Review

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Neurological Deterioration in Wilson's Disease—Types, Etiology, Course, and Management

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Wilson's disease (WD) is an inherited disorder of copper metabolism in which pathological copper accumulation, mainly in the liver and the brain, leads to hepatic and/or neuropsychiatric signs and symptoms. Chelators and zinc salts can successfully induce negative copper balance in many patients; however, neurological deterioration may still be observed. This phenomenon can be divided into: (1) early 'paradoxical' neurological deterioration, which usually develops in the first 6 months of anti-copper treatment and may be commonly related to drug type, or (2) late neurological deterioration, which mostly occurs after 6 months of treatment and is often related either to non-compliance with treatment, overtreatment resulting in copper deficiency, or adverse drug reactions. Another explanation, especially for early neurological deterioration, is natural WD progression, which can be difficult to differentiate from drug-related deterioration, but usually leads to a worse outcome. There is still no consensus on how to define neurological deterioration in WD using scales or biomarkers, how to distinguish it from the natural disease progression, its risk factors, and optimal management. This narrative review, based on the current literature, aims to provide definitions, prevalence, pathological mechanisms and factors related to neurological deterioration, and also proposes schemes for diagnosis and treatment.

Keywords: Wilson's disease; neurological deterioration; compliance; copper; anti-copper treatment

Introduction

Wilson's disease (WD) is a genetic disorder of copper metabolism with pathological copper accumulation in different organs, mainly the liver and brain, which results in associated clinical symptoms, most commonly hepatic and neuropsychiatric manifestations [1–3]. Initial hepatic symptoms range from an asymptomatic increase in liver function tests to cirrhosis-related symptoms (compensated or decompensated) and acute liver failure (ALF). Neurological symptoms include various movement disorders (mainly tremor, dystonia, choreoathetosis, and parkinsonism) with dysarthria, drooling, dysphagia and secondary gait and posture disturbances [1]. Psychiatric symptoms are less specific and include mainly behavioral and personality changes, mood disturbances, as well as cognition functions deficits, such as in attention and executive functions [1–3]. To counteract copper overload, treatment is based on inducing negative copper balance with (1) chelators (d-penicillamine [DPA] or trientine [TN]) to increase copper urinary excretion and (2) zinc salts (ZS) to decrease copper absorption from the gastrointestinal tract [1,2]. Liver transplantation is the ultimate treatment for patients with ALF or decompensated liver cirrhosis who do not respond to anti-copper drugs [1–5].

Generally, since DPA was introduced in 1956, outcomes with WD have been favorable, with improvement or stabilization in almost 85% of treated patients [5]. However, WD should be diagnosed as early as possible and should be treated long-life without interruptions to achieve the best possible outcome [2,6–10]. Other than delayed diagnosis, key therapeutic issues in treated patients are neurological deterioration and compliance with anti-copper treatment [6–12]. There are several guidelines from medical societies related to diagnosis, treatment, and maintaining compliance [1–3]; however, there are still no clear answers and recommendations on how to define neurological deterioration in WD. In 10–15% of all patients with WD and 22% with neurological manifestations, early neurological deterioration may be observed in the first 6 months following treatment initiation [8–12]. Late deterioration may occur in some patients, usually after more than 6 months of treatment [8–12]. Another explanation, especially for early neurological deterioration, is a natural progression of WD, which may be difficult to differentiate from drug-related paradoxical deterioration, but usually leads to worse outcomes [2].

Despite the significance of neurological deterioration in WD, considerable knowledge gaps exist with regard to definitions, risk factors, and appropriate management. We

performed this review to highlight the scope of the problem, proposing definitions as well as diagnostic and treatment options.

Neurological Deteriorations in WD — Definitions, Types, and Prevalence

Before neurological scales such as the Unified Wilson's Disease Rating Scale (UWDRS) or the Global Assessment Scale for WD (GAS for WD) were developed and introduced into WD management, patients were examined, described, and scored neurologically, generally with severity grading (0–3), and their neurological status was described as improved, stabilized, or worsened [13–25]. In 2014, a definition of neurological deterioration was created, which is most commonly used today: any deterioration in UWDRS part II (activity of daily living) or deterioration of at least 4 points in UWDRS part III (detailed neurological examination) or occurrence of neurological symptoms *de novo* [26,27]. Another interesting proposition was suggested by Poujois *et al.* [28] in 2020 where neurological worsening was defined as a minimum of a 20% increase in UWDRS and a 2-point increase in the modified Rankin Scale (mRS). However, other studies have defined neurological deterioration as any worsening using neurological scales. More currently, Litwin *et al.* [29] defined a minimally clinically important difference (MCID) in WD by different methods: an anchored-based method using UWDRS with Clinical Global Impression-Severity of Illness (CGI-S) and usinga standard error method (SEM). The MCID range reporting neurological worsening in such assessments varied between 2.28 points (anchored-based method with CGI-S) to 4.668 (SEM), with a mean result of 3.47 points in UWDRS part III calculated as the MCID for neurological worsening. The estimated UWDRS III distributional MCIDs obtained from this study were consistent with clinical judgments in the literature and our previously used propositions [29].

