ORIGINAL RESEARCH

To investigate the prognostic factors in patients who present with severe neurologic forms of Wilson disease

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Received: 10 June, 2023 Accepted: 13 July, 2023

ABSTRACT

Aim: To investigate the prognostic factors in patients who present with severe neurologic forms of Wilson disease. **Material and methods:** The investigation was carried out on a substantial cohort of individuals diagnosed with Wilson's disease (WD). The diagnosis of these patients has been established through the evaluation of their clinical manifestations, the identification of KF ring via slit-lamp examination, the observation of low levels of serum copper and ceruloplasmin, and the detection of elevated 24-hour urinary copper excretion. Clinical severity and disability status were scored using the Neurological Symptom Score (NSS)1, Chu staging2 and Modified Schwab and England Activities of Daily Living (MSEADL)3 scores. **Results:** The majority of patients exhibited low levels of serum caeruloplasmin (mean 9.01 ± 2.15 mg/dl) and elevated 24-hour urinary copper (mean 281.47 ± 22.54 µg/day,), with only four patients deviating from this pattern in each case. Upon initial assessment, it was observed that none of the individuals exhibited signs of substantial hepatic failure (with a mean serum bilirubin level of 0.71 ± 0.25 mg/dl and a mean serum albumin level of 3.97 ± 0.45 g/dl). The average MRI score was calculated to be 10.83 ± 1.14. The Neurological Symptom Scale (NSS) demonstrated a significant improvement, increasing from an initial mean value of 8.99 ± 1.85 to a final mean value of 27.44 ± 1.77. Similarly, the Chu stage exhibited notable progress, with an initial mean value of 1.9 ± 0.7 increasing to a final mean value of 2.8 ± 0.8. Additionally, the Modified Self-Efficacy for Activities of Daily Living (MSEADL) score showed substantial improvement, rising from an initial mean value of 26.14 ± 3.14% to a final mean value of 96.1 ± 10.2%. **Conclusion:** We concluded that individuals afflicted with severe manifestations of Wilson's disease (WD) may experience a favorable prognosis when subjected to appropriate therapeutic interventions.

Keywords: Wilson's disease, MSEADL, Chu stage, NSS

INTRODUCTION

The neurologic symptoms associated with Wilson disease (WD) were initially observed in 1912 by Wilson, who extensively documented the clinical manifestations of 12 patients with WD. These accounts included detailed descriptions of different movement disorders, drooling, dysarthria, and psychiatric symptoms [1]. The disease was originally designated as "hepatolenticular degeneration". Subsequently, it was elucidated that neurological symptoms are commonly preceded by liver involvement and can be averted if appropriate treatment is promptly initiated during the initial stage of the disease [2,3]. At the time of diagnosis, it has been observed that approximately half of patients presenting with neurologic symptoms also exhibit liver cirrhosis. The presence of neurologic symptoms in patients with Wilson's disease (WD) without any liver involvement remains uncertain [4]. Typically, the initial manifestations of Wilson's disease primarily manifest in the hepatic system. Subsequent to the progression of an untreated medical condition, particularly in instances of inadequate adherence to anti-copper treatment or the failure of said treatment, neurological and other symptoms associated with Wilson's disease typically manifest. Neurological symptoms observed in Wilson's disease (WD) are commonly regarded as indicators of a more progressed stage of the disease. These symptoms typically manifest in patients who have been misdiagnosed with liver disease or in cases where the hepatic stage of the disease is clinically asymptomatic

[5]. The term "neuro-WD" was coined in order to highlight the importance of neurological symptoms and their predominant impact on disability among certain patients with Wilson's disease (WD). While the primary focus of this paper pertains to neurologic symptoms, it is crucial to acknowledge that brain damage in Wilson's disease often results in concurrent psychiatric impairment [6].

