Behavioral aspect of Wilson Disease: Diagnostic & Management Challenge

KAZI ASHRAFUL ISLAMA, SYEDATABASSUME ALAMB, BIKUSH CHANDRA PAULC

Abstract:
Wilson disease (WD) is a multisystem disease of defective copper metabolism. Excess copper is accumulated in different organs 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. Psychiatric symptoms are affective mood disorder, psychotic behavioral, personality changes, anxiety & depression as well cognitive deterioration. Common neurologic symptoms are dystonia, hypertonias & 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.

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. 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 thereby 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. The landmark paper regarding this disease was written in 1912 by Samuel Alexander Kinnier-Wilson; 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 pigmented 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 Westphal 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 liver was found in WD cases. Neurological manifestations of WD are dystonia, hypertonias, rigidity, tremors and dysarthria. Disabling...
muscle spasms with contractures may develop leading to dysarthria, dysphonia and dysphagia. Some time there may be features of polyneuropathy or dysautonomia. 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. In another study Bayram et al found seven (58%) of the patients were presented with headache, seven (58%) were presented with tremor, three (25%) were presented 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. 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. That indicate common mechanism for development of the behavioral changes, mood disturbances, and anxiety syndromes may present in patients with BG disorders. 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 symptoms; even long after the diagnosis and during & on going treatment. Epidemiological data suggest that up to 30% of WD patients may present with psychiatric symptoms as the initial manifestation. 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. Other psychiatric symptoms was found are obsessive-compulsive disorder, anorexia nervosa, psychotic behavior, personality and cognitive changes. 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. Behavioral changes in WD are anxiety, depression, manic and hypomanic syndrome, cognitive deficits, sleep problems (dyssomnias) and sexual dysfunctions. Some patients also have substance abuse problems which may complicate the clinical course. A few other psychiatric conditions including catatonia, anorexia nervosa, bulimia, obsessive-compulsive disorder and ADHD had also been reported in WD. 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. Most patients develop at least one of the above mention psychiatric symptoms over the course of the disease; however they are variable between patients. A few other psychiatric conditions including catatonia, anorexia nervosa, bulimia, obsessive-compulsive disorder and ADHD had also been reported in WD. 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. Most patients develop at least one of the above mention psychiatric symptoms over the course of the disease; however they are variable between patients. 

### Table-I

<table>
<thead>
<tr>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Neurological (40–50%)</td>
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<tr>
<td>Involuntary movements - tremor, dystonia, ataxia, ballism, chorea, parkinsonian syndrome</td>
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<tr>
<td>Speech disturbances: dysarthria</td>
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<tr>
<td>Dysphagia</td>
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<tr>
<td>Autonomic dysfunction - salivation</td>
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<tr>
<td>Gait disturbances</td>
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<tr>
<td>Psychiatric (10–25%)</td>
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<tr>
<td>Personality disorders - antisocial behavior, irritability, disinhibition, etc.</td>
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<tr>
<td>Mood disorders - bipolar disorders, depression, suicidal attempts</td>
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<tr>
<td>Psychosis and other psychiatric alterations like anorexia, sleep disturbances, etc.</td>
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<tr>
<td>Cognitive impairment</td>
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<td>Ophthalmologic - K-F ring, sunflower cataract</td>
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Diagnosis: Where psychiatric symptoms occurs as the first manifestation of WD it is a diagnostic and therapeutic challenges. 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 the differential diagnosis, especially in young adults presenting with psychiatric episode. However, with all children suffering from WD should be 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 hours 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

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Expected findings in WD</th>
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<tbody>
<tr>
<td>Serum ceruloplasmin</td>
<td>&lt; 20 gm/dl</td>
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<tr>
<td>24 hours urinary copper</td>
<td>&gt;100 ug/24 hours</td>
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<tr>
<td>Copper in per gram of liver tissue</td>
<td>&gt;250 gram</td>
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<tr>
<td>Genetic study</td>
<td>Mutation in ATP 7 gene</td>
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<tr>
<td>K F ring</td>
<td>Present in 90% cases of neurologic WD</td>
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<tr>
<td>MRI of brain</td>
<td>Bilateral basal ganglia lesion, Copper deposition in midbrain resembling miniature panda sign</td>
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![Diagnostic algorithm for WD](image-url)
Modified Leipzig score – a new scoring system:
The Leipzig score of 1993 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 signs 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.

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. Among the chelating agent tetrathiomolibdate is the first choice but not available, second choice is zinc acetate and third choice is trientine & zinc. 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 agents is spite of this adverse effect some physician advocate the use of D-penicillamine with caution. 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 is non toxic and prevent deposition in other site thereby side effects.
For rigidity, beclofen & tizanidine can be used. For dystonia, trihexyphenidyl, tetrabenazine, codopa & clonidine can be used. With effective chelation therapy neurologic as well as psychiatric symptoms are reduced; decrease the requirement of pharmacotherapy for psychiatric symptoms. More often in some cases pharmacologic treatment is required for psychiatric symptoms. Recommendations could be made based on general psychiatry guideline. 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 first-line option as pharmacological treatment. Propranolol could be an interesting option in WD due to its multimodal action that includes efficacy for both neurologic (tremor) and liversymptoms (portal hypertension).

Antipsychotic agents those have minimum extrapyramidal side effects with good hepaticsafety profile are recommended as the first-line to treatment for psychosis in WD. Clinical experiencesuggest clozapine or quetiapine bears those properties. However, clozapine treatment should be reserved for the most severe and treatment-resistant cases due to there is an increased risk of development of leucopenia. Clozapine can also precipitate seizures so should be used with caution in cases associated with seizure.

Discussion: Starting a pharmacological agent of psychosis of WD patients warrants caution regarding neurological deterioration & hepatic injury. 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 lowest effective dosages. Agents with the lowest risk of extrapyramidal symptoms (like clozapine or quetiapine) should be chosen. Propranolol could be an interesting option in WD due to its multimodal action that includes efficacy for both neurologic (tremor) and liversymptoms (portal hypertension). 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. 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. Simple interventions such as psychoeducation, supportive psychotherapy, cognitive-behavioral therapy (CBT) and support groups might help to reduce anxiety and tension. 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. Aripiprazole has a very good safety profile, but its use for WD case study is conflicting. Olanzapine and quetiapine are two antipsychotics with moderate risk of liver injury. Amisulpride and sulphiride benazmines not metabolized in the liver and carry a low risk of hepatic injury as well extrapyramidal symptoms. Other antipsychotics with positive effects on controlling psychosis in WD include resperidone, haloperidol, perphenazine, thioridazine and chlorpromazine; however, their use causes neurological deterioration, including neuroleptic malignant syndrome. Long-acting antipsychotics should be used in patients with WD only with great caution.

WD should be included in differential diagnosis, in all psychiatric cases associated with extrapyramidal symptoms. Pharmacological treatment may be needed for behavioral 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:


