Journal of Bangladesh College of Physicians and Surgeons
Vol. 42, No. 3, July 2024

Clinical Profile of Wilson Disease with Neurological Presentations: A Cross Sectional Study in Bangladesh Perspective

K FATEMA[a], MM RAHMAN[b], MM HOSSAIN[c], F BEGUM[d], KA ISLAM[e], S AKHTER[f]

Abstract:

Objective: *Wilson Disease (WD) of neurological presentation is rare in pediatric population . Very limited study has been done in this disorder particularly from Bangladesh. This study was done to describe clinical profile of children with Wilson Disease with neurological presentation.*

Methods: *This cohort study was conducted in the Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), from July 2018 to July 2021. Children under 18 years of age having either neurological or combined hepatic and neurological features of WD were included.*

Results: *Total 74 patients were taken as study case. A male predominance was observed. Age of presentation was comparatively late in neuro-hepatic group. Jaundice and cirrhosis of liver was observed in more than two third cases of neuro-hepatic group. Most of the patients of both group presented with deterioration of school performance (100% and 88.89%, respectively), dystonia (95% and 75.63%, respectively), drooling (85% and 75.93%, respectively), altered activity of daily living (85% and 77.78%, respectively), dysphasia (95% and 81.48%, respectively). Patients with neuro-hepatic manifestations had significantly lower serum ceruloplasmin and serum albumin while that of urinary total copper excretion was significantly higher in this group. In MRI of brain, most affected parts were putamen, head of caudate nucleus and thalamus.*

Conclusion: *The most important clinical features were school performance deterioration, dystonia, impaired daily activity and jaundice. Patients with neuro-hepatic features had lower serum ceruloplasmin and higher urinary total copper. In MRI, most affected part was putamen, thalamus and head of caudate nucleus. Most patients showed some improvement or remained stable after treatment.*

Keywords: *Wilson Disease, Neurological, Biochemical, Neuro-Radiological*

(J Bangladesh Coll Phys Surg 2024; 42: 265-272)
https://doi.org/10.3329/jbcps.v42i3.74189

a. Prof. Kanij Fatema, Professor, Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

b. Prof. Md Mizanur Rahman, Professor, Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

c. Dr. Mohammad Monir Hossain, Assistant Professor, Department of Paediatric Neurology, National Institute of Neuroscience and Hospital, Dhaka, Bangladesh.

d. Dr. Fahmida Begum, Associate Professor, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University.

e. Dr. Kazi Ashraful Islam, Assistant Professor, Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University.

f. Dr. Shaheen Akhter, Professor, Department of Pediatric Neurology, Director, Institute of Paediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University Dhaka, Bangladesh.

Address of Correspondence: Dr. Kanij Fatema, Professor, Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. mailmonami@gmail.com. Cell: +8801713097751. Orchid ID: 0000-0002-2465-053X.

Received: 27 January 2024 **Accepted:** 28 April 2024

Introduction:

Wilson disease (WD) is a rare autosomal recessive disorder caused by mutation of ATP7B gene which is responsible for copper metabolism. As a result there is accumulation of copper in different part of body namely liver, brain, cornea causing copper toxicosis. Hepatic, neuropsychiatric and combined hepatic and neuropsychiatric are various phenotypes of WD.[1,2]

Pediatric WD are predominantly hepatic. Neuropsychiatric WD in childhood is a rare and underestimated entity. 1 Although typically initially hepatic manifestation precedes the neurological manifestations, sometimes hepatic features are absent and creates diagnostic dilemma. 2 Moreover, it is unclear why some patients develop hepatic features while other develops neurological or combined features.[3]Patients with neurological WD usually present with movement disorders. The common features are dysarthria, dysphagia, ataxia, dystonia, chreoathetosis, tremor etc. Psychiatric disorders observed here are emotional

lability, depression, hyperactivity disorder, inattention, psychosis, poor school performance etc.[4,5,6]6.