Pathological alterations in Wilson's disease (WD) are commonly observed within the central gray matter nuclei and white matter tracts located in the brainstem. The precise etiology behind the heightened vulnerability of these specific brain regions to the toxic effects of copper remains unclear [7,8]. From a macroscopic perspective, it is observed that the putamen, a brain structure, exhibits significant abnormalities, often characterized by a reduction in size, a soft texture, and a discoloration ranging from brown to yellow. In instances of significant severity, putaminal necrosis may be observed, characterized by the presence of iron-laden macrophages surrounding the necrotic cavity [9]. Cavitation has been observed to occur sporadically in regions such as the thalamus, dentate nucleus, and white matter. The prevalence of the latter condition was higher prior to the development of anti-copper treatment, and its occurrence in treated patients is now infrequent and sparsely documented [10].

MATERIAL AND METHODS

The investigation was carried out on a substantial cohort of individuals diagnosed with Wilson's disease (WD). The diagnosis of these patients has been established through the evaluation of their clinical manifestations, the identification of KF ring via slit-lamp examination, the observation of low levels of serum copper and ceruloplasmin, and the detection of elevated 24-hour urinary copper excretion. Clinical severity and disability status were scored using the Neurological Symptom Score (NSS)1, Chu staging2 and Modified Schwab and England Activities of Daily Living (MSEADL)3 scores.

The present study encompassed a sample size of 100 individuals. Patients were classified as having severe disease if, during the initial evaluation, they obtained a score of ≤50% on the MSEADL score or were assigned a Chu stage of 3, or met both criteria. A total of 13 patients met the specified criteria, with 5 patients classified as being in Chu stage 2. However, it is worth noting that despite their Chu stage 2 classification, these patients exhibited a score on the MSEADL assessment that exceeded 50%. Two patients did not satisfy both criteria during the initial evaluation; nevertheless, their condition deteriorated significantly during the subsequent follow-up period.

The data from 20 patients who satisfied the inclusion criteria were examined, encompassing clinical, biochemical, and radiological information. All of the patients included in this study underwent individualized assessments throughout the designated research timeframe. The prognostic value of several laboratory tests was assessed, including liver function tests, serum copper levels, serum caeruloplasmin levels, 24-hour urinary copper levels, renal function tests, haemoglobin levels, total leukocyte counts, and platelet counts. Information pertaining to drug adherence was also recorded. During the subsequent assessment, it was observed that 9 patients experienced progressive deterioration, which will be referred to as group A. On the other hand, 11 patients, referred to as group B, demonstrated consistent improvement and achieved a score of greater than 50% on the Modified Self-Efficacy for Activities of Daily Living scale (MSEADL). All of the patients included in the study were administered de-coppering agents such as penicillamine and zinc, along with symptomatic therapy as required.

During the initial assessment, MRI scans were performed on all of the patients. The study observed the anatomical distribution of abnormalities and assigned grades according to the severity of changes in signal intensity of focal lesions and any accompanying atrophy. The grading scale ranged from 0 (indicating no abnormality) to 3 (indicating change in signal intensity with severe atrophy). The structures that were evaluated for the purpose of grading encompassed the caudate, putamen, internal capsule, thalamus, midbrain, pons, medulla, cerebellum, as well as white matter and cortical alterations. The grading system yielded a composite score ranging from 0 to 30, where a score of zero denoted a normal scan and a score of 30 indicated the presence of severe changes. Furthermore, apart from the evaluation of the websites, the study also took into consideration the level of engagement and distinct characteristics such as the representation of the giant panda, central pontine myelinolysis, and pallidal hypointensity.

The statistical analysis was conducted using SPSS version 25.0 software. The statistical analysis employed in this study involved the utilization of the Student's t-test to compare the clinical, biochemical, and radiological parameters between group A and group B. The significance level for the data was set at $p \leq 0.05$.