Classifying neurological deteriorations, the literature recognizes two main types – early and late – generally based on a cutoff of 6 months from the time of anti-copper treatment initiation [12,26,30–36]. From a retrospective analysis of 163 patients with neurological symptoms, Mohr *et al.* [35] recently proposed new time frames based on the common distribution of deteriorations in these patients: early (<3 months of treatment initiation) and late (>12 months). However, a small number of patients with neurological deterioration who had received 6–12 months of treatment (1 adherent to anti-copper treatment and 2 non-adherent) could not be classified with this approach. In a previous study by Litwin *et al.* [26], the mean time to deterioration across 15 patients was 2.3 months; however, 7 patients (46%) worsened between 4 and 6 months [27]. Based on these data, the cut-off point of 6 months seems to be most appropriate to allow classification of all patients.

The rationale for time-dependent classification of neurological deterioration is based on the course of WD with treatment [13–48]. Early neurological deterioration is typically associated with the use of chelators, especially DPA [12], while late deteriorations are often attributed to treatment non-compliance, with only 70% of patients remaining compliant, especially over long follow-up periods [2,49–51]. Moreover, the phenomenon of WD overtreatment, with copper deficiency may lead to the aggravation of neurological symptoms or *de novo* occurrence, which has been seen approximately 15.7 years after initiating anti-copper treatment [52,53].

Various hypotheses have been proposed to explain early neurological deterioration, including that the rapid mobilization of copper from the liver following treatment onset may release 'free' copper into the blood, leading to a transient increase [15–22,54]. The transient blood free copper overload may cause oxidative stress and potentially damage the central nervous system (CNS) due to secondary copper redistribution. Chelators, especially DPA, which acts faster than ZS, may theoretically result in more frequent neurological deteriorations and has even led to the opinion that ZS are safer than DPA for WD patients with neurological symptoms [24]. Early reports from the 1980s highlighted severe 'paradoxical' neurological deterioration particularly in patients who started DPA treatment at the full dose (1500–2000 mg) [17–20,25,55,56]. After the association between full-dose DPA and neurological deterioration was established, the number of devastating deteriorations rapidly decreased; however, subsequent studies have described deteriorations with all drugs used in WD treatment (ZS, TN), albeit at lower frequency [14–17,36].

Another cause of early neurological deterioration may be the natural course of WD, which is challenging to distinguish from treatment-related early deterioration based on current definitions [53]. Some patients with neurological symptoms and brain changes may progress despite anti-copper treatment. Brain magnetic resonance imaging (MRI) studies have shown that some changes are reversible (acute, reflecting edema and demyelination), while others are irreversible, reflecting neuron necrosis and atrophy [6,12,27]. Reversible brain MRI changes in WD could completely recover during anti-copper treatment. However, irreversible changes like necrosis and atrophy will persist [6,7,13]. In such cases, anti-copper treatment mainly halts the progress of neurological disease but may not reverse the neurological symptoms. Hence, the initial severity of brain changes in MRI, as well as neurological symptoms, may be a risk factor [26]. In previous studies, e.g., evaluating molybdenum salts, subjective judgments by investigators were common; however, objective methods are needed to avoid bias in such analysis [39]. There are conflicting reports regarding the prevalence of early neurological deterioration in WD [13–27], especially in older studies documenting a relatively high occurrence of this phe-

Table 1. Proposed risk factors of early neurological deterioration.

Reference	Study details	Risk factors for early neurological deterioration
Ziemssen *et al.* [27]	Retrospective analysis of 61 WD patients (neurological, hepatic and asymptomatic)	- initial sNfL concentrations - initial severity of neurological WD scored by UWDRS part II and III - initial brain MRI chronic damage score using a semiquantitative brain MRI WD scale
Hou *et al.* [38]	Retrospective analysis of 47 neurological WD patients	- younger age at onset of neurological WD symptoms - dystonic symptoms present - severe WD mutation genotype – patients who carried a frameshift, splicing and/or nonsense mutation in the *ATP7B* gene
Członkowska *et al.* [37]	Case report	- DPA introduced too fast (750 mg as initial dose with ZS)
Litwin *et al.* [26]	Retrospective analysis of 143 patients	- initial severity of neurological WD scored in UWDRS parts II and III - brain MRI lesions located in the pons and thalamus - concomitant treatment with drugs blocking dopamine neurotransmission
Kalita *et al.* [41]	Prospective study of 63 patients	- drooling - leukopenia - thrombocytopenia - splenomegaly - evidence of chronic liver disease
Porzio *et al.* [20]	Case report	- DPA introduced at full dose
Brewer *et al.* [19]	Case report	- DPA introduced at a high dose
Hilz *et al.* [17]	Case report	- DPA introduced at a high dose
Glass *et al.* [18]	Case report	- DPA introduced at full dose
Brewer *et al.* [25]	Case report	- DPA introduced at full dose

DPA, d-penicillamine; sNfL, serum neurofilament light chain; UWDRS, Unified Wilson's Disease Rating Scale; WD, Wilson's disease; ZS, zinc salts.

nomenon, up to 50% in some cases [16]. The most recent data as of 2023, from a systematic review, indicate a prevalence of 10–15% among all WD patients and up to 22% in neurological cases [12]. Furthermore, late deteriorations (mainly due to non-compliance and adverse drug reactions [ADRs]) are reported in almost 15% of patients (from 30% of non-compliant patients), resulting in an overall high proportion of neurological deterioration in about 30% of patients over the disease course [49].

