Quality of Life and Psychiatric Symptoms in Wilson's Disease: the Relevance of Bipolar Disorders

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Abstract: *Introduction:* Wilson's disease is an inherited disorder caused by a gene located on chromosome 13, which involved copper transportation across cell membranes. The disease can cause a reduced incorporation of copper into ceruloplasmin resulting in accumulation of this metal in the liver, central nervous system, kidneys and other organs. The objective is to define the frequencies of psychiatric disorders in WD, the amount of impairment of Quality of Life [QoL] in patients with WD and the relevance of the psychiatric disorders in the QoL of people suffering by WD.

Methods: This is a systematic review. The search of the significant articles was carried out in PubMed using specific key words.

Results: Such other neurological diseases, WD is characterized by chronic course and need of treatments, impairment of functional outcomes and high frequency of psychiatric symptoms, although a specific association between Bipolar Disorders and WD was recently found. Despite this, since today few studies are carried on WD patients' quality of life related to psychiatric symptoms. Some new reports showed a link between presence of Bipolar Disorders diagnosis, cerebral damage and low Qol.

Conclusion: Prospective studies on large cohorts are required to establish the effective impact of psychiatric disorders comorbidity, particularly Bipolar Disorders, on quality of life in WD and to clarify the causal link between brain damage, psychiatric disorders and worsening of QoL.

Keywords: Wilson's disease, psychiatric symptoms, quality of life, bipolar disorders, copper.

1. INTRODUCTION

Wilson's disease is an autosomal recessive inherited disorder of copper metabolism [1], caused by different mutations in a gene located on chromosome 13 [2, 3], which encodes the ATP 7B, an adenosine triphosphatase, involved in copper transportation across cell membranes [4]. There are over 200 mutations [5, 6] of the gene that can cause a reduced incorporation of copper into ceruloplasmin and a lower biliary excretion of copper, resulting in the accumulation of this metal in the liver, central nervous system, kidneys and other organs [7, 8].

The prevalence of WD in almost all ethnic groups is approximately 1:30,000 and the carriers are 1:90 [9]. WD is more frequent in communities isolated and characterized by a high consanguinity. In particular, in Sardinia [Italy] an incidence of 1/7.000 births has been found [10].

The age at presentation is mainly the pediatric age, usually between 6 and 8 years [11], but it's not infrequent to find clinical onset in adolescence and in young adults, however an onset above 40 years is rare [12].

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The clinical manifestations of WD are the result of the gradual accumulation of free copper in the tissues, which may cause damage in many organs. Early manifestations are hepatic [40% of cases], neurological [35%], psychiatric [10%] or other, such as hematologic, renal, ocular [15%] [13]. Most WD patients present signs of liver and central nervous system involvement. Indeed, the majority of patients with WD present with either predominantly hepatic or neuropsychiatric symptoms, with either clinically asymptomatic or symptomatic liver involvement. The remaining 15-20% patients present with symptoms attributable to the involvement of other organs [14-16].

Patients with hepatic WD usually present in late childhood or adolescence, and exhibit features of acute hepatitis, fulminant hepatic failure, or progressive chronic liver disease in the form of either chronic active hepatitis or cirrhosis of the macronodular type [17, 18]. The degree of liver involvement is variable, ranging from asymptomatic hepatosplenomegaly with mild elevations of certain liver enzymes, to complete liver failure. Associated symptoms include non specific general symptoms, ascites and jaundice, and symptoms such as hematemesis and melena that are caused by portal hypertension. Independently of the initial presentation, all WD patients will show abnormalities on liver biopsy [19]. A progression in hepatocellular carcinoma in these patients is rare [20].

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In suspected cases of hepatic WD, if the clinical and biochemical parameters are not supportive, a hepatic biopsy can be carried out and a measure of its copper content obtained by mass spectroscopy or atomic absorption spectroscopy. Normal values are up to 250 μg [microgram] per gram of dry tissue weight, and in WD this value is exceeded in about 80% of cases. Following biopsy, histochemical testing with rhodamine can also show copper and copper-associated protein, but their absence does not exclude a diagnosis of WD, particularly in children.