Abbassi N, Bourrahouat A, Bedoya EC, Belmalih A, El Hanafi FZ, Bost M, Sedki A, Lachaux A. Epidemiology, clinical features, and mortality rate of Wilson disease in Moroccan children: A pediatric case series. Arch Pediatr. 2022 Aug;29(6):453-458.

Patients with WD require lifelong management and meticulous follow up. Objective assessment is thus very essential for follow up the patients.[7]

Very limited studies have been done till date on pediatric WD. This study thus has been done to describe the clinical features, biochemical features, neuro-radiological features and treatment modalities of pediatric WD.

Methodology:

This was a cross sectional study undertaken in Department of Pediatric Neurology , Institute of Pediatric Neurodisorder (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU). This study was done from July 2018 to July 2021. The patients who were diagnosed as Wilson disease, either only neurological or neurological along with hepatic manifestations were included. Patients with only hepatic manifestations were excluded from the study. Prior to the start of the work, the permission from the institutional ethics committee was taken. Informed written consent from all the patients was obtained.

Study subject: Children less than 18 years of age were taken as study subject. Most of the patients were referred to this tertiary care center for proper evaluation and management. WD was diagnosed after taking detailed history, physical examination and targeted investigations. The diagnostic criteria used to establish the diagnosis were, i) the presence of Kayser-Fleischer rings,ii) a low serum caeruloplasmin concentration (less than 0.20 g/l), and a raised 24 hour urine copper excretion (Any 2 of the above).[8]

In every patient demographic and clinical characteristics were recorded. Detailed treatment history was also recorded. A formal ophthalmological evaluation was done to detect KF ring and sunflower cataract. Biochemical profile was done in every patient , the tests done were as follows: complete blood count, peripheral blood film, serum SGPT/ALT, serum bilirubin, urine routine examination , serum creatinine, prothombin time, serum ceruloplasmin, 24 hour urinary total copper (with or without challenge with penicillamine). USG of hepato-biliary system were done in each patient. In selected cases, endoscopy of upper gastrointestinal tract was done. MRI of brain was done in all the patients. An expert neuro-radiologist of the institute reviewed the imaging.

The patients were treated with either Zinc, Zinc with penicillamine or only penicillamine. Symptomatic management was given according to the manifestations of the patients (trihexyphenydyl for dystonia, tizanidine for spasticity, risperidone for hyperactivity etc). Patients were followed up for a period of minimum 6 months. Compliance, side effect of drugs and clinical status of the children were recorded.

Data was analyzed using SPSS (statistical package for social science) program version 23 for windows and for all the analysis a p value < 0.05 was considered statistically significant.

Result:

Total 74 patients were taken as study case. The cases with neuro-hepatic manifestations presented late in comparison to patients with only neurological manifestations although there was no statistically significant difference in both groups. However, age of assessment was late in neuro-hepatic and it was significant ($P<0.5$). Besides, most of the patients from both groups were from rural areas (55% and 75.93%, respectively). [Table 1]

Regarding the hepatic features, jaundice (66.67%) and cirrhosis (66.67%) were most frequent in neuro-hepatic group. Other features were portal hypertension (38.89%), ascites (24.07%), bleeding manifestation (12.96%), hepatitis (7.74%), hepatic encephalopathy (5.56%), and acute hepatic failure (1.85%). [Table 2]

Predominant neurological feature were dystonia (95% and 75.63%, respectively in neurological only and neuro-hepatic group), drooling (85% and 75.93%, respectively), altered activity of daily living (85% and 77.78%, respectively), dysphasia (95% and 81.48%, respectively), school performance deterioration (100% and 88.89%, respectively), and change in handwriting (100% and 87.04%, respectively). Chorea, athetosis and ataxia was present in both groups without any significant difference. None from both groups had any seizure or myoclonus.

