Atypical Presentation of Wilson's Disease – Need for High Index of Suspicion

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Introduction

Wilson's disease [WD] is a potentially treatable autosomal-recessive disorder, which present as various protean clinical manifestations. The initial presentation can be hepatic or neurological or other system dysfunction alone. No two patients of WD may have similar clinical characteristics even among the common sib-ship, which leads to delay in diagnosis.

Objective

To understand the various clinical presentations and rate of misdiagnosis in patients with Neuro-Wilson's Disease by using FERENCI SCORE.

Results

In our study total patients were 32, initial neurological clinical manifestations present in 41%. Remaining all patients presented with various initial clinical manifestations like fertility related complaints - 8%, musculoskeletal complaints-2.7%, jaundice-25%, ocular-5.5%, cognitive-2.7%, and psychosis-13.8%.

Conclusion

Therapeutic outcome of Wilson's disease (WD) significantly depends upon its early recognition, so high index of suspicion is required to diagnose WD in those who present with unexplained neurologic (especially non-extrapyramidal), psychiatric and other clinical profile at any age of presentation, but particularly at younger age.

Key Words: Wilson's Disease; Kayser-Fleischer Ring; Ceruloplasmin; Copper; Neuroimaging

Introduction

Wilson's disease (WD) forms an important treatable inborn metabolic genetic disorder of the hepatocyte copper trafficking. WD is an autosomal recessive genetic disorder of ATP7B gene on chromosome 13q [1,2]. The WHO estimates that the global prevalence of WD is 1/10,000 to 1/30,000. The prevalence of WD is considered to be higher in Asia when compared to West. The most common mutation in Europe and North America is p.H1069Q, and in Asia is p.Arg778L [3]. WD is a systemic disorder and the initial clinical presentation can be hepatic, neurological or other system dysfunction alone [4]. No two patients of WD may have similar clinical characteristics even among the common sib-ship and leads to delay in diagnosis [1,4]. WD is a treatable neurodegenerative genetic disease with prevention and cure are possible if treated early. But is commonly misdiagnosed due to its varied initial presentation. Diagnosis of WD depends on the clinical symptoms, laboratory tests and the mutational analysis. Genetic testing is impractical to confirm the diagnosis in all the patients due to socio-economic conditions.

Hence we have undertaken this study to interpret the various clinical presentations and analyze the rate of misdiagnosis with the various initial atypical clinical presentations.

Materials and Methods

This study was undertaken in a tertiary care hospital. Information was collected from all the available clinical and laboratory data from 2013 to 2016 that were diagnosed as Neuro-Wilson's Disease.

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Sub Date: October 2nd 2018, Acc Date: October 17th 2018, Pub Date: October 18th 2018.

Citation: Lakshmi Lavanya M, Butchi Raju G, GopiS, Sateesh Kumar T and Aruna Kumari U (2018) Atypical Presentation of Wilson’s Disease – Need for High Index of Suspicion. BAOJ Neurol 4: 60.

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Information was collected on the following points. Clinical features such as age at onset, duration of the disease, evolution of disease, the time taken from symptom onset to diagnosis, various systemic and neurological symptoms and family history. Other important features considered for the diagnosis of WD were the presence of KF ring, low Ceruloplasmin (<20 mg/dl), high 24-hour urine copper (100 µg/24 h), other biochemical parameters and MRI Brain. All these features are applied to Ferenci Score. This scoring system for the diagnosis of Wilson's disease was developed at the 8th International Meeting on Wilson's disease and Menkes Diseases, Leipzig 2002 (Table-1) [5]. Interpretation of the WD by using this Ferenci Score- 4 points: diagnosis of WD highly likely; 2–3 points: diagnosis of WD probable, more investigations needed; 0–1 points: diagnosis of WD unlikely. Even though, mutation analysis and liver biopsy were not done in this study due to non-availability locally, so the Ferenci Score of four or more is considered as diagnostic of WD [5,6,7]. In a study in pediatric population the cut-off score of four had high sensitivity and specificity [6].

Up to now, no single diagnostic test can confirm or exclude Wilson's disease with 100% certainty. Genetic testing and biopsy are impractical to confirm the diagnosis in all patients due to socio-economic reasons. So, in our study we considered other parameters like presence of KF ring, serum ceruloplasmin, typical radiology findings, serum copper and 24-hour urinary copper for the diagnosis with a Ferenci Score of four or more as per the diagnostic algorithm for WD which was adopted in the EASL clinical practice guidelines [7].

Results

Preliminary data: A total of 36 patients were studied. All were presented with Neuro-wilsonian features at the time of analysis. Data were studied retrospectively regarding the first clinical symptom. Ferenci scoring was applied based on the available data both at the index time and initial symptom onset period. The results were grouped accordingly.

