Behavioral aspect of Wilson Disease: Diagnostic & Management Challenge

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Abstract:

Wilson disease (WD) is a multisystem disease of defective copper metabolism. Excess copper is accumulated in different organ of body including liver, brain, kidney, eyes etc. Accumulated copper causes dysfunction of different parts of brain and produce signs and symptoms of neurological disease. Epidemiological data suggested psychiatric symptoms may be the presenting problem in 30% of WD patients. Psychiatric symptoms developed almost 100% cases of WD patients at any time of the disease course. Psychiatrc symptoms are affective mood disorder, psychotic behavioral, personality changes, anxiety & depression as well cognitive deterioration.

Common neurologic symptoms are dystonia, hypertonia & rigidity, tremors and dysarthria. Rarely patients may present with polyneuropathy or dysautonomia. So both neurologic and psychiatric evaluation and specific treatment is essential for both the conditions.

Diagnostic evaluations of Wilson disease include estimation of serum ceruloplasmin, 24 hours urinary copper, MRI of brain. Magnetic resonance (MR) imaging of the brain or computed tomography (CT) may detect structures involved like basal ganglia. Knowledge of behavioral problem of WD is helpful for early diagnosis of many cases and overall management. Mainstay of treatment of Wilson disease is dietary restriction of copper-rich diet, copper-chelating agents, symptomatic treatment for dystonia & rigidity as well as behavioral psychiatric therapy. For dystonia trihexy phenidyl, tetrabenazine, codopa & clonidine can be used. Neurologic as well as psychiatric symptoms would be reduced where chelation therapy is effective. More over sometimes pharmacologic treatment for psychiatric symptoms is required.

Key words: Behavioral aspect, Wilson Disease, Pharmacologic treatment

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Introduction:

Wilson's disease (WD) is a genetic disorder of copper metabolism that leads to accumulation of excess copper in various organs in the body; primarily the liver and brain.[1] Genetic defect of WD is in the ATP7B gene which is located in chromosome 13. Two cellular events are hampered due to this genetic defect; one is failure of incorporation of copper with apoceruloplasmin there by low serum ceruloplasmin and in availability of copper for utilization in peripheral tissue and another is failure of pumped out of copper into bile canaliculi for excretion. So excess copper is accumulated in hepatocytes and other organ leading to signs and symptoms of the disease.[1] The landmark paper regarding this disease was written in 1912 by Samuel Alexander Kinnier-Wilson;[1] who described a neurologic disorder associated with progressive lenticular degeneration of the brain and cirrhosis of the liver. Later the condition was described as Wilson's disease. Prior to Wilson's description, Kayser in 1902 had described pigmentary corneal ring, in a patient which is later known as KF ring. Dystonia was the predominate feature in the disease described by Wilson. In 1883 Westpahl describe another form of the disease in a young-adult predominant with of tremor and dysarthria. Parkinsonian features is also found as a major clinical feature of Wilson's disease. In 1913 first time defect in copper metabolism was linked with Wilson disease.Subsequently, in 1929 and 1930 excess copper in brain and liverwas found in WD cases.

Neurological manifestations of WD are dystonia, hypertonia, rigidity, tremors and dysarthria. Disabling

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muscle spasms with contractures may develop leading to dysarthria, dysphonia and dysphagia. Some time there may be features of polyneuropathy or dysautonomia.[3,4]In a study Ben et al found 9 patients (25%) had exclusively with neuropsychiatric symptoms, 14 (38.9%) patients had exclusively with hepatic symptoms, 11 (30.6%) patients had both hepatic and neuropsychiatric features (mixed presentation) and 2 (5.5%) patients were asymptomatic[5]. In another study Bayramet al found seven (58%) of the patients were presented with headache, seven (58%) were presented with tremor, three (25%) were pre-sented with dystonia, two (17%) were presented with ataxia, two (17%) were presented with dizziness, one (8%) was present-ed with acute weakness accompanied with numbness in the hands and one (8%) was presented with syncope. Among those six patients (50%)had a positive familial history[6]. As neuropsychiatric features of WD is due to basal ganglia (BG) lesion, similar neuropsychiatric symptoms may be the features of other condition where BG lesion occur[7].That indicate common mechanism for =-development of the behavioral changes, mood disturbances, and anxiety syndromes may present in patients with BG disorders.[8] So WD should kept in differential diagnosis in children with above features.