Both the groups had statistically similar distribution of psychiatric manifestations (as p >0.05), wherein psychosis, hyperactivity and personality change was present in 25%, 15% and 55% in neurological only patients and 31.48%, 18.52% and 62.96% in neuro-hepatic patients respectively. [Table 3]

All patients (100%) from neurological only group had KF ring, while 98.15% patients from neuro-hepatic group had KF ring. Sunflower cataract was seen in 1 patient from neurological only group andintwo patients from neuro-hepatic group. However, one patient from later group had renal manifestation and 6 patients had hyperpigmentation. On analysis of the biochemical profile, patients of neuro-hepatic group had significantly lower serum ceruloplasmin and albumin level in comparison to other group ($p<0.05$). Besides, total urinary copper (with and without challenge) was significantly higher in neuro-hepatic group($p<0.05$). No statistically significant difference was found in the other hematological profiles. [Table 4]

In patients with neuro-hepatic manifestations, cirrhosis (40.74%) was the most frequent finding of USG of liver. Other features werehepato-splenomegaly (16.67%), hepatomegaly (11.11%), ascites (5.56%), and splenomegaly (3.70%). Three patients (5.56%) had cirrhosis, ascites and splenomegaly, in trio. However, 16.67% patients of this group had USG of liver. Upper GI endoscopy showed that 42.59% patients had varices.[Table 5]

The most common finding MRI of brain of both the groups was hyperintensity of putamen. Other commonly involved areas were globus pallidus, thalamus and midbrain. Four patients of neuro-hepatic group had normal MRI of brain. No statistical difference was found in two groups in neuroimaging findings. [Table 6]

In both groups, almost similar treatment was given with Penicillamine and Zinc in 85% (neurological only group) and 92.59%(neuro-hepatic group), respectively. The duration was11.10±0.31 and 10.13±0.34 months respectively. The side effects were neutropenia, hypersensitivity,nephrotic syndrome etc. Most of the patients of both group remains stable or improved with treatment.

Table-I

Demographic characteristics of the studied group (n=74)

	Neurological only (n=20) No. (%)	Neuro-hepatological (n=54) No. (%)	p-value
Age of onset (years)	9.5±1.70	10.33±2.47	0.132 [á]
Age of diagnosis	10.28±1.59	11.38±2.41	0.062 [á]
Age of assessment	10.75±1.63	12.14±2.42	0.020 [á]
Gap to diagnose	10±5.69	11.87±9.30	0.668 [á]
Gender			0.988 [ã]
Male	13(65)	35(64.81)	
Female	7(35)	19(35.19)	
Residence			0.080 [ã]
Rural	11(55)	41(75.93)	
Urban	9(45)	13(24.07)	
Consanguinity	4(20)	11(20.37)	0.972 [ã]
Sib affected/death	3(15)	16(29.63)	0.201 [ã]

Values are expressed as Mean±SD and within parenthesis percentage (%) over column in total.

[á] = Mann-Whitney U test was performed

[â] = Student t-test was performed

[ã] = Pearson's Chi-squared Test (c^2) was performedThe average age of onset is about 9.5±1.70 and 10.33±2.47 years in neurological and neurohepatic group respectively. A male predominance is observed in both the groups. Consanguinity was observed in 20% of cases in the study subjects.

Table-II

Hepatic manifestation of the neuro-hepatic patients (n=54)

Hepatic manifestation*	n (%)
Jaundice	36(66.67)
Cirrhosis	36(66.67)
Portal hypertension	21(38.89)
Ascites	13(24.07)
Bleeding manifestation	7(12.96)
Hepatitis	4(7.74)
Hepatic encephalopathy	3(5.56)
Acute hepatic failure	1(1.85)

*multiple response

Regarding the hepatic cases, the most predominant features were jaundice, cirrhosis and portal hypertension.

