Mujib Medical University) and 24 h urinary copper were tested by Bangladesh Atomic Energy Commission (BAEC). For 24 h of urinary copper estimation after the DP challenge, oral Penicillamine 500 mg (2 tablets of 250 mg) was given twice, the first dose at the beginning of urine collection and the second 12 h after the first dose. Then, urine was collected for 24 h and the sample was sent to BAEC for the test. It was done by "atomic absorption spectrophotometer" (normal range < 40 μgm/day).

Case descriptions

Since asymptomatic WD was clinically silent, it was confirmed biochemically. During family screening or routine check-ups, symptom-free patients with

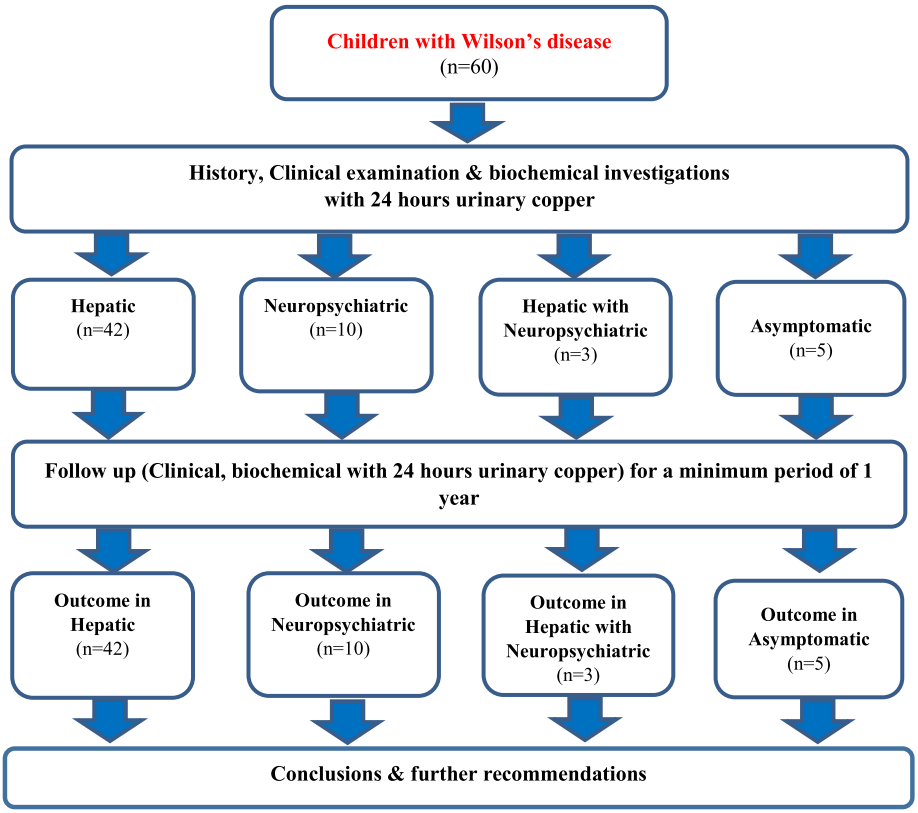

Fig. 1 Study flow chart of Wilson's disease ($n = 60$)

hypertransaminasemia and/or hepatomegaly were identified. Acute hepatitis was identified without any previous evidence of liver disease (clinically and biochemically). CLD was identified based on a long history of jaundice, the appearance of CLD stigmata, and biochemically, as well as, a low serum albumin level.

Portal hypertension was defined as hematemesis, melena, splenomegaly, and esophageal varices on upper GI endoscopy (PH). Children with ALF were described as having no indication of CLD and having biochemical evidence of acute liver injury with hepatic-based coagulopathy, according to the Pediatric Acute Liver Failure (PALF) Study Group. Parenteral vitamin K1 did not improve PT 15 s/INR to be 1.5 with characteristics of encephalopathy or PT 20 s/INR to be 2 with or without features of encephalopathy. The ALP to total serum bilirubin ratio was less than 4, and the AST to ALT ratio was larger than 2.2 [3, 8].

Neurological WD was diagnosed by regression of acquired milestones like progressive deterioration of school performances, difficulty in speech and basal ganglia lesions like athetosis, chorea, and dystonia. The neuropsychiatric presentation includes asymmetrical tremors, behavioral problems, difficulty in speaking, excessive salivation, clumsiness with the hands, and personality changes. A presence of both hepatic and neurological manifestations was considered a mixed type.

Treatments

After a final diagnosis, a child was treated with DP (Cap Artamine 250 mg, Chandra Bhagat Pharma, Mumbai) at a dose of 5 mg/kg/day followed by titration with an increment of 5 mg/kg every fortnightly to a maximum of 20 mg/kg/day. Drugs were given before meal in divided doses (after crushing granules of the capsule) along with supplementation of low copper diet, Zn, and pyridoxine. Zn was given in a dose of 25 mg per 12 h, 2 h after meal, for < 6 years, 25 mg per 8 h for 6–16 years and 50 mg per 8 h for > 16 years.

Follow-up

The clinical and biochemical parameters of the patients at the time of admission and at subsequent follow-ups were examined and compared to determine the outcome of the treatments. The side effects of DP were observed minutely throughout the year at each follow-up visit which includes clinical (pallor, fever, bleeding spots, bed side urine albumin) and lab

investigations (CBC, urine R/M/E, ALT, serum creatinine). The dose and duration of drug therapy were also recorded. After completion of a 1-year follow-up study, patients were advised to continue the drug and to come for follow-up.

Statistical analysis

SPSS 24.0 was used to perform the statistical analysis. After all subjects (60 patients) had been evaluated, the study population was separated into two major groups and analyzed independently again. The hepatic category includes all varieties of isolated hepatitis, as well as mixed and silent instances (biochemically anicteric hepatitis). Neuropsychiatric and mixed (hepatic with neuropsychiatric) disorders were included in the neurological group. Statistical measures of the data including mean, median, range, standard deviation, and percentages of different variables were reported.

Results

Basic features of the reported cases

The total number of patients included in the study was 60 with mean age of 8.42 ± 2.6 years. Hepatological presentation was found in most cases (70%) and neuropsychiatric presentation was seen in 16.7% cases. A mixed (hepatic with neuropsychiatric) presentation was observed in only 5% cases and an asymptomatic presentation was observed in 8.3% cases (Table 1).

Clinical presentations

Among hepatic presentation, 11 (22%) cases were acute hepatitis, 13 (26%) were each in ALF and CLD, 8 (16%) were CLD with PH and 5 (10%) were manifested as asymptomatically (Fig. 2).

Among neurological group, 10 (76.9.5%) cases were neuropsychiatric, 03 (23.1%) were mixed (hepatic with neuropsychiatric) (Fig. 3).

KF ring were found in 87.5% neuropsychiaytic cases. More specifically KF ring were found in 100% of the mixed cases, whereas only 42.8% cases were found with

Table 1 Age distribution of the studied children ($n = 60$)

Age in years	Hepatic *n* (%)	Neuropsychiatric *n* (%)	Hepatic with Neuropsychiatric *n* (%)	Asymptomatic ($n = 5$)%	Total ($n = 60$) (%)
3–6	3 (42.8)	0	0	4 (57.2)	**7 (11.7)**
7–10	39 (92.9)	2 (20.0)	0	1 (2.3)	**42 (70.0)**
11–14	0	5 (50.0)	2 (28.6)	0	**7 (11.7)**
15–18	0	3 (30.0)	1 (25.0)	0	**4 (6.6)**
Total	42 (70.0)	10 (16.7)	3 (5.0)	5 (8.3%)	**60 (100)**

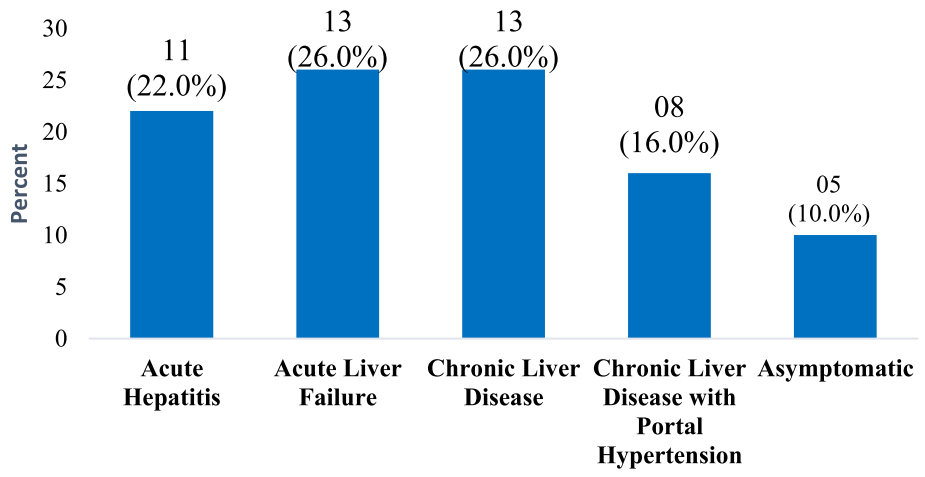

Fig. 2 Different types of hepatic presentation in the studied children ($n = 50$)

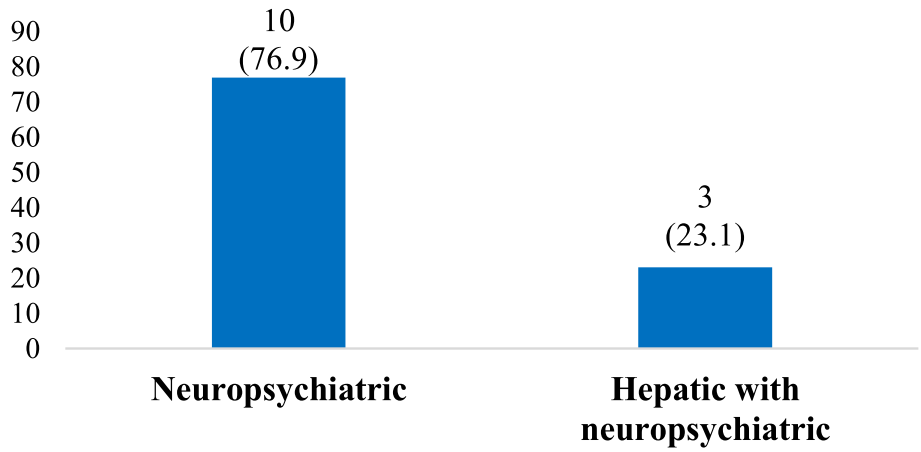

Fig. 3 Different types of neuropsychiatric presentation in the studied children ($n = 13$)

hepatological presentation. KF ring was absent in asymptomatic cases (Fig. 4).

Overall outcome

More than 50% cases improved, however, a little more than 20% children died, 18.4% were unchanged and 6.6% hepatic cases developed neuropsychiatric manifestations (Fig. 5).

Improvement was observed mainly among the hepatic and the asymptomatic cases. Among the 42 hepatic cases, more than 60% improved, a little less than 30% died and around 10% ended up with neurological manifestation. Number of neuropsychiatric and hepatic with neuropsychiatric patients were 10 and 3 respectively and the majority of them remained unchanged (Table 2).

Causes of death in the deceased patients were acute liver failure (10), chronic liver disease (1), chronic liver disease with portal HTN (1), and hepatic with neuropsychiatric (1). On the other hand, all 5 of the asymptomatic cases improved.

Outcome with hepatic presentations

Out of all hepatic cases ($n = 50$, including 3 hepatic with neurological and 5 asymptomatic cases), all the asymptomatic and acute hepatitis cases improved. Substantial improvements were observed among cases of CLD and CLD with PH. A very high mortality was found among cases of ALF. A few of CLD and CLD with portal hypertension cases ended up with added neurological manifestations (Fig. 6).

Substantial improvement was observed among hepatological WD evidenced by decreasing jaundice, anorexia, nausea, hepatomegaly and ascites (Fig. 7).

The DP therapy in hepatic WD of the present series caused gradual decrease in serum bilirubin from median initial value of 3.9 (2.1–5.3) mg/dl to a value of 1.2 (0.5–4.2) mg/dl at final follow-up. Similarly AST decreased from median admission value of 163.6 (70–225.6) IU/L to final up value of 24.5 (16–84), ALT decreased from median admission value of 141.7 (84.6-221) IU/L to final follow-up value of 17.5 (11–69) IU/L and INR decreased

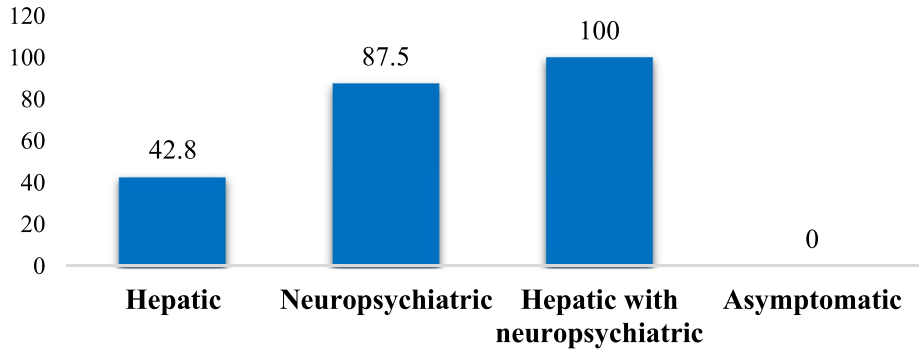

Fig. 4 KF ring in the studied children ($n = 60$)

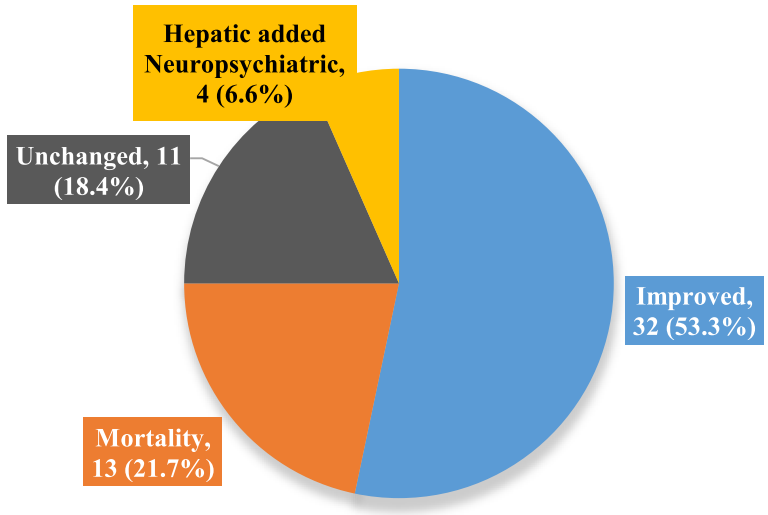

Fig. 5 Outcome of WD in the studied children ($n = 60$)

Table 2 Outcome of WD in different clinical presentation ($n = 60$)

Outcome	Improved *n* (%)	Unchanged *n* (%)	Hepatic with neuropsychiatric *n* (%)	Died *n* (%)
Hepatic ($n = 42$)	26 (61.9)	0 (0.0)	4 (9.6)	12 (28.5)
Hepatic with neuropsychiatric ($n = 3$)	0 (0.0)	2 (66.6)	0 (0.0)	1 (33.3)
Asymptomatic ($n = 5$)	5 (100.0)	00 (0.0)	0 (0.0)	0 (0.0)
Neuropsychiatric ($n = 10$)	1 (10)	9 (90.0)	0 (0.0)	0 (0.0)
Total ($n = 60$)	32 (53.3)	11 (18.4)	4 (6.6)	13 (21.7)