Kayser-Fleischer rings represent deposition of copper in Descemet's membrane of the cornea. When they are visible by direct inspection, they appear as a band of golden-brownish pigment near the limbus. A slit-lamp examination by an experienced observer is required to identify Kayser-Fleischer rings in most patients. They are not entirely specific for WD, because they may be found in patientswith chronic cholestatic diseases and in children with neonatal cholestasis; however, these disorders can usually be distinguished from WD on clinical ground. Kayser-Fleischer rings are present in only 44%-62% of patients with mainly hepatic disease at the time of diagnosis In children presenting with liver disease, Kayser-Fleischer rings are usually absent. However, Kayser-Fleischer rings are almost invariably present in patients with a neurological presentation, but even in these patients they may be absent in 5% of cases [21, 22].

Sunflower cataracts can be found in patients with Wilson's disease and these ocular abnormalities may resolve with chelation therapy.

It is possible the detection of hemolytic anemia that predisposes to cholelithiasis and may also represent the first presentation [23], and it is probably related to the release of large amounts of copper from damaged hepatocytes.

There may be manifestations of Fanconi syndrome and progressive renal failure with alterations of tubular transport of amino acids, glucose and uric acid.

Unusual manifestations include cardiomyopathy, arthritis and endocrinopathies, such as hypoparathyroidism [24].

Neurological symptoms occur later, mainly in adolescents and young adults [9].

The most common manifestations include postural and intentional tremors, dysphagia and contractions of facial muscles, dysarthria, bradykinesia, muscle hypertonia, choreo-athetosic movement of limb [25]. Imaging (CT, MRI, SPECT) shows unspecific changes in the basal ganglia, thalamus, cerebellum, brainstem and white matter [26].

Half of patients with neurological manifestations have a history of behavioral abnormalities in the five years prior to diagnosis. The clinical features are various and may include loss of emotional control [angry outbursts and bouts of crying], depression, hyperactivity, loss of sexual inhibitions, anxiety disorders, cognitive impairment, mental retardation, mania, behavioral abnormalities, personality changes and alcohol abuse [27]. These psychiatric symptoms can be the effects of brain tissues damage caused by copper accumulation, but might be also the consequence of a real comorbidity with affective disorders, bipolar disorder principally, which might co-segregate with the mutation causing the WD in closed community with high consanguinity. Psychiatric symptoms with late insurgence may be side effects of treatments used to control WD core symptoms. For example, treatment with D-penicillamine was proved to cause neurological exacerbation or the occurrence of neuropsychiatric manifestations, particularly movement disorders, seizures and psychosis. Sometime these events may be irreversible, and can occur even in previously asymptomatic patients [28, 29]. Whatever their origin, psychiatric symptoms further complicate the course of the disorder, since anxiety and depression negatively impact on quality of life and undermine the close compliance needed to achieve illness compensation; emotional and behavioral dyscontrol further and negatively impact on the social life of these patients, worsening the impairment and the disability caused by WD core symptoms.

Patient-reported point of view on health-related quality of life has become an interesting way to obtain information on the experience of disease, treatment efficacy and need of cares, as it reflects the individual's way to cope up with the illness.

Quality of life is a subjective, heterogeneous concept of wellbeing correlated with a number of factors, such as severity and duration of illness, use of medications and stress events. QoL has been defined to generally correspond to the total wellbeing and encompasses both the physical and the psychological determinants such as emotional wellbeing, behavioral competence, sleep and rest, energy and vitality and general life satisfaction [30]. The subjective perception of quality of life is a construct today considered of great relevance as a measure of outcomes in chronic disease [31, 32], particularly in those disorders that required long-term treatments and have great impairment and impact of daily life, and it has became central to evaluating the effectiveness of treatments in clinical research [33, 34].