Table-III

Neuro-psychiatric manifestations of the studied group (n=74)

	Neurological only (n=20) No. (%)	Neuro-hepatic (n=54) No. (%)	p-value[á]
Neurological Manifestations			
Tremor	7(35)	16(29.63)	0.658
Dystonia	19(95)	41(75.63)	0.063
Chorea	3(15)	7(12.96)	0.820
Athetosis	2(10)	3(5.56)	0.607
Drooling	17(85)	41(75.93)	0.40
Altered activity of daily living	17(85)	42(77.78)	0.493
Dysphasia	19(95)	44(81.48)	0.147
Altered School performance	20(100)	48(88.89)	0.182
Change in hand writing	20(100)	47(87.04)	0.091
Ataxia	9(45)	15(27.78)	0.160
Psychiatric manifestations			
Psychosis	5(25)	17(31.48)	0.588
Hyperactivity	3(15)	10(18.52)	0.724
Personality change	11(55)	34(62.96)	0.533

Values are expressed within parenthesis percentage (%) over column in total.

[á] = Pearson's Chi-squared Test (c^2) was performed

Altered school performances and dystonia were the predominant neurological features in both the groups. Other features were drooling, dysphasia, ataxia etc.

Table-IV

Biochemical profile of study participants (n=74)

	Neurological only (n=20) No. (%)	Neuro-hepatic (n=54) No. (%)	p-value
S. ceruloplasmin (mg/dL)	13.55±6.49	10.21±5.15	0.044[á]
S. bilirubin (mg/dL)	0.49±0.19	0.64±0.31	0.033[á]
ALT (IU/L)	32.50±8.10	55.37±58.04	0.023[á]
PT (in seconds)	12.35±1.27	13.48±2.09	0.039[á]
S. albumin (g/L)	36.00±4.27	32.04±5.71	0.003[á]
Urinary Cu (U/L)			
Without challenge	398.06±269.89	389.70±250.88	1.00[á]
With challenge	2155.00±728.90	3499.26±2398.59	0.345[á]
Total	749.45±813.19	1944.48±2305.68	0.031[á]
Haematology			
Anemia	4(20)	20(37.04)	0.164[â]
Thrombocytopenia	0(0)	9(16.67)	0.051[â]
Neutropenia	1(5)	2(3.70)	1.00[ã]

Values are expressed as Mean±SD and within parenthesis percentage (%) over column in total.

[á] = Mann-Whitney U test was performed

[â] = Pearson's Chi-squared Test (c^2) was performed

[ã] = Fisher's exact test was performed

Patients of neuro-hepatic manifestation had significantly lower serum ceruloplasmin and albumin level in comparison to other group ($p<0.05$). Besides, total urinary copper (with and without challenge) was significantly higher in neuro-hepatic group ($p<0.05$).

Table-V

Ultrasonography and upper GI endoscopy findings of neuro-hepatic patients (n=54)

Findings	n (%)
USG of liver	
Normal	9(16.67)
Cirrosis	22(40.74)
Ascitis	3(5.56)
Hepatomegaly	6(11.11)
Splenomegaly	2(3.70)
Hepato-splenomegaly	9(16.67)
Cirrhosis+Ascitis+Splenomegaly	3(5.56)
Upper GI Endoscopy	
Normal	22(40.74)
Varices	23(42.59)
Not done	9(16.67)

GI=Gastro-intestinal

In patients with neuro-hepatic manifestations, the predominant feature was cirrhosis in USG of liver. Other features were hepato-splenomegaly , hepatomegaly , ascites and splenomegaly .