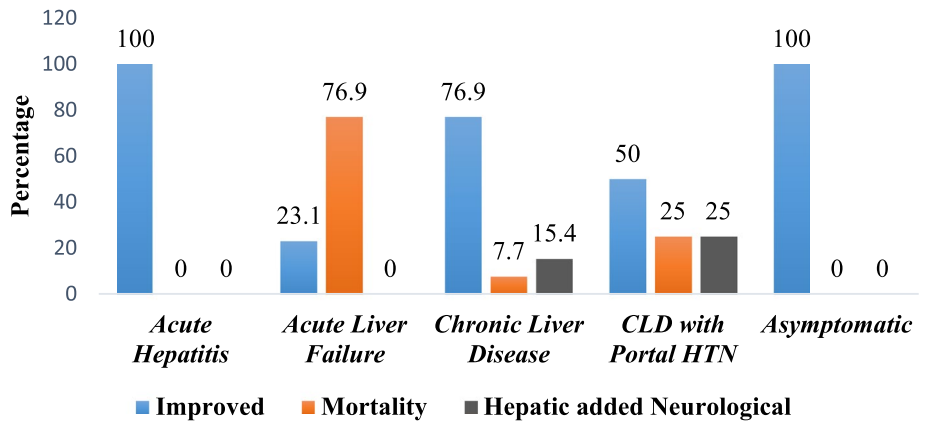

Fig. 6 Outcome of WD with different hepatic presentation ($n = 50$)

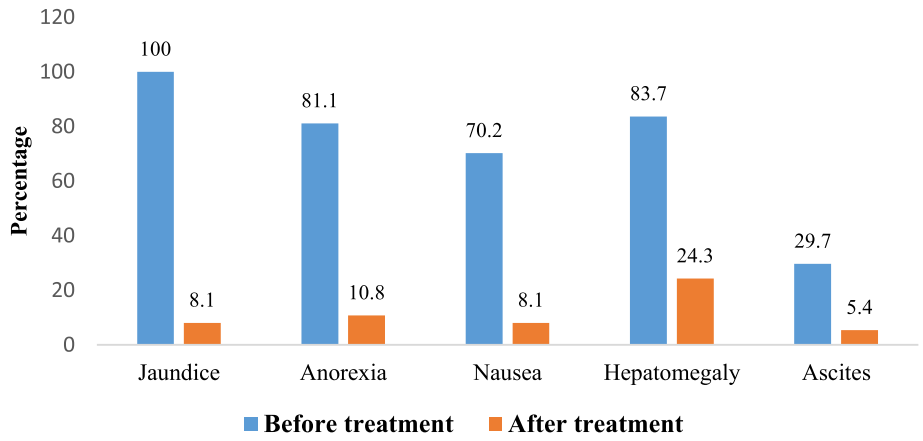

Fig. 7 Clinical improvement in hepatic WD (survived, $n = 37$)

from median admission value of 1.6 (1.5–1.8) to final follow-up value of 1.1 (0.9–1.3) (Fig. 8).

Outcome with neuropsychiatric presentations

Out of all ($n = 13$) neuropsychiatric cases, mostly ($n = 11$) remained unchanged without any improvement or mortality. Only one improvement was observed in 1 patient of neuropsychiatric manifestations and one case of hepatic with neuropsychiatric presentation was died (Fig. 9).

On the other side, dysarthria, dystonia, tremor, rigidity and drooling were persistent in neurological WD (Fig. 10).

Outcome by 24-h urinary copper

At the time of diagnosis, the average 24 h urinary copper was much lower in asymptomatic (174.9 μgm/day), pure hepatic (203.1 μgm/day) cases as compared to the mixed type (700.2 μgm/day) and neuropsychiatric (329.0 μgm/day) cases. In subsequent follow-ups, all types of WD gradually reduced the amount of copper in urine (Table 3).

Among the survived children ($n = 47$), median 24 h urinary copper was initially increasing up to 3 months with DP treatment. Then maintained the near equal level for the next 3 months (end of 6 months) and ultimately, gradually decreasing in subsequent follow-up (Fig. 11).

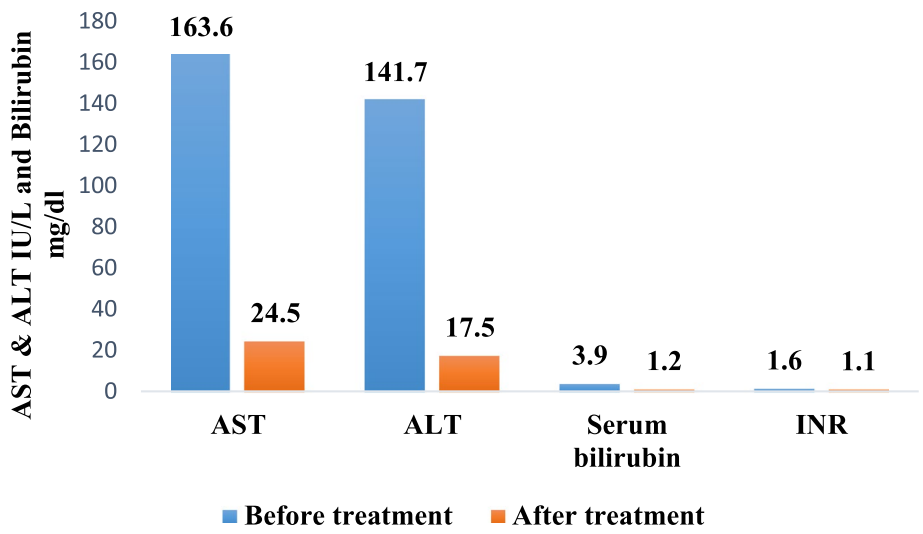

Fig. 8 Median LFT in hepatic presentation before and after treatment (survived, $n = 37$)