Neurological diseases are often characterized by chronic course and impairment of functional outcomes, so measurement of QoL in paradigmatic neurological diseases appears today very interesting for well understanding the burden of illness tolerated by patients. In literature there are several studies on QoL in multiple sclerosis and Parkinson's disease, which show the correlation between a single symptom [i.e. fatigue, pain, movement impairment] or symptoms cluster, or impact of treatments and QoL. There is not a systematic review of studies on QoL in WD.

This paper sets out to review studies on the prevalence of psychiatric symptoms in patients with WD, aiming at defining the associated impact on the quality of life in patients with WD, to determine the relevance of these symptoms and their consequences on the life of people diagnosed with WD.

Past reviews on the topic often did not consider issues in validity and reliability of the tools used in psychiatric assessment, or included studies that did not use standardized criteria for the diagnosis of WD. This systematic review aimed at identifying high quality papers, based on valid and reliable measures of quality of life and based on standardized criteria for the diagnosis of WD.

2. METHODS

The search of the significant articles was carried out in PubMed/Medline with the following key words: "Psychiatric symptoms and Wilson's disease"; "Depression and Wilson's disease"; "Depressive Disorder and Wilson's disease"; "Mood Disorders and Wilson's disease"; "Anxiety Disorders and Wilson's disease"; "Schizophrenia and Wilson's disease" and "Quality of life and Wilson's disease".

Interval was set from January 1981 To December 2011, and the search was further refined on 31 January 2012.

Over 400 [n = 452] papers were retrieved by the search. The abstract of the extracted papers were read and the more pertinent ones [n = 115] were obtained in full version and analyzed in deep.

Data on quality of life were searched with the following key words: "Quality of Life" and "Wilson's disease". Overall, 15 studies were found available on the argument of "general well-being", but only 3 published papers and one already presented at congress and currently submitted for publication in a peer review journal were focused on the assessment of health-related QoL.

3. RESULTS

3.1. Psychiatric Symptoms in WD

The psychiatric manifestations of WD have been frequently reported, since the original paper of S.A.K Wilson, who described psychiatric symptoms in 8 out of his 12 cases, 2 of them with schizophrenia-like psychosis. [35, 36]. Psychiatric symptoms may be the symptom of presentation of the disease. According to case series, one third of patients with WD may initially present behavioral abnormalities, and failure to recognize these may lead to misdiagnosis and delay in starting specific treatment [37]. Currently, nearly 20% of patients undergo psychiatric treatment before specific chelation therapy begins [38].

A wide set of psychiatric, psychological and psychosocial impairments have been reported; these include: mental retardation [39], confusional states [40], cognitive impairment [41], dementia [42], poor school performance [43], anxiety [44], depression [45], emotional lability [46], mania, abnormalities of behavior and personality disorders [47], schizophrenia-like states [48, 49], suicide [25]. The frequency and relative clinical significance of different psychiatric manifestations are difficult to determine from the literature; while the possible association with schizophrenia-like states has attracted much interest, debate such states are infrequent, the exact lifetime prevalence of psychiatric symptoms in patients with WD is unclear but the estimates range is from 30 to 100% of symptomatic patient [49].

The psychiatric manifestation in WD have categorized into five clusters [49]: 1) cognitive impairment; 2) personality disorders; 3) affective disorders; 4) psychosis; 5) other psychiatric alterations.

3.1.1. Cognitive Impairment

Cognitive impairment occurs in less than 25% of patients [25, 36] and it is generally mild [44]. However, cognitive impairment worsens with progression of disease and the concomitance of neurological disorders [50]. A clear dementia is less common, and impairment of consciousness occurs almost always in terminal stages of disease [27]. The exact mechanisms by which this deficit is established remain unclear. Some authors related these changes to a reduce speed of the motor component rather than a slowing of information processing [51]. Others have suggested that abnormalities on neuropsychological tests in WD patients are due to a subclinical hepatic encephalopathy [52].

