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Psychiatric aspects of Wilson disease: a review

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ABSTRACT

Objective: To review the current evidence about psychiatric symptoms in Wilson's disease (WD).
Method: We searched Ovid, PsychInfo, CINHAL and PubMed databases from May 1946 to May 2012 using the key words *Wilson('s) disease* in combination with *psychiatry*, *psychiatric*, *psychosis*, *schizophrenia*, *depression*, *mania*, *bipolar*, *mood*, *anxiety*, *personality* and *behavior*.
Results: 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. When psychiatric symptoms preceded neurological or hepatic involvement, the average time between the psychiatric symptoms and the diagnosis of WD was 864.3 days. The prevalence of psychiatric disorders in WD patients varies wildly (major depressive disorder, 4–47%; psychosis, 1.4–11.3%). Certain gene mutations of *ATP7B* may correlate with specific personality traits.
Conclusions: Psychiatric manifestations represent a significant part of the clinical presentation of WD and can present at any point in the course of the illness. Psychiatric manifestations occurring without overt hepatic or neurologic involvement may lead to misdiagnosis. A better understanding of the psychiatric presentations in WD may provide insights into the underlying mechanisms of psychiatric disorders.

1. Background

Wilson's disease (WD) is an autosomal recessive illness characterized by excessive accumulation of copper in liver, brain and other tissues. The lifetime prevalence is estimated at around 1:30,000, but a recent study of abnormal gene frequency point to a possible higher prevalence of 1:7026 [1]. WD is attributed to a defect of the gene *ATP7B* (on chromosome 13), which encodes an ATP-dependent copper transporting transmembrane protein mainly expressed in the liver. A defect in ATP7B function leads to the accumulation of copper, primarily in the liver and subsequently in the brain. Formal diagnostic criteria were reviewed and outlined by Roberts and Schilsky (2008) [2]. Since the illness is inherited in an autosomal recessive fashion, 25% of the siblings of affected individuals can be patients, 50% carriers and 25% unaffected. Therefore, screening of the first-degree relatives is recommended. Without treatment, WD is progressive and fatal, with patients dying of liver failure or complications of their neurological illness. The first medical therapy was an intramuscularly delivered chelating agent, dimercaprol (also known as British anti-lewisite), that was introduced in 1951 [3]. This was followed by the introduction of oral agents, penicillamine in 1956 [4], zinc salts in early '60s [5] and trientine in 1969 [6].

Various psychiatric symptoms have been attributed to WD since it was first described in 1912. In Wilson's 1912 monograph, 8 of 12 cases had had psychiatric symptoms [7]. At that time, and for the next several decades, WD was recognized only by the neurological presentation with movement disorder or characteristic Parkinsonism. Furthermore, there was no medical therapy until the 1950s, and the natural history of the disease prior to that era was progressive neurological disability or death from liver failure. Less well characterized at that time were the psychiatric aspects of this disorder with respect to the natural history of WD. Only in the 1950s and 1960s it was found that psychiatric symptoms can occur at any point in the course of the disease or as side effects of the medications used to treat symptoms or WD itself. Psychiatric symptoms had been typically thought to be present along with neurological symptoms, and patients were often labeled as having neuro-psychiatric disturbances. More recently, however, it has become obvious that neurologic and psychiatric symptoms do not always present jointly. Some authorities have speculated that psychiatric symptoms indicate a more severe or advanced disease, may be related to irreversible brain damage secondary to copper toxicity, or are secondary to alternative metabolic influences produced by the malfunction of the liver such as hyperammonemia associated with hepatic encephalopathy [8].

The lack of recognition of these signs and symptoms as due to WD often leads to significant delays in diagnosis and treatment that can result in irreversible neurologic damage. Furthermore, many patients with WD will have psychiatric symptoms develop after diagnosis and

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initiation of treatment or following lapses in therapy [9]. Recognition of the relationship of the psychiatric symptoms to WD can help with administration of appropriate therapy aimed at both the psychiatric issues and underlying WD. Thus, knowledge of the psychiatric aspects of WD is essential for psychiatrists and other medical specialists and allied health professionals practicing in the general hospital.

The objectives of this article are to review the existing information about the nature and course of psychiatric problems in WD as well as to review the existing evidence regarding treatment efficacy for this clinical presentation.

2. Methods

Our review protocol is registered online with Prospero — the international prospective (P) register for systematic reviews (CRD 42013005176). We performed the literature search according to the PRISMA flow diagram (http://www.prisma-statement.org/statement.htm). We searched Ovid, PsychInfo PubMed and CINAHL databases from 1946 to May 2012 using the key words *Wilson's disease* and *Wilson disease* in combination with *psychiatry*, *psychiatric*, *psychosis*, *schizophrenia*, *mood*, *depression*, *mania*, *bipolar*, *anxiety*, *personality* and *behavior*. After removing the duplicates, the remaining articles were screened for date of publication (after January 1st, 1983), subjects (pertaining to humans only) and relatedness to the topic (to address as stated psychiatric symptoms in the course of WD). The remaining publications were assessed in full text for eligibility based on the following criteria: (a) diagnosis of WD; (b) assessment of psychiatric symptoms; (c) number of cases in the case series for prevalence studies.