RESULTS

In a cohort of 100 individuals undergoing regular medical monitoring, consisting of 72 males and 28 females, it was observed that 44 patients had parental consanguinity, while 23 patients had a documented family history. In 13 families, there was a minimum of one fatality that was attributed to WD. None of the aforementioned relatives had undergone any form of medical intervention. All patients were administered standard de-coppering agents, such as penicillamine and zinc sulphate, along with additional supportive care. A total of 20 patients presented with severe neurological manifestations of Wilson's disease (WD). A comparison was conducted between the profiles of

20 patients meeting the criteria for severe neurological Wilson's disease (WD) and the remaining 80 patients who did not meet these criteria. This comparison encompassed the entire duration of their medical journey, from the initial evaluation to the final follow-up. No statistically significant differences were observed between the two groups in terms of gender, age at onset and diagnosis, delay in diagnosis, consanguinity, family history of WD, and biochemical profile during the initial evaluation.

Table 1 basic profile of the patients

	Severe form=20		**Non Severe form =80**		**P Value**
Gender	Number	Percentage	Number	Percentage	0.21
Male	14	70	58	72.5	
Female	6	30	22	27.5	
Age	12.41±2.52		15.25±2.85		
Family history	7	35	16	20	0.32
Consanguineous parentage	12	60	32	40	0.07
Deaths due to WD in family	5	25	8	10	0.02
Serum copper (µg/dl)	60.41 ± 5.47		74.18 ± 6.11		0.25
Serum caeruloplasmin (mg/dl)	9.01 ± 2.15		7.71 ± 2.16		0.47
24-h urinary copper (µg/day)	281.47 ± 22.54		462.58 ± 25.58		0.51

Table 2. NSS, Chu, MSEADL and MRI score

	Severe form=20	**Non Severe form =80**	
NSS (0–46)	27.11 ± 2.15	8.99 ± 1.85	0.001
Chu stage (1–3)	2.8 ± 0.4	1.9 ± 0.7	0.001
MSEADL (0–100%)	25.01 ± 3.25	83.12 ± 5.47	0.001
MRI scores (0–30)	10.83 ± 1.14	5.58 ± 1.47	0.001

Out of the cohort of 20 individuals presenting with a severe neurological phenotype of Wilson's disease (WD), 14 were identified as male while the remaining 6 were identified as female. The average age at which symptoms first appeared in the subjects was 12.11±2.47 years. The administration of de-coppering therapy was frequently postponed, with an average time lapse of 1.8 ± 0.54 years from the initial onset. A total of 10 patients exhibited the presence of parental consanguinity. A total of seven patients exhibited a familial predisposition to Wilson's disease, with each of these seven families reporting at least one recorded fatality associated with the disease.

Table 3 Comparison of parameter between patients with poor outcome (group A) and good outcome (group B)

	Poor outcome		**Good outcome**		**P Value**
Gender	Number	Percentage	Number	Percentage	0.21
Male	7	77.78	7	63.64	
Female	2	22.22	4	36.36	
Age	12.11±2.47		15.12±2.54		
Family history	2	22.22	5	45.45	0.32
Consanguineous parentage	4	44.45	6	54.55	0.07
Deaths due to WD in family	2	22.22	4	36.36	0.02
Serum copper (µg/dl)	50.74 ± 4.27		64.47 ± 4.11		0.36
Serum caeruloplasmin (mg/dl)	8.14 ± 1.25		7.21 ± 1.19		0.41
24-h urinary copper (µg/day)	258.74 ± 12.74		431.78 ± 12.78		0.29

Table 4. NSS, Chu, MSEADL and MRI score

	Poor outcome	Good outcome	P Value
NSS (0–46)	27.49 ± 2.69	27.44 ± 1.77	0.001
Chu stage (1–3)	2.9 ± 0.5	2.8 ± 0.8	0.001
MSEADL (0–100%)	25.45 ± 2.25	26.14 ± 3.14	0.001
MRI scores (0–30)	10.91 ± 1.19	10.88 ± 1.41	0.001

The average scores for disease severity during the initial evaluation were as follows: for NSS, the mean score was 27.11 with a standard deviation of 2.15; for Chu stage, the mean score was 2.81 with a standard deviation of 0.4; and for MSEADL, the mean score was 25.01 with a standard deviation of 3.25%. The majority of patients exhibited low levels of serum caeruloplasmin (mean 9.01 ± 2.15 mg/dl, N>15 mg/dl) and elevated 24-hour urinary copper (mean 281.47 ± 22.54 μg/day, N<70 μg/day), with only four patients deviating from this pattern in each case. Upon initial assessment, it was observed that none of the individuals exhibited signs of substantial hepatic failure (with a mean serum bilirubin level of 0.71 ± 0.25 mg/dl and a mean serum albumin level of 3.97 ± 0.45 g/dl). The average MRI score was calculated to be 10.83 ± 1.14.