3.1.2. Personality Disorders

Lifetime prevalence of personality changes ranges from 46% to 71% [53, 26], and typical symptoms are irritability or aggressiveness [25, 26]. These symptoms have been correlated with the presence of dyskinesia, dysarthria and lesions of putamen and pallidum [54].

Irritability and aggression are often related to the displaying of incongruous behavior and personality changes [27]. Typically, incongruous behavior results from a dissociation between environmental cues and behavioral outcome, and expresses with disinhibited, bizarre and reckless behaviors.

3.1.3 Mood Disorders

Depression is an extremely common psychiatric problem in WD patients. Estimated prevalence of depression ranges 30 to 60% of cases, but its presence in patients with WD is underestimated [49].

Whether depression is a psychological reaction to WD or is due to biological impairment is unresolved. The situational aspects of living with a debilitating illness can give rise to demoralization, hopelessness, loss of self-worth, and expression of a wish to die. This fact is intuitively obvious to clinicians, patients, and families, and sometimes leads clinicians prematurely to assign a reactive explanation to the patient's symptoms [55]. In vivo neuroimaging studies suggest that depression and other neuropsychiatric disorders are associated with central serotonergic deficits. In a prospective study [38] on 23 adult patients with WD was revealed that depressive symptomatology (assessed using the Hamilton rating scale for depression (HAMD)) is related to an alteration of presynaptic serotonin transporters (SERT) availability as measured by (123I)-2beta-carbomethoxy-3beta-(iodophenyl)tropane ((123I) beta-CIT) and high-resolution single-photon emission computed tomography (SPECT). Data were correlated with the presynaptic serotonin transporter density (SERT density) in the thalamus-hypothalamus and the midbrain-pons regions measured with high-resolution single-photon emission computed tomography (SPECT). A significant negative correlation was found between HAMD and SERT density in the thalamus-hypothalamus region ($r = -0.49$, $p = 0.02$), but not in the midbrain-pons ($r = -0.31$, $p = 0.15$).

Overall, the prevalence of depression is higher in WD patients than in patients with other chronic disabling diseases, such as rheumatic arthritis, even with a similar level of disability [56]. This finding suggests that some biological component, probably the effect of brain tissues damage, is in cause in the production of symptoms of expression in patients with WD. The high prevalence of depression in WD is generally thought associates to a high risk of suicide. Suicidal behavior occurs from 4% to 16% of patients with WD

across studies [25, 49]. A correlation between the degree of disability and the presence of depression is not yet established.

Other affective disorders, such as hypomania and mania, have also been reported in WD.

There are few case-reports in the literature of typical Bipolar Disorder as presenting symptom of WD [47, 57- 61].

Costa Machado and colleagues [62] suggested a higher association between Bipolar Disorder and WD than previously reported in the literature. In their case series, which describes the neurological manifestations of 119 patients with WD, the authors observed a wide array of psychiatric symptoms: catatonia, agitation, aggression, delusional thoughts, and mania. In a study involved 50 confirmed patients with Wilson's disease [63], evaluation of the psychiatric co-morbidity was assessed by structured clinical interview for DSM-IV Axis-I disorders (SCID): 12 patients (24%) fulfilled the diagnostic criteria for syndromic psychiatric diagnosis: Bipolar Disorder (18%), Major Depressive Disorder (4%), and dysthymia (2%). Recently a study was carried out by our group [64] using a case-control desing with cases randomly selected from a community survey [64] to determine the association between neurological damage and mood disorders. Psychiatric diagnoses according to DSM-IV criteria were determined with structured interview tools (ANTAS-SCID) [65, 66] and brain damage was detected using SPECT to observe focal or diffuse decrease of uptake in grey matter. The results indicated that the lifetime prevalence of DSM-IV Bipolar and Major Depressive Disorders is higher in people with WD than in sex- and age-matched controls. The OR was 12.9 for Bipolar Disorders and 6.7 for Major Depressive Disorders, and there was an association between SPECT positivity and Bipolar Disorders.

3.1.4. Bipolar Disorder and Trace Elements Accumulation

It is interesting to consider that it was hypothesized for the mood disorders a pathogenic mechanism involving trace elements accumulation.

In the literature, early studies showed that women affected by chronic depression sometimes have copper, zinc, and cesium deficiencies [67, 68], while later studies suggest that the presence of depression and other neuropsychiatric symptoms is due to the deposit of copper in the Central Nervous System [69]. In a study of 2003 [38] it was demonstrated, by SPECT, a reduction in thalamic and hypothalamic presynaptic dopamine and serotonin transporter due to the accumulation of copper. It was also highlighted a negative correlation between the density of presynaptic dopamine transporters and the severity of depression, assessed using the Hamilton Rating Scale for Depression. Another study [70] had hypothesized trace elements to be implicated as a causative factor for Bipolar mood Disorders, through a neurodegenerative mechanism of pathogenesis, while elevated vanadium and molybdenum levels have been reported in serum samples from Bipolar Disorders patients. This latter study showed, using DSM-IV standard diagnostic criteria and classification of Bipolar Disorders into types I, II, and V according to the concept of Young and Klerman, that Na, K, P, Cu, Al, and Mn were elevated significantly in Bipolar I [Mania] [$P<0.001$]. In Bipolar II-Hypomania, Na, S, Al, and Mn were increased significantly [$P<0.02$], while in Bipolar II-Depression, Na, K, Cu, and Al were increased significantly [$P<0.001$]. Finally, in Bipolar V, Na, Mg, P, Cu, and Al were increased significantly [$P<0.002$] compared to a control group. A more recent study by Gonzales-Estecha and colleagues [71] found higher serum copper and zinc, blood lead and cadmium, and urine lead, cadmium, and thallium concentrations in patients diagnosed with Bipolar Disorders compared to a control group.

Moreover, accumulation of copper was shown related to oxidative stress: in bivalve species [72] and in skeletal muscle of broilers under heat stress, copper decreases as effects of dietary Selenium, Vitamin E and their combination, in parallel with increases of antioxidant defense [73]. In Humans accumulation of copper was associated with oxidative stress in allergic asthma patients, in which introduction of nutritional supplement therapy decreases both oxidative stress and copper plasma levels, improving immune response and pulmonary function [74]. Oxidative stress may determine damages in Central Nervous System. Brain, which contains large amounts of polysaturated fatty acids and possesses low antioxidant capacity, is particularly vulnerable [75]. Copper levels were found elevated in several brain areas in a degenerative disease as Niemann-Pick C [76], which was specifically indicated to be associated to Bipolar Disorders [77].

Altered oxidative stress parameters were found associated to the pathophysiology and therapeutics of Bipolar Disorders, including changes in the levels of enzymes superoxide dismutase [SOD], catalase [CAT] and thiobarbituric acid reactive substances [TBARS] [78]. The well-known stabilizing agent Lithium was shown able to reverse increased oxidative stress parameters in Bipolar Disorders by limiting the enzyme activity, potentially lowering hydrogen peroxide and hydroxyl radical formation [79, 80]. For instance, in valproate and lithium-treated rats were observed a decline in lipid peroxidation and an increase in CAT levels [81, 82].

If the results of our study are confirmed, and the hypothesis that accumulation of minerals such as copper plays an etiological role in psychiatric disorders through an increase of oxidative stress damage may also be confirmed, WD may serve as a pathogenic model of Bipolar Disorders.