Psychiatric symptoms are found in almost 100% of WD patients over their course of illness; symptoms may occur before the onset of neurologic features or at the commencement of others ymptoms; even long after the diagnosis and during & on going treatment[9]. Epidemiological data suggest that up to 30% of WD patients may present with psychiatric symptoms as the initial manifestion.[10] In a review, author mention 20% of WD patients had been reported to psychiatrist as their first physician, and 30–40% found to some form of psychiatric manifestations at the time of diagnosis. The common psychiatric manifestation of WD found in childhood is the declining of school performance, inappropriate behavior or impulsiveness[11]. Other psychiatric symptoms was found are obsessive-compulsive disorder, anorexia nervosa,[12]psychotic behavior, personality and cognitive changes[13,14] Personality disorders in WD are antisocial behavior, irritability, disinhibition etc. Mood disorders in WD are bipolar disorder, depression, suicidal attempts. Rarely anorexia, sleep disturbances are also found.[15]Behavioral changes in WD are anxiety, depression, manic and hypomanic syndrome, cognitive deficits, sleep problems (dyssomnias) and sexual dysfunctions.[16,17,18] Some patients also have substance abuse problems which may complicate the clinical course[9,10]A few other psychiatric conditions including catatonia, anorexia nervosa, bulimia, obsessive-compulsive disorder and ADHD had also been reported in WD.[19] However, an improvement of most of the symptoms were typically observed after the correct diagnosis of WD and proper treatment particularly with lorazepam followed by ECT in catatonia; SSRI along with behavioral therapy in obsessive- compulsive disorder.[11,20]Most patients develop at least one of the above mention psychiatric symptoms over the course of the disease; however they are variable between patients[9, 21]

Table-I

The most often clinical manifestation of WD and its frequency at disease diagnosis.[12]

WD presentation and its frequency Symptoms
Neurological (40–50%)
Involuntary movements - tremor, dystonia, ataxia, ballism, chorea, parkinsonian syndrome
Speech disturbances: dysarthria
Dysphagia
Autonomic dysfunction - salivation
Gait disturbances
Psychiatric (10–25%)
Personality disorders - antisocial behavior, irritability, disinhibition, etc.
Mood disorders - bipolar disorders, depression, suicidal attempts
Psychosis and other psychiatric alterations like anorexia, sleep disturbances, etc.
Cognitive impairment
Ophthalmologic - K-F ring, sunflower cataract

Diagnosis: Where psychiatric symptoms occurs as the first manifestation of WD it is a diagnostic and therapeutic challenges[22,23] Approximately 3% of first-episode psychosis cases are organic etiology. So there is a guideline to screen all first-episode psychotic

patients for WD. However still such procedures are not routine, and sometimes only serum ceruloplasmin level is measured, which is not sufficiently to exclude WD.[11,24]So there is often an extremely long delay in diagnosis for patients with initial psychiatric symptoms. WD should therefore be included in differential diagnosis, especially in young adults presenting with psychiatric episode. However with all children suffering from WD should evaluated for behavioral problem in every clinic visit. So both psychiatric evaluation and specific treatment is essential for all cases. The Diagnostic algorithm for WD in Figure -1.

Diagnostic tests will be considered significant of Wilson disease estimation of serum, 24 hours urinary copper, MRI of brain; magnetic resonance (MR) imaging of the brain or computed tomography (CT) may detect structural abnormalities[25,26] Tests done in suspected WD with expected findings in Table:2.