The mean age of the presentation was 14.5 years (7 – 41 years) with slight female preponderance (female: male - 1.4:1). The mean duration of the illness was 1.8 years. Demographic data was shown in the Table-2. K-F ring on slit lamp examination was noted in 31 patients initially. It is noteworthy that there were 21 patients misdiagnosed during first evaluation, with a mean delay in diagnosis on average being 5-9 months. In our study, only 41% have initial neurological clinical manifestations. Others were with various clinical manifestations like fertility related problems (8%), musculoskeletal complaints-2.7%, jaundice-25%, ocular-5.5%, cognitive-2.7%, psychosis-13.8% (Fig-1).

All patients were again sub classified into various groups based on the axis of involved neurological symptoms (Fig-2). Most common presentations were dyskinesia (58.3%), young onset Parkinson's like presentation (13.5%) (Fig-3), ataxia (8.3%) and mixed presentation (19.4%). Among the dyskinesia group most common presentation was dystonia (38%) (Fig-4), followed by chorea (19%), tremor (9.5%), athetosis (4.7%) and mixed way of presentation (28.5%). Biochemical and neuroimaging features were shown in the Table-2 & 3.

Ferenci scoring was applied both at the index time and initial symptom onset period. Only clinical symptoms were applied differently. Available abnormal biochemical parameters of the patient's laboratory data were kept as constant in both the analysis. By applying the initial symptom onset to the scoring, the diagnostic rate is only 42%, whereas at time of neurological presentation and the final diagnostic stage, the diagnostic rate is 88.5% i.e. the rate of misdiagnosis at the time of initial presentation is around 58.7%. Remaining two patients were diagnosed in the pre-symptomatic stage (family members).

Discussion

Prevalence of Wilson's disease is 12-29 per 1, 00,000 in European countries, 33-68 per 1, 00,000 in Asian countries and carrier rate is 1 in 122, not as rare as once believed [8]. In a recent population based study in Chinese population of Hong Kong the prevalence was 17.93 per million [9]. Usually, males are affected more common than females. We should consider WD first in the differential diagnosis of any patient presented with extra pyramidal or psychiatric or abnormal behavioral illness in a young patient. The salient demographic profile and clinical types of WD across the country has been summarized in Table-3 comparing with the present study [10].

Though hepatic involvement occurs early in the course of WD, it may go unrecognized and may not be the first symptom for seeking clinical attention. In the series by Walshe et al., hepatic presentation was the major presenting symptom in approximately 40% of patients followed by neurological manifestations in 40% of patients [1]. However, in other series, neurological manifestations were the presenting feature in about 60% of patients [10]. In our study neurological manifestations are noted in 41.6% followed by jaundice in 25% as initial presentation (Table-3).

Kayser-Fleischer (KF) rings on slit lamp examination is considered to be hallmark in diagnosis of WD, as was evident in one study of 282 patients where it is present in 100% of the cases with neurological dysfunction [11]. But, KF ring was seen in 86% of our cases at initial presentation and so absence of KF ring will not exclude WD [2,4].

Our study highlighted the various other systemic presentations and their misdiagnosis initially. It is noteworthy to special mention about two cases of atypical presentation in our group. A seven-year old boy presented initially to the ophthalmology department in form of frequent changes in the refractive error, later found to have presenile cataracts in both eyes followed by behavioral problems and finally presented to our department with dystonia after 3½ years of initial symptom (Fig-5). Sunflower cataract is considered as a pathognomonic sign in WD and these patients can present with visual disturbances [12]. Another interesting case is a young...
woman, initial consultation was to the obstetrician with the complaints of infertility, later developed isolated tongue tremor and finally diagnosed as WD with delay in diagnosis of two years (Fig-6).

Various studies on diagnostic errors with specific clinical syndromes show that clinical diagnoses are incorrect at variable frequency. Hu et al noted that among 1011 cases of hepato-lenticular degeneration, 516 cases were initially misdiagnosed, 193 cases failed to be diagnosed as a specific disease [13]. Taly et al noted that diagnostic errors or no diagnosis by referring doctors were detected in 192 (62.5%) of 307 patients [14]. In a study by Xie and Wu, only 44 out of 133 (33.1%) patients are initially correctly diagnosed as WD [15]. In our study initial misdiagnosis rate was 58%. In an epidemiological study of 490 patients of WD nearly 8.6% had history of seizures [16]. Kishore D et al has reported a case of adolescent onset of WD as psychosis [17]. In a case report, a thirty year old who had history of chronic arthritis was diagnosed to have WD after twelve years of initial presentation with joint pains [22]. Due to atypical presentation and misdiagnosis, whole-genome sequencing (WGS) is considered potentially universal time and cost effective molecular diagnostic tool [2,23]. Mutations in copper transporting gene ATP7B were implicated in the cause of WD and nearly 600 pathogenic variants have been identified [24]. A total of 308 mutant chromosomes of ATP7B were identified in India, out of which 86 are unique [25]. In view of multiple pathogenic variant mutations, identification of few specific mutations may be negative as seen in one study from North India due to genetic and ethnic heterogeneity [26].