3.1.5. Psychosis and New Perspective on Bipolar Disorder

Schizophrenia and other form of psychosis in WD have been reported but it is widely accepted that these conditions are not more frequent in patients with Wilson's disease than the general population [27, 25] and are more frequent [8%] in patients with neurological involvement [83]. This correlation, however, can lead to errors in diagnosis because the presence of neurological manifestations in a patient with psychosis may be misinterpreted as the side effect of neuroleptic treatment.

The strong association between bipolar disorders and WD should be interpreted, keeping in mind the modification of the diagnostic criteria and the evolution of the concept of "Bipolar Spectrum Disorders" in the last few decades [84]. It seems likely that literature reports in the past of "schizophrenia-like psychosis" in WD were due to use of a different definition of schizophrenia compared to current psychiatric diagnostic criteria. In contrast, the association of WD and

bipolar disorder may explain the frequent descriptions of "loss of emotional control, hyperactivity, or loss of sexual inhibition, irritability" reported in WD patients [85, 62].

3.1.6. Other psychiatric disorders

Other psychiatric disorders have been associated with WD, such as anxiety disorders, substance abuse, catatonia and anorexia; their prevalence in WD patients compared with general population is difficult to determine from the literature [48].

3.2. Treatment of Psychiatric Disorders in WD

Specific treatment of WD itself can improve psychiatric and behavioral manifestation, although most studies focus purely on neurological changes rather than on psychiatric changes [49].

Treatment with D-penicillamine can lead neurological exacerbation or the occurrence of neuropsychiatric manifestations, particularly movement disorders, seizures and psychosis. These events may be irreversible and can occur even in previously asymptomatic patients [28, 29].

Treatment with Tetrathiomolybdate was associated with excellent results both for neurological symptoms and for psychiatric ones [83].

Follow-up studies have shown that mood stabilizers are effective in the management of mood disorders. Neuroleptics must be avoided routinely as their use may lead to significant worsening of parkinsonian features, tardive dyskinesia or other extrapyramidal symptoms, allowing creating errors in the diagnosis and management of these patients [37].

Some reports have demonstrated the efficacy of clozapine [86], quetiapine [87] and olanzapine [88].

Lithium has proven useful in the management of maniacal symptoms in patients who did not respond to antipsychotics; moreover lithium, unlike other drugs, is not metabolized by the liver and does not cause weight gain. However it may cause a worsening of tremor. The efficacy and the risk-benefit of treatment with psychotropic drugs in patients with Wilson's disease remains to be determined.

Literature offers few and discordant data regarding the curative effects of orthotopic liver transplantation [OLT] under psychiatric aspects. It has been described both the curative effect of the transplant on neuropsychiatric symptoms [89] and the severe worsening of psychiatric illness [90]. From a recent study it was emerged an excellent prospective of resolution also of psychiatric symptoms accompanied by late-postoperative persistent improvement [91].

3.3. Quality of Life in WD

There are few studies on QoL in WD: 3 published papers out of 15 were specifically focused on the assessment of health-related QoL; we added a fourth study, recently presented in a congress.

Komal Kumar and coll. [92] published a study with a small sample of WD patients [30 patients] evaluated using Neurological Symptom Score [NSS] for clinical severity and WHO-BREF for QoL. Patients [M:F = 23:7] had a mean age of 27.97 ± 11.16 years at evaluation and the mean duration of treatment of 9.2 ± 6.4 years. All four domains of WHO-QoL-BREF [Physical, Psychological, Social and Environmental] correlated well with each other [$p < 0.01$], indicating that QoL domains are interlinked, giving a holistic view of health. Individuals with limited functional mobility and ability to interact within their environment and society will most likely perceive their QoL to be poor, with NSS inversely correlated with the Physical domain [$p < 0.02$], while the duration of treatment had a positive correlation with the Physical domain [$p < 0.01$]. The Physical domain of the QoL assessment was the only domain affected by duration and severity of disease: the psychological, social and environmental domains of QoL did not relate to severity of disease or duration of symptoms. Nevertheless, the small sample size and study restrictions [patients with inability to respond to the questionnaire due to behavioral problems, low IQ or other disease related factors were excluded] don't consent to generalize the results.