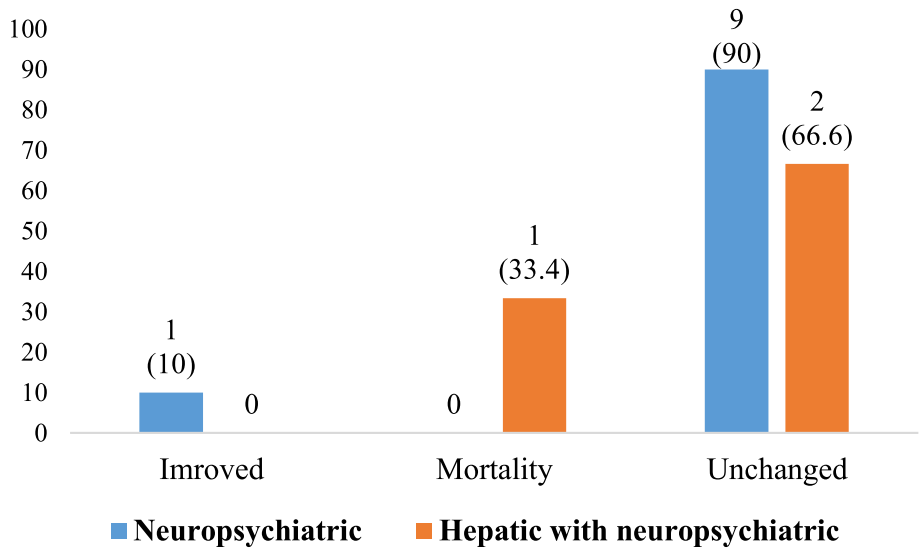

Fig. 9 Outcome of WD with different neuropsychiatric presentation ($n = 13$)

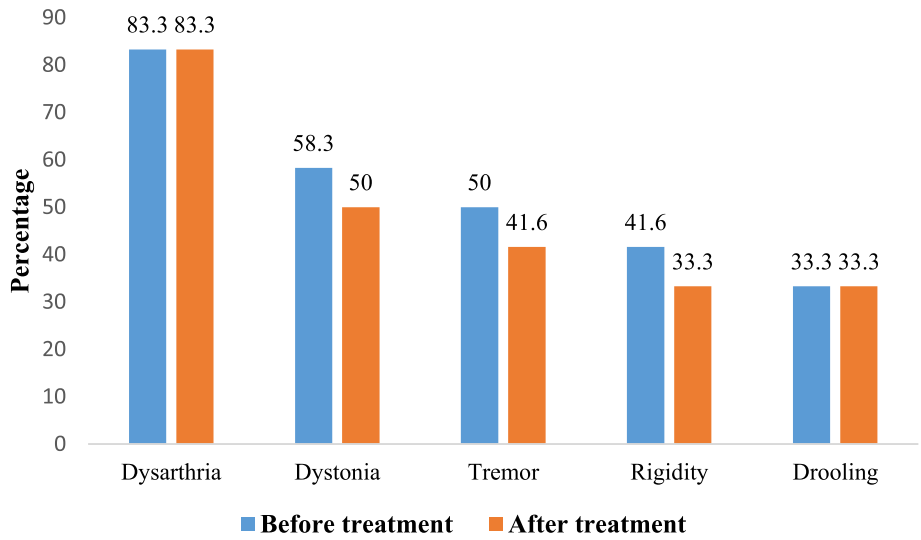

Fig. 10 Clinical improvement in neuropsychiatric WD (survived, $n = 12$)

Side effects following DP therapy

No side effects were observed in two-third of the children following DP therapy. Vomiting 3(6.3%), low WBC count 3(6.3%), low platelet count 2(4.3%), anorexia 2(4.3%), loss of taste 2(4.3%), rash 2(4.3%), diarrhea 1(2.1%), and proteinuria 1(2.1%) were observed in few cases (Fig. 12)

Discussion

In Bangladesh, liver illness is a prevalent medical concern. More and more cases of WD are being diagnosed these days, as a result of diagnostic facilities. For a favorable impact, early diagnosis and treatment are essential [18].

As mentioned earlier, DP, trientine, ammonium TTM, and zinc are some of the medications used to treat WD. Because of easy availability, low cost, and efficacy, DP was chosen. DP and Zn were utilized as first-line therapies in our study. A copper-restricted diet was recommended for all of the patients [19].