We included only articles in which the diagnosis of WD was made through clinical and biochemical criteria or by molecular diagnosis of *ATP7B* mutations. Typical testing includes clinical examination (CE) and ophthalmologic evaluation for Kayser–Fleischer rings, measurements of serum copper and ceruloplasmin, 24-h urine copper excretion, liver histology and quantitative copper.

For information regarding prevalence of psychiatric symptoms in patients with WD, we included randomized controlled studies, case-controlled studies and case series with a minimum of five subjects. Where multiple publications reported on same cohort of subjects, we chose the study with the highest design quality (e.g., P rather than retrospective (R), with standardized assessments rather than lack of thereof).

3. Results

The initial search resulted in a total of 4070 publications, with 1266 remaining after removal of duplicates. During the initial screening of the 1266 publications, we selected articles published after Jan 1st, 1983, pertaining to humans only and those whose title indicated that they are addressing our topic. Full text review was performed for 270 publications. A total of 181 publications were excluded due to lack of direct connection with our topic (104), consisting in opinion reviews (18), insufficient evaluation of WD (8), insufficient evaluation psychiatric symptoms (19), assessing exclusively cognitive function (10) or duplicating the data already reported elsewhere (7). We are presenting the summary of 90 articles, out of which are 57 case reports, 12 cohort studies (5 P, 7 R), 3 case controls (CCs) and 4 case series.

3.1. Psychiatric symptoms as the initial presentation of WD

In association with neurological or hepatic symptoms, psychiatric symptoms are found in the initial presentation of WD in 30–64% of cases [10,11]. In a R study of 42 patients with WD, 64.8% reported psychiatric symptoms at the time of the initial presentation, most commonly being personality changes (45.9%), depression (27%) and hyper sexuality (14.2%).With treatment, symptoms tend to improve; however, a plateau is reached after 2 years of treatment [10]. Another R study of 195 patients with WD indicated that 51% of the patients had the psychiatric symptoms upon initial presentation and 20% had seen a psychiatrist prior to the diagnosis of WD [11]. There is growing evidence that the disease can present with psychiatric symptoms alone for many years, with hepatic and neurologic involvement becoming clinically noticeable only years later. In these individuals, delays in diagnosis and treatment are common.

Table 1 summarizes the case reports found in the literature in which the psychiatric symptoms appeared as the initial presentation of WD [12–46]. The ages of the patients ranged between 5 and 59 years, 75% were males, with an average age for the onset of psychiatric symptoms being 22.6 years (S.D.= 11.2). The most common psychiatric presentation was psychosis (36.11%), followed by depression (22.2%); personality changes and learning related problems were each present in 8.3% of patients. The average time between the psychiatric symptoms and the diagnosis of WD was 2.42 years (S.D.= 2.97). Commonly, psychiatric symptoms appeared, and the patient was started on neuroleptic treatment; subsequently, neurologic symptoms occurred and were assumed to be due to neuroleptics. The diagnosis of WD was suspected only after liver abnormalities were noted or severe neurological problems developed. In comparison, the median time between initial symptoms and when the diagnosis of WD was first established was 1.5 years for neurological WD and 0.5 years for hepatic WD [47].

3.2. Psychiatric symptoms in the course of WD

We found a total of 20 case series and cohort studies describing psychiatric symptoms in the course of WD. Their findings are summarized in Table 2. Thirteen of these 16 studies use structured psychiatric or psychological assessments [8,48–50,47,51–58] while 8 reported the psychiatric symptoms based on routine clinical evaluation [10,59–64]. Of 20 studies, 10 were cross-sectional studies [8,49,54–57,51–53,58], 3 were P studies [47,65,66] and 7 were R reports [10,60,62–64,67,61]. In addition, we found 16 case reports of psychiatric presentations during the course of WD, which are summarized in Table 3 [68–83].

Dening and his group were the first to prospectively study the psychopathology of WD. Their work resulted in several publications, the most comprehensive being a report of 129 cases [48]. Patients were assessed at their initial presentation and then at two follow-up visits using the Association for Methodology and Documentation in Psychiatry (AMDP) system. The most common psychiatric symptoms were depression (30%), incongruous behavior (30%), cognitive impairment (28%) and irritability (22%). The cognitive impairment diminished over time and was present in only 5% of patients assessed at the second follow-up visit. Twenty-five percent of patients seen in follow up were diagnosed as depressed [48]. In a smaller P study, 57% of patients were rated as having personality changes [84]. The authors concluded that psychiatric and neurological symptoms are significantly correlated. In another P study, depression, cognition and psychosis were assessed via structured instruments (Table 2). Two separate neurologists assessed the neurological symptoms defined by means of the rating scales of Webster, Starosta-Rubinstein and Young. Again, the psychiatric symptoms were found only in patients who also exhibited neurological findings [47].

Subsequently, several studies psychiatrically assessed patients with neurological WD. An analysis of 48 patients with WD presenting in the neurology clinic showed that 44% of them had psychiatric and/or sleep abnormalities. In this study, psychiatric symptoms are listed among other neurological findings. Irritability (present in 10.4% of the patients), hallucinations (6.25%), depression (4.16%) or inappropriate laughing (4%) and deterioration in school performance (10.4%) were all reported as first manifestations of WD [62]. When personality traits