Serum ceruloplasmin<20 mg/dl,24 hour urinary copper >100 ug/24 hour are suggestive of WD. Increased density on CT and hyperintensity on T2WI MR imaging in the region of the basal ganglia are most frequently found changes (Fig-2).There is also T2 WI MR imaging at the level of mid brain showing miniature panda sign. MR imaging may be more sensitive in detecting these lesions

Significant abnormalities on brain imaging may even be present in some individuals prior to the onset of symptoms.[27]

Table-II

Tests done in suspected WD with expected findings

Investigations	Expected findings in WD
Serum ceruloplsmin	< 20 gm/dl
24 hours urinary copper	>100 ug/24 hpurs
Copper in per gram of liver tissue	>250 gram
Genetic study	Mutation in ATP 7 gene
K F ring	Present in 90% cases of neurologic WD
MRI of brain	Bilateral basal ganglia lesionCopper deposition in midbrain resembling miniature panda sign

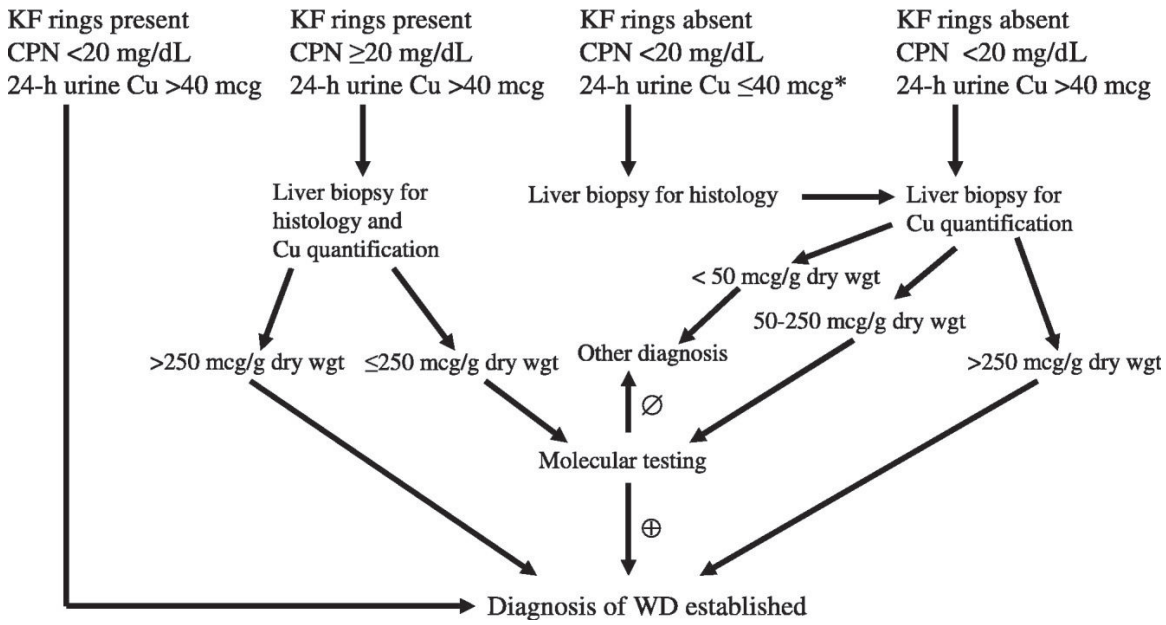

Fig.-1: *Diagnostic algorithm for WD*

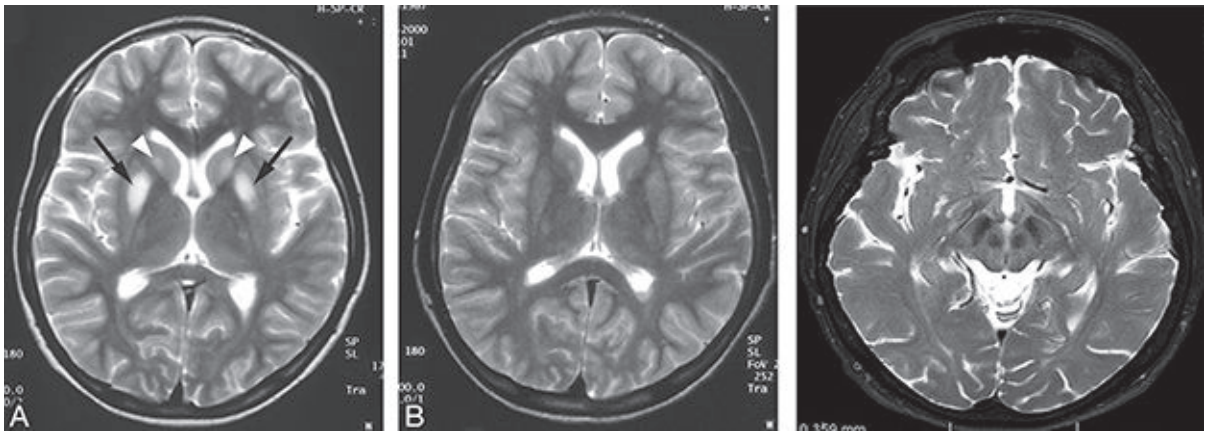

Fig.-2: *A T2WI MR imaging showing bilateral basal ganglia hyper intensity in WD; B normal T2W MR imaging*

Modified Leipzig score – a new scoring system:

The Leipzig score of 1993 [24] was modified by our consensus group members and the new "modified Leipzig score" (Table 3) was validated in 70 patients with proven WD. In this new score, additional points were given for family history suggestive of WD. In addition, weight age was also given to a serum ceruloplasmin value of 5 mg/dL. There are more than 600 mutations identified in the world although unlike the West, there are no common mutations identified in India. Mutational analysis was retained in the new score as genetic tests are now more accessible and may be performed in individuals in whom diagnosis is difficult to establish by clinical and biochemical testing. As there are variability of symptoms and sign a criteria is set to diagnose Wilson disease; where two of the following features are present WD is considered, 1) Kayser Fleischer ring, Low serum ceruloplasmin level, significantly high urinary copper excretion.[23]

