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Neuropsychiatric Manifestations and Neuroimaging Changes of Neurologic Wilson Disease–A Cross Sectional Study

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Abstract:

Background: *Wilson disease is genetic disorder of copper metabolism which causes hepatic & neurologic manifestation mainly. Chelator therapy is usually given as first line treatment in symptomatic wilson disease.*

Objective: *Objective of our study was to evaluate the neuropsychiatric menufestations of wilson disease.*

Methods: *A Cross sectional study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, a tertiary care premier Postgraduate Medical Institution of Bangladesh. Forty five (45) patients of neurologic wilson disease were evaluated at In-patient department of Paediatric Neurology, during the period of January 2015 to December 2020.*

Diagnosis of Neurologic wilson disease was done, based on the characteristic clinical features of progressive deterioration of scholastic performances, dysarthria and gait disorder along with ophthalmologic findings, biochemical & neuroimaging findings.

Results: *Total numbers of studied cases were 45. Mean age was 124.65± 20.69 months and male to female ratio was 1.8:1. Most of the patient (83.33%) arrived from poor socio-economic background and rural area (66.67%) of Bangladesh. Among them 20.0% had history of consanguineous mating parents and 17.78% had another affected sibs. Common presenting features were progressive deterioration of school performance (89.74%), gait disturbance (92.31%), dysarthria (92.31%) and dystonia (41.03%) of our studied children. Neuropsychiatric manifestations were very common among the affected children. Changes in behavior was present in 62.22% cases, and among them mania were present in 57.77% children. Other common neuropsychiatric manifestations were depression (35.55%), generalized anxiety disorder in 31.11% and loss of memory in 20% cases. Ophthalmological manifestations like KF ring (83.33%) also found in majority of patient. Neuroimaging study showed basal ganglia hyperintensity in 63.63.% , white matter hyper intense signal changes 18.18% cases and ischemic change in grey matter in 18.18% cases.*

Conclusion: *In our study about two third cases of Neurologic Wilson diseases may present with Neuropsychiatric manifestations in children. Behavior changes were commonest neuropsychiatric manifestations which includes depression, mania, generalized anxiety disorder and loss of memory.In neuroimaging study bilateral basal ganglia hyperintensity were found in about three-fourth cases of our studied children.*

Key words: **Wilson disease (WD), Neuropsychiatric menifestation.**

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Introduction:

Wilson disease is genetic disorder of copper metabolism which causes hepatic & neurologic manifestation mainly (Aggarwal and Bhatt, 2009). It is an inherited autosomal recessive disorder of copper metabolism leading to hepatic damage and neurological disturbance of variable degree (Aggarwal and Bhatt, 2009, Litwin et al., 2019). The defective gene, *ATP7B*, encodes a hepatic copper-transporting protein, which plays a key role in human copper metabolism (Bandmann et al., 2015, Dening and Berrios, 1989). It usually manifests within the first three decades with liver dysfunction, extrapyramidal, neuropsychiatric, or Osseo muscular (i.e., skeletal or musculoskeletal) symptoms and has marked inter- and intra-familial clinical heterogeneity (Dening and Berrios, 1989, Walshe, 1962).

WD is a rare with an estimated prevalence of symptomatic disease of 1 in ~30,000 with a heterozygous *ATP7B* mutation carrier frequency of 1:90 (almost 1% of a population). Mutations in ATP7B result in impaired

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biliary copper excretion with consecutive copper overload primarily in the liver and later in the brain causing hepatic and neuro-psychiatric symptoms.

Clinical manifestations are related to copper accumulation predominantly in the liver and brain. Hepatic disease are ranging from mild hepatitis to acute liver failure or cirrhosis and/or neurological symptoms are dysarthria, dystonia, tremor, and psychiatric disturbances (Walshe, 1962, Dastur et al., 1968).