Table-VI

Neuroimaging profile of studied subject (n=74)

	Neurological only (n=20), No. (%)	Neuro-hepatic (n=54), No. (%)	p-value
Normal	0(0)	4(7.41)	0.569[â]
Cortical atrophy	12(60)	30(55.56)	0.732[â]
Globus Pallidus	9(45)	23(42.59)	0.853[â]
Caudate Nucleus	13(65)	31(57.41)	0.555[â]
Putaman	16(80)	42(77.78)	0.837[â]
Thalamus	10(50)	18(33.33)	0.189[â]
Midbrain	2(10)	7(12.96)	0.729[â]
Pons	2(10)	4(7.41)	0.659[â]
Cerebellum	1(5)	1(1.85)	0.458[â]
Giant panda sign	1(5)	3(5.56)	1.00[â]
Claustrum	1(5)	1(1.85)	0.458[â]
White matter change	0(0)	3(5.56)	0.558[â]
Internal capsule	0(0)	2(3.70)	1.00[â]

Values are expressed within parenthesis percentage (%) over column in total.

[â] = Pearson's Chi-squared Test (c^2) was performed

[â] = Fisher's exact test was performed

The most common abnormality in the MRI of brain in both the groups were hyperintensity of putamen. Other features were cortical atrophy, hyperintensity of caudate nucleus and thalamus.

Discussion:

Neurological WD is an important but uncommon degenerative disease particularly in pediatric population.[8] This study highlights the varied presentation of two sets of patients, one group had sole neurological presentation while other group had both neurological and hepatic presentation. Both subjective and objective assessment of studied subject was done here.

Average age of diagnosis in neuro-hepatic WD was 10.33±2.47 years while that of neurological only WD it was 9.5±1.70. Gap to diagnosis was about 11.87±9.30 and 10±5.69 months in those groups respectively. A male predominance was observed like the previous studies, most of the study population belonged to rural people in both the groups. 2 About 20% of the both group had consanguinity while affected sib was more in the neuro-hepatic group although it was not statistically significant.

Most predominant movement disorder in both the groups was dystonia, other prominent features were tremor, chorea, athetosis and ataxia. However, the most common neurological manifestation was altered school performances in the form of poor hand writing, poor memory, and poor reading skills. Dysphasia was present in more than 80% subjects of both the groups, while altered daily activity and drooling was present in more than 75% of the patients. In a related study in pediatric population the predominant movement disorders were dystonia (92%), tremor (52%) and chorea (24%). Seizure was observed in 12% study subjects of this group, which was absent in our study group. In another study, the commonest presentation was tremor (58%), headache (58%), dystonia (25%) and ataxia (17%).

Psychiatric disorders are common feature of WD yet often recognized late. About 20% patients have psychiatric disorders prior to diagnosis while 30-40% had these at the time of diagnosis. The common psychiatric disorders are behavioral and personality changes, anxiety, depression, manic and hypomanic syndrome, cognitive deficits, sleep problems (dyssomnias) etc. In this study subjects, the most commonly occurring psychiatric problem was change

of personality observed in more than half of the patients in both groups. While other disorders were psychosis and hyperactivity. All the psychiatric disorders were more in neuro-hepatic group, although no statistically significant difference was observed.

Apart from neurological and hepatic manifestations, there are some important signs of WD observed in other system. Eye finding is the most important and aids in diagnosis. Here all study subjects of neurological and 98.15% of neuro-hepatic group had KF ring in both eye. In related study, KF ring was present in 100% patient in a study of neurological WD in children, while it was found only in 50% of subjects in another study done in children with mixed features (hepatic and neurological)of WD.[10,11] While sunflower cataract was found in 3 patients. Six patients of neuro-hepatic group had hyperpigmentation which is a rare manifestation of WD and one patient of the same group had renal involvement in the form of nephrotic syndrome.

Biochemical markers are important key to diagnosis of WD as many times the clinical features are non-conclusive. Low serum ceruloplasmin, low serum copper and high urinary copper excretion is highly predictable of WD diagnosis.1 Serum ceruloplasmin level was low in most of the subjects in this study and there was significantly low value in neuro-hepatic group. Besides, total urinary copper (with and without challenge) was significantly higher in neuro-hepatic group. Hematological disorders were in the form of anemia, neutropenia and thrombocytopenia in this study.

MR imaging (MRI) is a sensitive method for evaluation of neurologic WD. The most affected areas in brain are basal ganglia particularly putamen, head of caudate nucleus and thalamus. Bilateral involvement is characteristic of WD. In this study also bilateral hyperintensity of putamen is the most predominant finding. Other areas involved were globus pallidus and midbrain. Cortical atrophy was found in more than half of the patients of both groups. Some uncommon findings like giant panda sign, cerebellar involvement, white matter involvement and claustrum hyperintensity were observed.

Conclusion:

This study highlights the profile of neurological WD children of Bangladesh. The most important clinical features were deterioration of school performance, dystonia, impaired daily activity, dysphasia and jaundice. Patients with neuro-hepatic features had lower serum ceruloplasmin and higher urinary total copper. In MRI, most affected part was putamen, thalamus and head of caudate nucleus.

Conflict of interest:

We have no conflict of interest to declare

Reference:

1. Fernando M, van Mourik I, Wassmer E, Kelly D. Wilson disease in children and adolescents. Arch Dis Child. 2020 May; 105(5):499-505. https://doi.org/10.1136/archdischild-2018-315705 PMid:31974298
2. Güngör ª, Selimoðlu MA, Varol FÝ, Güngör S. Pediatric Wilson's disease: findings in different presentations. A cross-sectional study. Sao Paulo Med J. 2018; 136(4):304-309. https://doi.org/10.1590/1516-3180.2018.0210230718 PMid:30304203 PMCid:PMC9881691
3. Chang IJ, Hahn SH. The genetics of Wilson disease.HandbClin Neurol. 2017;142:19-34. https://doi.org/10.1016/B978-0-444-63625-6.00003-3 PMid:28433102 PMCid:PMC5648646
4. Dev S, Kruse RL, Hamilton JP, Lutsenko S. Wilson Disease: Update on Pathophysiology and Treatment. Front Cell Dev Biol. 2022 May 2;10:871877 https://doi.org/10.3389/fcell.2022.871877 PMid:35586338 PMCid:PMC9108485
5. Chanpong A, Dhawan A. Wilson disease in children and young adults - State of the art. Saudi J Gastroenterol. 2022 Jan-Feb;28(1):21-31. . https://doi.org/10.4103/sjg.sjg_501_21 PMid:35042319 PMCid:PMC8919932
6. Abbassi N, Bourrahouat A, Bedoya EC, Belmalih A, El Hanafi FZ, Bost M, Sedki A, Lachaux A. Epidemiology, clinical features, and mortality rate of Wilson disease in Moroccan children: A pediatric case series. Arch Pediatr. 2022 Aug;29(6):453-458.. https://doi.org/10.1016/j.arcped.2022.03.010 PMid:35705388
7. Aggarwal A, Aggarwal N, Nagral A, Jankharia G, Bhatt M. A novel Global Assessment Scale for Wilson's disease (GAS for WD).MovDisord. 2009 Mar 15; 24(4):509-18. https://doi.org/10.1002/mds.22231 PMid:19115420
8. Roberts EA, Schilsky ML. Current and Emerging Issues in Wilson's Disease. N Engl J Med. 2023 Sep 7;389(10):922-938. . https://doi.org/10.1056/NEJMra1903585 PMid:37672695

9. Noureen N, Rana MT. Neurological Wilson disease in children: a three years' experience from Multan. J Pak Med Assoc. 2011; 61(8):743-8.