Treatment: Mainstay of treatment of Wilson disease includes dietary restriction of copper-rich diet, copper-chelating agents, as well behavioral psychiatric therapy and symptomatic treatment for dystonia & rigidity[27]. Among the chelating agent tetrathiomolibdate is the first choice but not available, second choice is zinc acetate and third choice is trientine& zinc.[26,2829]D-penicillamine is the oldest drug is not routinely recommended as it causes worsening of neurologic symptoms in 10 – 50% cases treated with this drug. Due to unavailability of other agentsis spite of this adverse effect some physician advocate the use of D-penicillamine with caution.[30,31]Tetrathiomolibdate showed clear superiority among chelators because it increase urinary excretion of copper without drug related neurologic deterioration.; Tetrathiomolibdate form a tripartite complex with copper & protein within circulation which isnon toxic and prevent deposition in other site thereby side effects[25]

KF rings	
Present	2
Absent	0
Serum ceruloplasmin	
Normal (>20 mg/dl)	0
0–5 mg/dl	3
6–11 mg/dl	2
11–20 mg/dl	1
24-h urinary copper (in the absence of acute hepatitis)	
>100 mcg	2
40–100	1
<40 mcg	0
Coomb's-negative hemolytic anemia with liver disease	
Present	1
Absent	0
Mutational analysis	
On both chromosomes detected	4
On one chromosome detected	1
No mutation detected/test not done	0
Liver biopsy for histology S/O WD	
Orcein- or rhodanine-positive granules	1
Neurobehavioral symptoms	2
Typical features on MRI brain	1
History of Wilson disease in a family member	
Sibling death from liver disease/ neurological disease suggestive of WD	1
Total score	**Evaluation**
≥4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
≤2	Diagnosis very unlikely

KF, Kayser-Fleischer; MRI, Magnetic Resonance Imaging; S/O, suggestive of; WD, Wilson's Disease.