During the study period, it was observed that there was no notable decline in health or mortality among the cohort of 80 patients who did not meet the established criteria for severe Wilson's disease. The clinical severity score exhibited a general amelioration throughout the duration of the follow-up period.

The Neurological Symptom Scale (NSS) demonstrated a significant improvement, increasing from an initial mean value of 8.99 ± 1.85 to a final mean value of 27.44 ± 1.77. Similarly, the Chu stage exhibited notable progress, with an initial mean value of 1.9 ± 0.7 increasing to a final mean value of 2.8 ± 0.8. Additionally, the Modified Self-Efficacy for Activities of Daily Living (MSEADL) score showed substantial improvement, rising from an initial mean value of 26.14 ± 3.14% to a final mean value of 96.1 ± 10.2%. The average scores for disease severity during the follow-up evaluation were as follows: NSS 27.49 ± 2.69, Chu stage 2.9 ± 0.5, and MSEADL 25.45 ± 2.25. A total of 9 patients, referred to as group A, experienced progressive deterioration or did not exhibit any therapeutic response. Conversely, 11 patients, referred to as group B, demonstrated notable improvements in their clinical status and disability scores. There were no significant differences observed in the baseline demographic, clinical, laboratory features, and MRI scores between the groups during the initial evaluation and follow-up period (Table 3 and 4).

DISCUSSION

During the early 20th century, individuals diagnosed with Wilson's disease (WD) experienced an unrelenting and progressive clinical course, leading to premature mortality. The exploration of the connection between copper and its impact on health, initiated by Cumings, prompted the investigation into therapeutic approaches aimed at reducing copper levels [11]. The clinical prognosis of Wilson's disease (WD) has experienced significant advancements subsequent to the implementation of diverse pharmaceutical interventions, such as dimercaprol, penicillamine, trientine, zinc, and tetrathiomolybdate.The user has provided a numerical range of [12, 13]. These pharmaceutical agents decrease the burden of copper by means of chelation, which involves binding to copper within the body, or by inhibiting the process of copper absorption and subsequent deposition in the body. The timely identification of a medical condition, immediate initiation of appropriate therapy, and consistent adherence to prescribed medication are crucial factors for achieving favorable treatment outcomes. The predictability of the prognosis of Wilson's disease (WD) is not consistent across all cases, and there exists a subgroup of patients who do not exhibit a response to de-coppering agents. There is a scarcity of scholarly literature that specifically examines the prognostic aspect of Wilson's disease (WD), both in its general form and specifically in its severe manifestation.[14-16] The clinical, laboratory, and MRI features that could potentially serve as predictors of clinical outcomes were examined in a substantial cohort of individuals with Wilson's disease, with a particular focus on those presenting with predominant neuropsychiatric manifestations. The study was conducted at a tertiary care hospital.

The evaluation of the seriousness of a medical condition and its long-term consequences can be accomplished through the measurement of impairment, disability, handicap, and quality of life. The severity of the disease and its impact on the functional status of the patient were assessed using MSEADL and Chu scores. A score of 50% or less on the MSEADL scoring system signifies that the patient necessitates assistance with fifty percent of their daily tasks and encounters challenges in carrying out all activities, thereby indicating the severity of the illness. The clinical outcome was assessed by assigning grades based on the scores obtained during the initial presentation and final evaluation. A total of 20 patients fulfilled the specified criteria for the severe manifestation of Wilson's disease (WD) during their initial assessment, with 9 of them exhibiting either a lack of improvement or a progressive deterioration in their condition. The clinical characteristics and biochemical markers of the patients who did not respond to treatment and did not achieve a score of

>50% during the same follow-up period were not found to be significantly distinct from those of the 11 patients who did respond to treatment. Although there was no significant difference in the overall MRI severity scores between the two groups, it was observed that group A exhibited more extensive white-matter changes.