A little more than half of the cases (53.3%) improved after a year of treatment while 21.7% deteriorated within 1 month of treatment and died, primarily due to hepatic

Table 3 Mean 24 h urinary copper excretion at admission and subsequent follow-up (survived, $n = 47$)

Tests	Hepatic ($n = 30$) median (range) µgm/day	Neuropsychiatric ($n = 10$) median (range) µgm/day	Hepatic with neuropsychiatric ($n = 02$) median (range) µgm/day	Asymptomatic ($n = 05$) median (range) µgm/day
At diagnosis	**203.1** (64.0–443.0)	**329.0** (244.3–454.8)	**700.2** (433.2–889.6)	**174.9** (143.9–201.2)
1st follow-up (at 3 months)	**2341.6** (1245–3565)	**2801.2** (2393–3042)	**2884.0** (2433–3187)	**1282** (1176–1432)
2nd follow-up (at 6 months)	**2153.1** (1096–3431)	**2658.7** (2248.5–2850)	**2770.3** (2231–3099)	**1131.6** (987–1321)
3rd follow-up (at 9 months)	**1421.8** (544–2343)	**1735.5** (1338–1919.5)	**1832.0** (1488–2021)	**788.0** (654–976)
4th follow-up (at 12 months)	**981.1** (387–1675)	**1275.4** (986.5–1853)	**1412.3** (999–1671)	**478.8** (343–564)

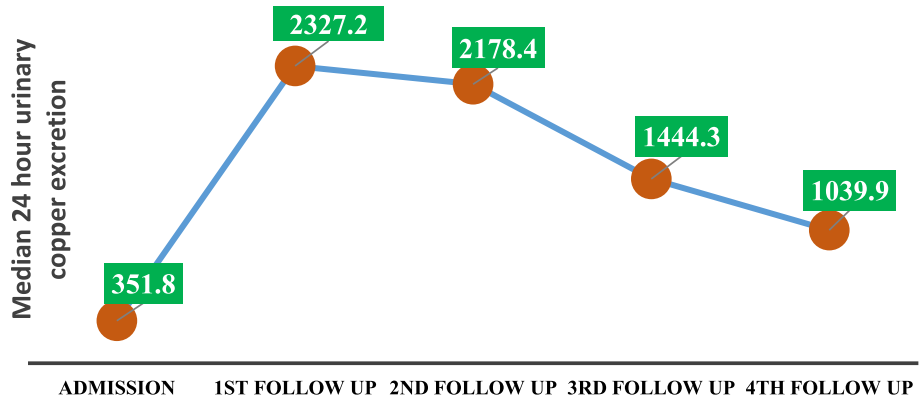

Fig. 11 Median 24 h urinary copper by line chart (survived, $n = 47$)

decompensation. An earlier study on Bangladesh on 16 cases also reported a similar result on improvement of 43.7%, and death of 18.7% of WD cases [20]. On the other hand, several studies evidenced the improvement in the majority of the cases treated with [21–24].

Four hepatic cases of our study ended with added neurological manifestations. Some patients developed severe neurological symptoms although their hepatic condition improved. However, there is no marked correlation of the course of neurological and hepatic symptoms while under treatment [25]. We speculate that the pathophysiological disturbances leading to organ damage in Wilson's disease are not completely the same for the liver and the brain. Here, differential expression or polymorphisms of other genes related to copper and oxidative stress may influence organ susceptibility [1].

Out of all hepatic ($n = 50$) cases in this study, all the cases of asymptomatic and acute hepatitis improved. The findings are supported by some earlier studies, which also observed an improvement of aymptomatic and acute patients after effective therapy without any worsening or side effects [19, 20, 26].

Our study observed a high mortality of cases of ALF, and also some mortality of cases of CLD and CLD with PH. Saha et al. [20] also reported that 33.3% of the children died with hepatic WD, especially with ALF. However, as there is no option for liver transplantation in our country, for those who were non-responding to DP treatment, death was the ultimate result.

In the present study, significant clinical improvement of hepatic WD evidence was observed by decreasing jaundice, anorexia, nausea, hepatomegaly and ascites. In neuropsychiatric Wilson, following treatment with DP, some symptoms and signs improved gradually but that was not, at all, satisfactory. The unsatisfactory neuropsychiatric improvement was probably related to the

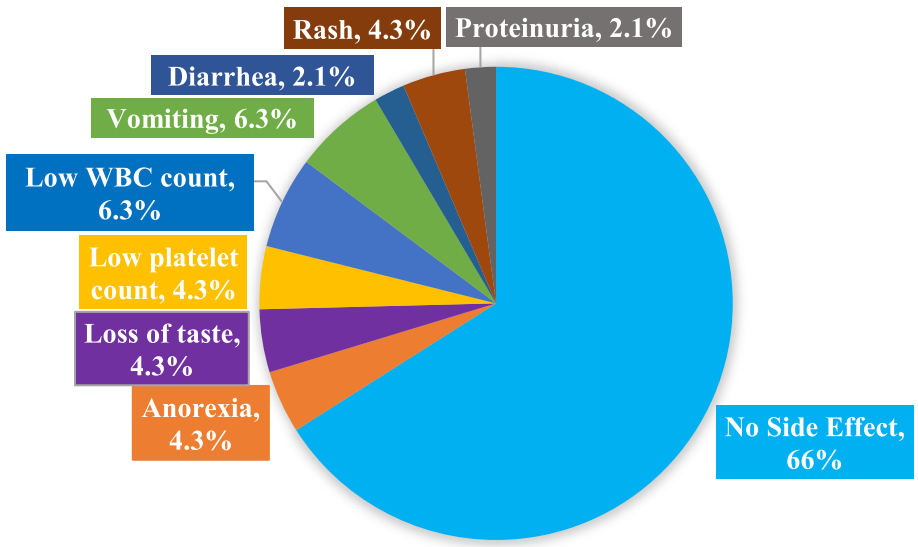

Fig. 12 Adverse effect of penicillamine (survived, $n = 47$)

irreversible changes in basal ganglia as part of pathogenesis. These findings are similar as Saha et al. [20], Kini et al. [19], Kalra et al. [22], and Ala et al. [27].