Fig.-3: *T2 WI MR imaging at the level of mid brain showing miniature panda sign*

For rigidity, beclofen & tizanidine can be used. For dystonia,trihexyphenidyl, tetrabenazine, codopa& clonidine can be used[32]With effective chelation therapy neurologic as well as psychiatric symptoms arereduced; decrease the requirement of pharmatherapyfor psychiatric symptoms r. More over in some cases pharmacologic treatment is required for psychiatric symptoms. Recommendations could be made based on general psychiatryguideline.[33] Behavioral therapy could be applied, depending on the severity of the symptoms and their impact on the daily functioning of the affected patients. SSRIs can reduce irritability and could be a relatively safefirst-line option as pharmacological treatment[34]. Antiepileptic medications may also have some anti-aggressive and mood stabilizing effects, and showed promising results with carbamazepine, lamotrigine, gabapentin, oxcarbamazepine and valproate.[33]Antiepileptic drugs, gabapentin and levetiracetam are considered to be mostly safe for patient withhepatic injury as those drugs excreted mostly through kidney.Antipsychotic agents those have minimum extrapyramidal side effects withgood hepaticsafety profile are recommended as the first-line to treatment forpsychosis in WD. Clinical experiencesuggest clozapine or quetiapine bears those properties.[35,36] However, clozapine treatmentshould be reserved for the most severe andtreatment-resistant cases due to there is an increased risk ofdevelopment of leucopenia. Clozapine can also precipitateseizures so should be used with caution in cases associated with seizure.[23]

Discussion: Starting a pharmacological agent of psychosis of WD patients warrants caution regarding neurological deterioration & hepatic injury.[13,37]Antipsychotic drugs only should be used in severe cases as they may pose risk of causing deterioration of extrapyramidal symptom also can produced neuroleptic malignant syndrome . Therefore, their use should be restricted to the shortest effective time course with the lowesteffective dosages.Agents with the lowest risk of extrapyramidal symptoms (like clozapine or quetiapine) should be choosen.[36] Propranolol could be an interesting option in WD due to its multimodal action that includes efficacy for both neurologic (tremor) and liversymptoms (portal hypertension).[23] The diagnosis of WD can be a major stressor of daily living, often leading to significant life style changes, difficulties with normal functioning, and can lead to a decline in social and mental status.[38] Many patients with WD suffer from various forms of adjustment disorders, manifesting as a mixture of anxiety, depression, phobia, insomnia and tension, also irritability, anger and conduct disorders.[39]Simple interventionssuch as psychoeducation, supportive psychotherapy, cognitive-behavioral therapy (CBT) and support groups might help to reduce anxiety and tension[33] Unfortunately, currently there are no data documenting the effectiveness of these specific strategies for WD. More severe forms of adjustment disorder might need pharmacological treatment; here SSRI may use as a first-line treatment.[34, 41]Aripiprazole has a very good safety profile, but its use for WD case studiesconflicting.[23,40] Olanzapine and quetiapine are two antipsychotics with moderate risk of liver injury.[41]Amisulpride and sulpirideare benzamidesnot metabolized in the liver and carry a low risk of hepatic injury as well extrapyramidal symptoms,.[42] Other antipsychotics with positive effects oncontroling psychosis in WD include resperidone, haloperidol, perphenazine, thioridazine and chlorpromazine; however, their use causes neurological deterioration, including neuroleptic malignant syndrome.[43,44] Long-acting antipsychotics should be used in patients with WD only with great caution.[44]

WD should be included in differential diagnosis, in all psychiatric casesassociated with extrapyramidal symptoms.[12, 24,42] Pharmacological treatment may be needed for bahavioral problem of some cases of Wilson disease, side effects should monitor closely.