In view of varied and atypical presentation, there is a concern that larger number of patients affected by WD may remain undiagnosed or treated very late in the course of disease. Even absence of family history may preclude the clinician for diagnosis of WD unaware of the varied genetic inheritance pattern associated with ATP7B mutations [4,27]. So, the physician should be aware of the typical hepatic, neurologic and psychiatric presentations, but also other rare manifestations of WD like osseo-muscular, renal, endocrine, hematologic phenotypes [27].

Our study highlights the awareness among health professionals about varied presenting features of WD and also the need of very high index of suspicion. This may have prognostic implications in young patients with extra pyramidal features, unexplained neuropsychiatric manifestations and liver disease and especially with various atypical systemic presentations.

**Table 1 Ferenci Score**


Abbreviations: K-F ring, Kayser-Fleischer ring; MRI, magnetic resonance imaging; ULN, upper limit of normal; WD, Wilson disease

<table>
<thead>
<tr>
<th>Ferenci Score: Scoring system for the diagnosis of Wilson’s disease developed at the 8th International Meeting on Wilson’s Disease and Menkes Diseases, Leipzig 2002</th>
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<tbody>
<tr>
<td><strong>K-F Rings</strong></td>
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<tr>
<td><strong>Neuropsychiatric symptoms suggested WD (for Typical brain MRI)</strong></td>
</tr>
<tr>
<td><strong>Coombs negative hemolytic anemia</strong></td>
</tr>
<tr>
<td><strong>24-h urinary copper excretion (in the absence of acute hepatitis)</strong></td>
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<tr>
<td><strong>Liver copper quantitative</strong></td>
</tr>
<tr>
<td><strong>Rhodanine positive hepatocytes (only in cases lacking a copper quantitative assessment)</strong></td>
</tr>
<tr>
<td><strong>Serum Ceruloplasmin (nephelometric assay, normal&gt;20mg/dL)</strong></td>
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<tr>
<td><strong>Mutation analysis</strong></td>
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</tbody>
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Table 2: Demographic Data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Result</th>
<th>Special Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-F ring</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>Low Serum Ceruloplasmin</td>
<td>87.5%</td>
<td></td>
</tr>
<tr>
<td>Abnormal 24 hr CU excretion</td>
<td>83.3%</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>78.8%</td>
<td>Bilateral basal ganglion: 63%, thalamus: 8.3%, brain stem: 5.5%, sub cortical white matter: 2.7%, combination: 5.5%, normal: 13.8%</td>
</tr>
</tbody>
</table>

Table 3: Biochemical and imaging profile


| Clinical Characteristics of Wilson's Disease patients in various Indian Studies |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Place of study                  | Bombay          | Pondicherry     | Vellore         | Hyderabad       | Pune            | New Delhi       | Ranchi          | Bangalore       | Visakhapatnam   |
| No. of cases (M:F)              | 23 (15:8)       | 08 (5:3)        | 30 (22:08)      | 12 (11:1)       | 124 (20:2)      | 22 (38:11)      | 49 (196:86)     | 36 (15:21)      |                |
| Mean age at onset               | 13.4            | 13.3            | NA              | 13.3            | 8.4             | 18.5            | 13              | 15.9            | 14.5            |
| (Range)                         | (4.25)          | (3.25)          | (6.50)          | (7.21)          | (4.60)          | (10.33)         | (8.23)          | (3.50)          | (7-41)          |
| Clinical Pattern                | Hepatic         | 1               | 3               | 11              | 1               | 67              | -               | 42              | 7               |
|                                | Neurological    | 10              | 3               | 13              | 10              | 28              | 34              | 195             | 15 (first symptom) |
|                                | Hepatic Neurological | 2           | 0               | -               | 1               | 0               | 15              | 10              | 1               |
|                                | Musculoskeletal | 3               | 2               | 6               | 0               | 0               | -               | 6               | 1               |
|                                | Psychiatric     | 0               | 0               | -               | 0               | 0               | -               | 7               | 2               |
|                                | Others          | 5               | 0               | -               | 0               | 10              | -               | 7               | 7               |
|                                | Asymptomatic    | 2               | 0               | -               | 0               | 19              | -               | 15              | 2               |
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Figure 1: Clinical data - First clinical presentation

Figure 2: Various Neurological Presentations

Figure 3: Young Onset Parkinson's disease; Imaging
Fig-4: Dystonia - Imaging

Figure- 5: K-F ring and Presenile Cataract; Imaging

Fig: 6: Tongue Tremor - Imaging
References