Psychiatric symptoms occur before, concurrent with or after the diagnosis and treatment for WD. Thirty to forty percent of patients have psychiatric manifestations at the time of diagnosis, and 20% had seen a psychiatrist prior to their WD diagnosis (Litwin et al., 2018). Mixed presentations occur frequently. Early recognition of wilson disease can be done by means of clinical, biochemical or genetic examination.

Untreated wilson disease is fatal (Walshe and Dixon, 1986). Chelation therapy is usually given as first line treatment in symptomatic wilson disease. Wilson disease can be treated successfully with pharmacologic agents. Two groups of drugs are currently used: chelating agents such as, d-penicillamine(Walshe, 1956), tetrathiomolybdate, and trientine, which increase urinary copper excretion, and zinc salts, which inhibit copper absorption in the digestive tract..

In spite of adequate treatment some neurologic deficits may persist and further neurologic deterioration may be observed after treatment initiation with chelating agents specially by penicillamine with conventional dose. Such patients may require additional treatment to alleviate neurologic symptoms but most of the time very difficult to treat this case.

Early diagnosis and early initiation of treatment with penicillamine for neurological wilson disease has a good outcome. a delay in the diagnosis or misdiagnosis occurs when Psychiatric manifestations occurring without overt hepatic or neurologic involvement and also causes poor outcome. Our aim was to observe the early diagnosis of neuropsychiatric menufestations of wilson disease.

Methodology:

A Prospective observational study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, a tertiary care premier Postgraduate Medical Institution of Bangladesh.

Thirty nine (45) patients of Neurologic Wilson disease were evaluated at In-patient department of paediatric neurology, BSMMU during the period of January 2015 to December 2020. Diagnosis of Neurologic wilson disease was based on the characteristic clinical features along with biochemical & neuro-imaging findings and ophthalmologic findings.

All patient with neurologic wilson disease who presented at In-patient department of paediatric neurology were included in this study evaluated for Neuropsychiatric manifestation .

Behavioral change like Depression, mania, anxiety was diagnosed according to DSM 5 criteria of major depressive illness, acute bipolar disorder and generalized anxiety disorder. Loss of memory was identified by bedside mini mental test.

Institutional Review Board of BSMMU approved this study. In addition, an informed written consent of participation in the study were signed by the parents or the legal guardians. Data analysis was performed by Statistical Package for Social Science (SPSS), version-22. Results were presented as text and tables.

Result:

Total numbers of studied children were 45. Mean age was 10.38 ± 1.74 years (124.65±20.69 months) and male to female ratio was nearly 1.8:1. Among them 20.0% had history of consanguineous mating parents.

Progressive deterioration of school performance (91.11%), gait disturbance (86.67%), dysarthria (88.88%) and dystonia (82.22%) and were the main presenting feature of our studied children. Ophthalmological manifestations like KF ring was found in nearly all (97.8%) patients. Neuroimaging study showed basal ganglia hyperintensity in 57.77% cases. Neuropsychiatric manifestations were very common among the affected children. Changes in behavior was present in 62.22% cases, and among them mania were present in 57.77% children. Other common neuropsychiatric manifestations were depression (35.55%), generalized anxiety disorder in 31.11% and loss of memory in 20% cases.

Table-I

Baseline Characteristics of studied cases (n=45)

Characteristics	Number of patients N=45	Percentage
Age(yr):		
5-10	6	13.33%
11-15	37	82.22%
16-20	2	4.45%
Sex:		
Male	29	64.45%
Female	16	35.55%
Consanguinity:		
Consanguineous	9	20.0%
Non-consanguineous	36	80.0%
Affected sibs:		
Sibs affected	8	17.78%
Sibs not affected	37	82.22%

Table I showed that more than three fourth (82.22 %) patients belonged to age 11-15 years. The mean age was 124.65±20.69 (Mean±SD) months with ranged from 78 to 160 months. Nearly two third (64.45%) patients were male and 35.55% were female. Male female ratio is 1.8:1. About 20.0 % patients came from consanguineous mating family and history of sibs affected in 17.78 % patients.

Table-II

Distribution of Neurologic menifestations in studied cases (n-45)

Symptoms	Number of patients N=45	Percentage
Deterioration of school Performance	41	91.11%
Gait disturbance	39	86.67%
Dysarthria	40	88.88%
Dystonia	37	82.22%
Drooling of saliva	11	24.45%
Chorea/Athetosis	11	24.45%
Tremor	2	4.45%
Seizure	1	2.22%

Table 2 showed Progressive deterioration of school performance occured in 91.11% children followed by gait disturbance in (86.67%), dysarthria in (88.88%), dystonia in (82.22%), and Drooling in 24.45% cases

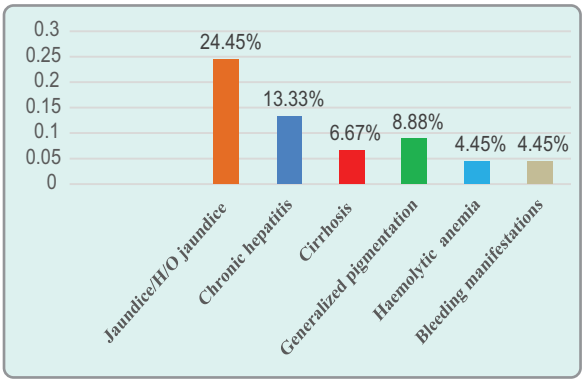

Figure- 1: *Distribution of Hepatic and other manifestations in studied cases (n-45)*

Figure 1 showed the hepatic and other manifestations in studied patients. Jaundice found in 24.45% children followed by chronic hepatitis in 13.33%, generalized pigmentation in (8.88%), and bleeding manifestations in 4.45% and haemolytic anemia in 4.45% cases.

Table-IV

Distribution of Neuropsychiatric manifestations in studied cases(n-45)

Neuropsychiatric manifestations	Number of patients	Percentage
Change in behavior	28	62.22 %
• Depression	16	35.55 %
• Mania	26	57.77 %
• Anxiety	14	31.11%
Loss of memory	9	20.00 %

Table 4 Showed behavior change found in 62.22% children followed by depression in 35.55% anxiety in 31.11% and mania in 57.77%, and loss of memory in 20.0 % cases.

Table-V

Ophthalmological evaluation in studied cases(n-45)

	Features	Number N=45	(%)
Ophthalmological Evaluation	Normal	0	0
	Abnormal: K F Ring (44), Sunflower cataract(1)	45	100%

Table 5. Abnormal ophthalmological findings (K F Ring, Sunflower cataract) found in 100% of cases.

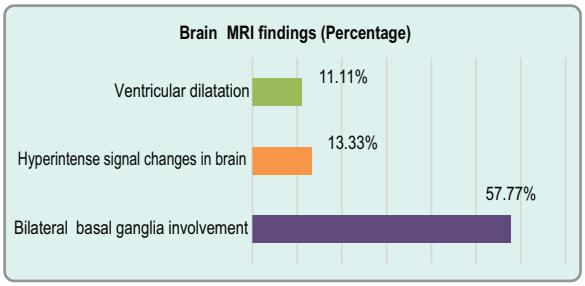

Figure -2: *Distribution of Neuroimaging findings (MRI) in studied cases (n=45)*

Figure – 2 MRI of brain showed bilateral basal ganglia involvement in 57.77% children followed by hyperintense signal changes 13.33% and ventricular dilatation in 11.11% of cases.

Discussion:

An estimate prevalence of WD is 12.7 per 100,000 population, though previously it was been estimated as 1 in 30,000 (Gao et al., 2019). The age of first symptoms varies widely from the 5-35 years, even though most patients develop symptoms in adolescence to early adulthood(Hedera, 2017).