Recently, Svetel *et al.* [93] carried on a cross-sectional study to identify clinical and demographic factors influencing health-related QoL in 60 treated, clinically stable patients with WD using a generic questionnaire, the Medical Outcomes Study Short-Form 36-Item Health Survey [SF-36]. The level of disability and grading of WD severity were assessed by the Global Assessment Scale for WD [GAS for WD]; cognitive impairment and depressive features were assessed respectively by the Mini Mental State Examination [MMSE] and the 21-item Hamilton Depression Rating Scale [HDRS]. Lower scores on the SF-36 domains were found in patients with neurological and psychiatric symptoms compared with those with a predominantly hepatic form of WD. Significant inverse correlations were obtained between the various SF-36 domains and the period of latency from the first symptoms/signs appearance and treatment initiation, MMSE and HDRS scores, and the level of disability and grading of WD multi-systemic manifestations assessed by the Global Assessment Scale for WD [GAS for WD].

Sutcliffe and colleagues [94] published a paper on long-term follow-up and quality of life data obtained prospectively for 24 patients who underwent liver transplantation between 1988 and 2000 for Wilson's disease associated with severe liver disease. In long-term survivors, quality of life was assessed using the 36-Item Short Form 36 Health Survey Questionnaire. After a median follow-up of 92 months, all survivors [22 patients] have satisfactory graft function [5-year patient and graft survival, 87.5%], with quality-of-life scores [assessed in 86% of survivors] comparable to age- and sex-matched controls from the general population.

The above cited case-control study [66] aimed also to evaluate the impairment of quality of life due to mood disorders in WD. The results indicated that there was an association between SPECT positivity, Bipolar Disorders, and low quality of life as measured using SF-12. However, the power of the study did not allow to clarify whether the bipolarity caused the low quality of life or whether this was a confounding factor due to the same etiology [brain damages due to the copper accumulation, as demonstrated by SPECT positivity] for bipolarity and low quality of life.

4. DISCUSSION

Neurological diseases with high frequency, such as stroke, Multiple Sclerosis, Parkinson's and Alzheimer's disease, characterized by severe psychiatric symptoms, are being detected for QoL assessment in several studies [95, 96]. Although the typical presentation of WD involves severely hepatic and nervous systems, initial symptoms are variable, often characterized by a mild, psychological distress, and making an early diagnosis difficult. In spite of this clinical condition is rare, it results medically and socially requiring, as those patients which receive a diagnosis during childhood have to endure the burden of disease and chronic treatment or will need liver transplantation decades later. Moreover, early treatments are often critical, especially in patients with neurologic disorders.

The association between WD and Bipolar Disorders appears today more frequent than believed in the past, dues to the more specific diagnostic criteria allowing to include as Bipolar Disorders cases that early researchers defined "schizophrenia-like psychosis" or "behavioral abnormalities" [97]. Several recent studies hypothesized that Bipolar Disorders etiopathogenesis may be due to trace elements accumulation [such as copper] in brain tissues, causing neurodegeneration. WD etiopathogenesis is analogue, and if the hypothesis that minerals such as copper play an etiological role in psychiatric disorders may be confirmed, WD may serve as a pathogenic model of Bipolar Disorders. Furthermore, in a recent study [64] the presence of brain damages detected by SPECT in WD patients was associated with a higher prevalence of lifetime DSM-IV Major Depressive Disorder and Bipolar Disorders, and lower SF-12 scores than controls. Nevertheless, prospective studies on large cohorts are required to establish the effective impact of psychiatric disorders, particularly Bipolar Disorder comorbidity on quality of life in WD patients and to clarify the causal link between brain damage, psychiatric disorders and worsening of QoL.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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