Conclusion:

Psychiatric assessment with emphasis on behavioral issue should be considered in all cases of WD at diagnosis and follow up visit.

Conflict of interest: Nothing to declare

References:

1. Wilson, S. Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of theliver. *Brain* 1912; 34: 295–509.
2. Walshe, JM. Wilson's disease: yesterday, today, and tomorrow. *Mov. Disord.* 1988; 3: 10–29.
3. Jung KH, Ahn TB, Jeon BS. Wilson disease with an initial manifestation of polyneuropathy. Arch Neurol 2005;62:1628-1631.
4. Bhattacharya K, Velickovic M, Schilsky M, et al. Autonomic cardiovascular reflexes in Wilson's disease. ClinAuton Res 2002;12:190-192.

5. Schmitt de Bem R, Muzzillo DR, Deguti MM. et al. Wilson's disease in southern Brazil: a 40-year follow-up study CLINICS 2011;66(3):411-416
6. Bayram AK, Gümüº H, Arslan D, et al.Neurological features and management of Wilson disease in children: an evaluation of 12 cases Turk PediatriArs 2016; 51: 15-21
7. Ring HA and Serra-Mestres J. Neuropsychiatry of the basal ganglia. *J NeurolNeurosurg Psychiatry* 2002; 72: 12–21.
8. Lafer B, Renshaw PF and Sachs GS. Major depression and the basal ganglia. *PsychiatrClin N Am* 1997; 20: 885–896.
9. Akil M and Brewer GJ. Psychiatric and behavioral abnormalities in Wilson's disease. *AdvNeurol*1995; 65: 171–178.
10. European Association for the Study of the Liver Disease. EASL clinical practice guidelines: Wilson's disease. *J Hepatol*2012; 56: 671–685.
11. Zimbrean PC and Schilsky ML. Psychiatric aspects of Wilson's disease: a review. *Gen Hosp Psychiatry* 2014; 36: 53–62.
12. Kumawat BL, Sharma CM, Triphati G*, et al*. Wilson's disease presenting as isolated obsessivecompulsive disorders. *Indian J Med Sci*2007; 61: 607–610.
13. Matthew T. LorinczNeurologic Wilson's disease Ann. N.Y. Acad. Sci. 2010;1184:173–187
14. Denning TR. Psychiatric aspects of Wilson's disease. *Br J Psychiatry* 1985; 157: 677–682.
15. Litwin T, Dusek P, Szafrañski T, et al Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment *Ther Adv Psychopharmacol*ÿþ 1– 13 DOI: 10.1177/ 2045125318759461, 2018.
16. Cummings J. Subcortical dementia: neuropsychology, neuropsychiatry and pathophysiology. *Br J Psychiatry* 1986; 149: 682–697.
17. Frota NAF, Caramelli P and Barbosa ER. Cognitive impairment in Wilson's disease. *Dement Neuropsychol*2009; 3: 16–21.
18. Iwanski S, Seniow J, Lesniak M*, et al*. Diverse attention deficits in patients with neurologically symptomatic and asymptomatic Wilson's diseases. *Neuropsychology* 2015; 29: 25–30.
19. Duggal HS and Nizamie H. Wilson's disease presenting with obsessive-compulsive disorder. *Indian J Psychiatry* 2000; 42: 312–316.
20. Mura G, Zimbrean PC, Demelia L*, et al*. Psychiatric comorbidity in Wilson's disease. *Int Rev Psychiatry* 2017; 29: 445–462.
21. Aisen AM, Martel W, Gabrielsen TO.et al. Wilson disease of the brain: MR imaging. Radiology 1985;157:137-141.
22. Chung YS, Ravi SD and Borge GF. Psychosis in Wilson's disease. *Psychosomatics* 1986; 27: 65–66.
23. Litwin T, Dusek P and Czlonkowska A. Neurological manifestations in Wilson's disease: possible treatment options for symptoms. *Expert Opin on Orphans Drugs* 2016; 4: 719–728.
24. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int. 2003;23:139–142.
25. Alam ST, Rahman MM, Islam KA, FerdouseZNeurologic manifestation, diagnosisand management of Wilson disease in children – an update. Mymenshing Med J 2014Jan 23(1)
26. Frank Y &Stephen A. 2018 Hepatolenticular degeneration: Wilson's disease, In: Swaiman KF, Ashwal Stephen, Ferriero DM et al ed. Swaiman's Pediatric Neurology 6thed Elsevier, Philadelphia.
27. van Wassenaer-van Hall HN, van den Heuvel AG, Algra A, et al. Wilson disease: findings at MR imaging and CT of the brain with clinical correlation. Radiology 1996;198:531-536.
28. George J, Grewer, Fredk Ansari Wilson disease: clinical management and therapy. Journal of hepatology. 2005;42:513-521
29. Kundu GKNeurologic Wilson's Disease and its Management - An Update *BANGLADESH J CHILD HEALTH* 2013; VOL 37 (3) : 158-169
30. Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol 1987;44:490-493.
31. Walshe JM, Yealland M. Chelation treatment of neurological Wilson's disease. Q J Med 1993;86:197-204.
32. Erika FA & Jonathan WM 2011.Dytonia. In: Kliegman RM, Stanton BF, St. Geme JW et al. ed. Nelson Textbook of Pediatrcs 20thedd Elsevier, Philadelphia
33. Groves M, van Dujin E, Anderson K*, et al*. An international survey-based algorithm for the pharmacologic treatment of irritability in Huntington's disease. *PLoSCurr*2011; 3: RRN1259.
34. Krim E and Barroso B. Psychiatric disorders treated with clozapine in a patient with Wilson's disease. *Presse Med* 2001; 30: 738.
35. Basu A, Thanapal S, Sood M*, et al*. Catatonia: an unusual manifestation of Wilson's disease. *J Neuropsychiatry ClinNeurosci*2015; 27: 72–73.
36. Litwin T, Dzie¿yc K, Karliñski M*, et al*. Early neurological worsening in patients with Wilson's diseases. *J NeurolSci*2015; 355: 162–167.