The age of first symptoms varies widely from the first decade to the fourth and fifth decades of life, even though most patients develop symptoms in adolescence to early adulthood(Merle et al., 2007). In this study the mean age was 10.38 ± 1.74 years (124.65±20.69 months) and male to female ratio was nearly 1.8:1. In a similar study with 54 children diagnosed as Wilson disease found the mean age at diagnosis was 9.27 ± 3.62 years, range 4 months – 18 years) (Manaloki et al., 2009).

In an another study among 50 children with neurological symptoms of Wilson disease, mean age at onset of symptoms was 9.06 ± 2.65 years with Male female ratio was 2.1:1 (Noureen and Rana, 2011).

In this study, presence of another affected siblings were present in 17.78 % cases which is nearly similar (24%) to another study(Noureen and Rana, 2011)

Initial signs and symptoms of WD are hepatic in ~40% of patients, neurologic in ~40%–50% and primarily psychiatric manifestation can be seen in ~10% of patients (Merle et al., 2007). However, most of them typically develop combined hepatic and neuro-psychiatric symptoms (Hedera, 2017).

In various study it is showed that most patients initially have behavioural change along with mild cognitive deterioration and clumsiness. In the course of time Specific neurological symptoms appear in the form of rigidity, bradykinesia or slowed movements and a lack of balance (parkinsonism) (Lorincz, 2010). Similar finding was present in this study where it was found that most common neurological features are progressive deterioration of school performance (91.11%) followed by gait disturbance (86.67%), dysarthria (88.88%) and dystonia (82.22%).

In various study, dystonia was commonly found in 10-65% cases (Machado et al., 2006, Prashanth et al., 2005). It can be focal, segmental or in severe cases generalized dystonia resulting in abnormal posturing of the trunk, neck or extremities and subsequently causing debilitating symptoms with secondary skeletal changes and inability to walk.

In this study among the study population there are also some common features like typical hand tremor, masked facial expressions, slurred speech, drooling, ataxia and Seizure (2.2%) which is also support some other studies also (Ala et al., 2007). Wing-beating tremor (prototypical tremor in WD) appearing when the patient holds semi-flexed outstretched arms, and its amplitude increases with a longer duration of posture holding.

After the hepatic and neurologic features, the 3rd most common symptoms are psychiatric and behavioural symptoms. They are also very non-specific and can range from depression to acute psychotic episodes (Shanmugiah et al., 2008, Svetel et al., 2009). Psychiatric symptoms are commonly seen in conjunction with neurological symptoms and but in many instances present as the initial manifestation. The percentage of neuropsychiatric manifestation varies according to various researchers from 46% to 72%, and around 30% of wilson disease patient initially present with psychiatric symptoms (Zimbrean and Schilsky, 2014). Common psychiatric symptoms in wilson disease are - behavioral and personality changes, anxiety, depression, manic and hypomanic syndrome, cognitive deficits, sleep problems (dyssomnias) and sexual dysfunctions including excessive sexual drive (Zimbrean and Schilsky, 2014). Similar findings were present in this

study also, where common psychiatric problems were behaviour change (62.22%), mania (57.77%) followed by depression (35.55%), and generalized anxiety disorder (31.11%).

Conclusion: Psychiatric manifestations represent a significant part of the clinical presentation of WD and can present at any point in the course of the illness. In our study about two third cases of Neurologic Wilson diseases may present with Neuropsychiatric manifestations in children. Behavior changes were commonest neuropsychiatric manifestations including mania followed by depression, generalized anxiety disorder, and loss of memory.In neuroimaging study bilateral basal ganglia hyperintensity were found in about three-fourth cases of studied children.

Recommendation:

From this study we recommend to search for other clinical and radiological evidences for wilson disease when an adolescent come with various neuropsychiatric manifestations.

Limitation

The data was a one point source data and so could not evaluate the trends over time.

Conflict of Interest

There is no conflict of interest regarding the research, authorship and publication of this article.

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