10. Bayram AK, Gümü° H, Arslan D, Özçora GK, Kumanda° S, Karacabey N, et al. Neurological features and management of Wilson disease in children: an evaluation of 12 cases. Turk PediatriArs. 2016 Mar 1; 51(1):15-21. https://doi.org/10.5152/TurkPediatriArs.2016.3080 PMid:27103860 PMCid:PMC4829162

11. Litwin T, Dusek P, Szafrański T, Dzie¿yc K, Cz³onkowska A, Rybakowski JK. Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. TherAdvPsychopharmacol. 2018 Jul; 8(7):199-211. https://doi.org/10.1177/2045125318759461 PMid:29977520 PMCid:PMC6022881

12. Chevalier K, Rahli D, de Veyrac L, Guillaume J, Obadia MA, Poujois A. Quality of life and depression in Wilson's disease: a large prospective cross-sectional study. Orphanet J Rare Dis. 2023 Jun 29;18(1):168. https://doi.org/10.1186/s13023-023-02777-4 PMid:37386576 PMCid:PMC10308610

13. Chand PK, Murthy P. Mania as a presenting symptom of Wilson's disease. ActaNeuropsychiatr 2006; 18: 47-49. https://doi.org/10.1111/j.0924-2708.2006.00108.x PMid:26991983

14. Loganathan S, Nayak R, SinhaS,Taly AB, Math S, Barghese M. Treating mania in Wilson's disease with lithium. J Neuropsychiatry ClinNeurosci 2008; 20: 487-489. https://doi.org/10.1176/jnp.2008.20.4.487 PMid:19196936

15. Rybakowski JK, Litwin T, Chlopocka-Wozniak M, Czlonkowska A. Lithium treatment of a bipolar patient with Wilson's disease: a case report. Pharmacopsychiatry 2013; 46: 120-121. https://doi.org/10.1055/s-0032-1323784 PMid:23037949

16. Zimbrean PC, Schilsky ML. The spectrum of psychiatric symptoms in Wilson's disease: treatment and prognostic considerations. Am J Psychiatry. 2015 Nov 1;172(11): 1068-72. . https://doi.org/10.1176/appi.ajp.2015.15030371 PMid:26575449

17. Zimbrean P, Seniów J. Cognitive and psychiatric symptoms in Wilson disease. HandbClin Neurol. 2017;142:121-140.. https://doi.org/10.1016/B978-0-444-63625-6.00011-2 PMid:28433097

18. Frota NAF, Caramelli P, Barbosa ER. Cognitive impairment in Wilson's disease. Dement Neuropsychol 2009; 3: 16-21 https://doi.org/10.1590/S1980-57642009DN30100004 PMid:29213604 PMCid:PMC5619026

19. Nandi M, Sarkar S, Mondal R. Generalized hyperpigmentation in Wilson's disease: An unusual association. J Neurosci Rural Pract. 2013 Jan; 4(1):70-2. https://doi.org/10.4103/0976-3147.105621 PMid:23546359 PMCid:PMC3579056

20. Yu XE, Yang RM. 132 cases brain imaging of hepatolenticular degeneration. J ApoplNerv Dis 2007;1:30-34

21. Rêdzia-Ogrodnik B, Cz³onkowska A, Bembenek J, Antos A, Kurkowska-Jastrzêbska I, Skowroñska M, Smoliński £, Litwin T. Brain magnetic resonance imaging and severity of neurological disease in Wilson's disease - the neuroradiological correlations. Neurol Sci. 2022 Jul;43(7):4405-4412. https://doi.org/10.1007/s10072-022-06001-2 PMid:35275318

22. Yang RM. Hepatolenticular Degeneration. 1st ed. Beijing: People's Health press, 2015: 126-127.

23. Zhong W, Huang Z, Tang X. A study of brain MRI characteristics and clinical features in 76 cases of Wilson's disease.J ClinNeurosci. 2019 Jan;59:167-174. https://doi.org/10.1016/j.jocn.2018.10.096 PMid:30385165

24. Ranjan A, Kalita J, Kumar S, Bhoi SK, Misra UK. A study of MRI changes in Wilson disease and its correlation with clinical features and outcome. ClinNeurolNeurosurg. 2015 Nov;138:31-6. https://doi.org/10.1016/j.clineuro.2015.07.013 PMid:26278999