Our study finds that the DP therapy in hepatic WD of the present series caused a gradual decrease in serum bilirubin. Similarly, AST and INR decreased from the median admission value to the median value of the final follow-up. Earlier studies showed that improvement in the synthetic function of the liver and clinical signs like jaundice occur during the first 2 to 6 months of treatment, but further recovery can occur during the first year of treatment [19, 20, 28, 29, 37]. Early administration of DP in patients with severe hepatic insufficiency might be associated with survival without liver transplantation [24, 27].

Following the treatment with DP, the 24 h excretion of copper increases gradually at the initial phase, reaches a steady state thereafter until it begins to fall again with the exhaustion of abnormally deposited copper [26]. An improvement in the clinical features following 2–3 months of treatment, continuing over a period of 1–2 years along with an increase in 24 h urinary copper has also been reported in the literature [29–31]. The majority of the patients of this study achieved adequate cupriuresis at 3 months following DP that was maintained till 6 months, thereafter started declining. None of the patients in the present study achieved maintenance cupriuresis (200–500 μgm/day) at 1-year follow-up, documenting that more time might be required to achieve that state.

Studies suggested that, treatment should be started with low dose DP [32] and although DP is an effective chelator although associated with several side effects where the major side effect of the treatment was the initial neurological symptoms [9, 16, 25, 32]. The mechanism of this initial worsening may be the aggressive mobilization of copper by DP leading to further elevation of the brain copper temporarily [17]. Fortunately, no major side effects were observed in 31(66%) of the studied children following DP therapy in this study. However, a few children developed some recognized side effects [30] including neurological symptoms like dystonia, dysarthria and abnormal gait while on treatment, probably due to very small initial dose of DP followed by a gradual increase in the dose up to optimum level. Might be noted that some other studies did not report deterioration or side effects following DP therapy [26]. However, sample size of all these studies are very small and hence should be carefully generalized.

Limitations of the study

First, it was a single center study with a limited sample size. Second, hepatic copper estimation and mutation analysis could not be done due to unavailability of the diagnostic procedures in the country. Third, treatment options were limited due to unavailability of specific drugs.

Conclusions

WD is a treatable metabolic cause of liver disease. The majority of children were presented with hepatic manifestations. More than half of patients with WD treated by DP improved. Most of the asymptomatic, acute hepatitis,

and chronic liver disease without portal hypertension cases improved. Significant mortality was found in acute liver failure whereas neuropsychiatric presentations had persistent abnormalities. All the clinical and biochemical markers of WD improved gradually. Adequate cupriuresis occurred at 3 months; none achieved maintenance cupriuresis till 1 year after administration of the drug. No major side effects of DP were observed in most of the cases. Early diagnosis and prompt treatment were crucial for a better outcome.

Abbreviations

WD: Wilson's disease; AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; INASL: Indian National Association for the Study of Liver; WHO: World Health Organization; CLD: Chronic liver disease; PH: Portal hypertension; PALF: Pediatric acute liver failure; KF: Kayser-Fleischer; CBC: Complete blood count; ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; PT: Protrombine time; INR: International normalized ratio; PCT: Penicillamine challenge test; MRI: Magnetic resonance imaging; NIO: National Institute of Opthalmology; BSMMU: Bangabandhu Sheikh Mujib Medical University; BAEC: Bangladesh Atomic Energy Commission; DP: D-Penicillamine; TTM: Tetrathiomolybdate; LT: Liver transplantation.

Acknowledgements

The authors are thankful to all the participants and institute.

Authors' contributions

The author(s) read and approved the final manuscript.

Funding

The study is self-funded.

Availability of data and materials

The dataset used in the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical clearance was taken from ethical review committee of Bangladesh Shishu Hospital & Institute (No. Admin/1039/DSH/2021). Written informed consents were obtained from parents of individual participants at the time of admission.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Received: 12 April 2022 Accepted: 8 November 2022
Published online: 18 November 2022