There is a dearth of scholarly literature that specifically addresses the prognosis and outcome of individuals with severe neurological manifestations of Wilson's disease (WD). Nevertheless, there exists a limited body of research examining the clinical outcome and prognosis of Wilson's disease (WD). In a cohort consisting of 100 patients, a majority of 80 individuals with a less severe manifestation of the ailment, along with 11 out of 20 patients exhibiting a more severe neurological presentation, demonstrated notable and statistically significant progress upon undergoing de-coppering therapy throughout the course of their follow-up. In a study conducted by Walshe, a total of 137 patients who received intensive treatment were examined. Within this cohort, it was observed that 35 patients exhibited a suboptimal therapeutic response. However, no discernible clinical or biochemical prognostic markers associated with this response were identified.14]. In their study, Nazer et al. developed a prognostic index for the hepatic manifestation of Wilson's disease (WD) by utilizing serum bilirubin levels, serum aspartate transferase levels, and prothrombin time.[15] Each parameter was evaluated using a scale ranging from 0 to 4, with a score of 6 or lower indicating a favorable prognostic indicator for chelation therapy. Additionally, it was observed that the presence of jaundice and ascites was correlated with increased mortality rates. In the present study, it was observed that patients belonging to group A did not exhibit any discernible signs of hepato-cellular failure that could explain the progressive deterioration observed. Moreover, it should be noted that the prognostic index under consideration is not applicable to other variations of Wilson's disease (WD), including the specific case examined in this study, which primarily focused on neuropsychiatric symptoms.

The clinical outcome is negatively impacted by delays in diagnosis and the administration of chelating therapy.[16-19] A phenomenon characterized by the counterintuitive exacerbation of symptoms in individuals with Wilson's disease (WD) following the initiation of penicillamine treatment has been observed in a range of 10% to 50% of patients. Furthermore, a subset of these individuals may experience irreversible damage as a consequence.[20,21]. In the conducted study, it was observed that two patients experienced paradoxical deterioration subsequent to the administration of penicillamine at the prescribed dosage. The individuals in question were discontinued from the administration of penicillamine and instead received zinc sulphate as a form of treatment. Upon recommencing administration of low-dose penicillamine, no additional deterioration was observed. The adherence to medication regimens is a crucial factor in the management of medical conditions and has the potential to significantly impact clinical outcomes. There is evidence to suggest that individuals who have been prescribed medications for an extended period of time may experience a decline in their condition after even a short discontinuation of the treatment.[16,22]. In the current investigation, it was observed that patients belonging to Group A, who exhibited inadequate therapeutic response, experienced a higher frequency of treatment interruptions and were unable to achieve a positive response upon resumption of therapy. The potential prognostic significance of discontinuing treatment during a critical phase of illness cannot be ruled out.

The diverse clinical manifestations of Wilson's disease (WD) can be attributed to the presence of genetic heterogeneity. Over 200 distinct mutations have been identified in individuals diagnosed with Wilson's disease, which potentially play a role in the diversity of clinical manifestations observed.[23-26]

CONCLUSION

We concluded that individuals afflicted with severe manifestations of Wilson's disease (WD) may experience a favorable prognosis when subjected to appropriate therapeutic interventions. However, it is important to note that a subset of patients within this population may exhibit an inadequate response to treatment or even experience a deterioration of their condition. The presence of significant white matter alterations observed on magnetic resonance imaging (MRI) may offer insight into the unfavorable prognosis. The implementation of early diagnosis, timely initiation of de-coppering therapy, gradual escalation of penicillamine dosage to prevent paradoxical deterioration, and patient adherence to treatment may contribute to a more favorable prognosis.

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