37. Carta MG, Mura G, Sorbello O*, et al*. Quality of life in psychiatric symptoms in Wilson's disease: the relevance of bipolar disorders. *ClinPractEpidemiolMent Health* 2012; 8: 102–109.

38. Grover S, Somaiya M, Kumar S*, et al*. Psychiatric aspects of Parkinson's disease. *J Neurosci Rural Pract*2015; 6: 65–76.

39. Kulaksizoglu IB and Polat A. Quetiapine for mania with Wilson's disease. *Psychosomatics* 2003; 44: 438–439.

40. Bleakley S. Identifying and reducing the risk of antipsychotic drug interactions. *ProgNeurol Psychiatry* 2012; 16: 20–24.

41. Kontaxakis V, Stefanis C, Markidis M*, et al*. Neuroleptic malignant syndrome in a patient with Wilson's disease. *J NeurolNeurosurg Psychiatry* 1988; 51: 1001–1002.

42. Chroni E, Lekka NP, Tsibri E*, et al*. Acute progressive akinetic-rigid syndrome induced by neuroleptics in a case of Wilson's disease. *J Neuropsychiatry ClinNeurosci*2001; 13: 531–532.

43. Ozcan O and Selimoglu MA. Self-injury in an adolescent with Wilson's disease. *Eur Child Adolesc Psychiatry* 2009; 18: 761–762.

44. Litwin T, Dzie¿yc K, Karliñski M*, et al*. Psychiatric disturbances as a first clinical symptom of Wilson's disease. *Psychiatr Pol* 2016; 50: 337–344.