References

1. Roberts EA, Schilsky ML (2008) AASLD practice guidelines: a practice guideline on Wilson disease. Hepatology. 47:2094–2108
2. Gungor S, Selimoglu MA, Varol FL, Gungor S (2018) Pediatric Wilson's disease: findings indifferen resentations: a cross-sectional study. Sao Paulo Med J 136(4):304–309
3. Li N, Krishna S, Hinton A, Conwell D, Mumtaz K. Characteristics and outcome of hospitalized patients with Wilson's disease in the United States: a national survey. Annals of Hepatology2021; 25: 100362; https://doi.org/10.1016/j.aohep.2021.100362
4. Tao TY, Gitlin JD. Hepatic copper metabolism: insights from genetic disease. Hepatology. 2003;37(6):1241-1247. PMID: 12773998; doi:https://doi.org/10.1053/jhep.2003.50281.
5. Lutsenko S, Petris MJ (2003) Function and regulation of the mammalian copper-transporting ATPases: insights from biochemical and cell biological approaches. J Membr Biol. 191(1):1–12. PMID: 12532272;. https://doi.org/10.1007/s00232-002-1040-6
6. Ferenci P (2006) Regional distribution of mutations of the ATP7B gene in patients with Wilson disease: impact on genetic testing. Hum Genet. 120(2):151–159. PMID: 16791614;. https://doi.org/10.1007/s00439-006-0202-5
7. EASL Clinical Practice Guidelines (2012) Wilson's disease European association for the study of the liver. J Hepatol. 56:671–685
8. Rukunuzzaman M (2015) Wilson's disease in Bangladeshi children: Analysis of 100 cases. Pediatr Gastroenterol Hepatol Nutr 18(2):121–127
9. Nagral A, Sarma MS, Matthai J, Kukkle PL, Devarbhavi H, Sinha S et al (2019) Wilson's Disease: Clinical Practice Guidelines of the Indian National Association for Study of the Liver, the Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition, and the Movement Disorders Society of India. J CLIN EXP HEPATOL 9:74–98
10. Socha P, Janczyk W, Dhawan A et al (2018) Wilson's disease in children: a position paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology And Nutrition. J Pediatr Gastroenterol Nutr. 66:334–344
11. Liu J, Luan J, Zhou X, Cui Y, Han J (2017; Nov) Epidemiology, diagnosis, and treatment of Wilson's disease. Intractable Rare Dis Res. 6(4):249–255
12. Lo C, Bandmann O (2017) Epidemiology and introduction to the clinical presentation of Wilson disease. Handb Clin Neurol. 142:7–17
13. Taly AB, Prashanth LK, Sinha S (2009) Wilson's disease: an indian perspective. Neurol India. 57:528–540
14. Bayes F, Karim ASMB, Helaly L, Bayes F, Rukunuzzaman MD, Ahmed S et al (2014) Spectrum of hepatic presentation of Wilson's disease in children attending a tertiary care centre of Dhaka City. Bangladesh J Child Health 38(2):79–85
15. Sokol RJ, O'connor JA (2007) Copper metabolism and copper storage disorders. In: Suchy FJ, Sokol RJ, Balistreri WF (eds) Liver disease in children, 3rd edn. Cambridge University Press, NewYork, pp 626–652
16. Noureen N, Rana MT (2011) Neurological Wilson disease in children: A three year experience from Multan. J Pak Med Assoc 61(8):743–748
17. Kleine RT, Mendes R, Pugliese R, Miura I, Danesi V, Porta G (2012) Wilson's disease: An analysis of Brazilian children. CLINICS 67(3):231–235
18. Kumagi T, Horiike N, Michitaka K, Hasebe A, Kawai K, Tokumoto Y et al (2004) Recent Clinical feature of Wilson's disease with hepatic presentation. J Gastroenterol 39:1165–1169
19. Kini S, Handattu K, Konda KC, Bhat R (2019) Clinical profile and outcome of Wilson disease in Indian children: a single centre study. Sri Lanka J Child Health 48(2):134–139
20. Saha NC, Sultana A, Mollah MAH, Begum T, Rahman AKMM, Fatmi LE (2009) Therapeutic response of Wilson's disease to D-Penicillamine in Pediatric population: a one year follow up study. J Dhaka Med Coll 18(1):37–43
21. Socio SDA, Ferreira AR, Fagundes EDT, Roquete MLV, Pimenta JR, Campos LDF et al (2010) Wilson's disease in children and adolescents:diagnosis and treatment. Rev Paul Pediatr 28(2):134–140
22. Kalra V, Khurana D, Mittal R (2000) Wilson's disease- early onset and lessons from a pediatric cohort in India. Indian Pediatr. 37:595–601
23. Shakya S, Agarwal JP (2004) Clinical profile of Wilson's disease. Nepal J Neurosci. 1:120–122
24. Durand F, Bernuau J, Giostra E et al (2001) Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of Dpenicillamine. Gut. 48:849–852
25. Merle U, Schaefer M, Ferenci P, Stremmel W (2007) Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. Gut 56:115–120
26. Kalita J, Kumar V, Chandra S, Kumar B (2014) Worsening of Wilson disease following penicillamine therapy. Eur Neurol 71:126–131
27. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML (2007) Wilson's disease. Lancet 369:397–408

28. Roberts EA, Schilsky ML (2003) AASLD practice guidelines: a practice guideline on Wilson disease. Hepatology. 37:1475–1492
29. Bertrand MVC, Degenhart HJ, Visser HKA, Sinaasappel M, Bouquet J (1985) Oral zinc sulphate for Wilson's disease. Arch Dis Child. 60:656–659
30. Das SK, Ray K (2006) Wilson's disease: an update. Nat Clin Prac Neurol. 2:482–493
31. Karim MB, Rahman MM, Islam MS (2007) Wilson's disease with hepatic presentation in childhood. Mymensing Med J 16:29–32
32. Sinha S, Jha DK, Sinha KK (2001) Wilson's disease Eastern India. J Assoc Physicians India 49:881–885

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