Risk Factors for Early Neurological Deterioration in WD

In the literature, there are several proposed risk factors for early neurological deterioration (Table 1, Ref. [17–20,25–27,37,38,41]). In most studies, almost all patients who neurologically worsened had neurological symptoms at diagnosis before anti-copper treatment was introduced [12]. As mentioned, another proposed mechanism of early neurological deteriorations is the type of anti-copper treatment [4]. The comparative efficacy and safety of the different drugs available to treat WD, chelators (DPA or TN) and ZS, are often discussed by physicians and scientists as there are no head-to-head studies comparing treatment regimens and recommendations [1,2] are mostly based on center experience. In several studies, case and series reports, chelators (especially DPA) are associated with a higher risk of neurological deteriorations than other drugs [16–23,25]. One of the first, spectacular, and most often cited papers regarding DPA and neurological deteriorations, from 1987, was based on questionnaires, not objective neurological assessments. Only 28 out of 54 patients completed the questionnaire, but of those who did, early neurological deterioration was seen in 52% of patients treated with DPA [16]. Three patients had no neurological symptoms and deterioration occurred between 6–12 months (late) in 3 cases. Reanalyzing the results from the paper, the prevalence of neurological deterioration was 18.5% (10/54), comparable with later studies [16]. Several case reports of neurological deterioration after treatment initiation, especially on DPA but also on TN and ZS, have been published and documented in a systematic review [12], mostly in patients initiating high-dose DPA. Based on the findings of the systematic review, several papers additionally analyzed early neurological deteriorations on different anti-copper drugs (DPA, TN, and ZS) in retrospective analyses, giving inconclusive results according to drug effect. For example, a retrospective study of 405 patients by Weiss *et al.* [43] found neurological deterioration in 2% of patients treated with first-line DPA, 3.4% of patients on second-line DPA, 10.5% on first-line TN and 7.8% on second-line TN, without a statis-

tically significant difference between the treatments. Further, the same group of authors, analyzing retrospectively another 288 WD patients, found neurological deterioration in 9.1% of patients on DPA, 8.8% on TN and 9.5% on ZS as second-line treatment, also without statistical significance [50]. Similarly, in an analysis of 143 WD patients, Litwin *et al.* [26] did not find a statistically significant difference between treatments. Four systematic reviews and meta-analyses compared the rates of neurological deterioration in patients taking different anti-copper drugs [12,57–59]. Wiggelinkhuizen *et al.* [57] found more frequent neurological deteriorations in WD patients taking DPA compared with ZS (5.7% versus 0.8%). Appenzeller-Herzog *et al.* [58] also found that treatment with DPA versus ZS was associated with an increased likelihood of early neurological deterioration (odds ratio [OR] 2.86; 95% confidence interval [CI] 1.18–6.93). In a systematic review by Tang *et al*. [59], WD patients treated with DPA had a significantly higher prevalence of neurological deterioration compared with ZS (n = 386; relative risk 1.96, 95% CI 1.31–2.93%; $p < 0.01$). And finally, Antos *et al*. [12], analyzing 217 patients with early neurological deterioration from 1512 WD patients, concluded that the drug type did not appear to represent a risk factor.

Other documented risk factors include initial severity of neurological disease scored by the UWDRS (part II and III) as well as by a brain MRI semiquantitative scale (acute toxicity and chronic damage), and additionally by WD-related lesions in the thalamus or pons [26,27]. These findings may be related to the natural history of disease progression since patients with severe neurological deficits or severe brain MRI changes usually have irreversible changes in the brain, including necrosis, which cannot improve. Also, the most disabling and treatment refractory neurological symptoms (usually leading to higher UWDRS scores), such as dystonia, may not improve and often worsen.

One of the most promising biomarkers for assessing the risk of neurological deterioration is initial levels of serum neurofilament light chain (NfL), a member of the family of neurofilament proteins that maintains the structural integrity of neuronal cytoskeleton. NfL is released into cerebrospinal fluid and blood during CNS injury and, as such, is a highly reliable liquid biomarker for neuroaxonal injury and for monitoring the progression of various neurodegenerative conditions (e.g., Parkinson's disease, multisystem atrophy, Alzheimer disease) and neuroinflammatory disorders (e.g., multiple sclerosis) [60–64]. In WD, positive correlations have been observed between sNfL levels and the severity of neurological disease including neurological phenotype (compared to hepatic and asymptomatic) and neurological disease severity scale (UWDRS) [27]. Ziemssen *et al.* [27] analyzed 61 newly diagnosed WD patients and found that initial sNfL concentration was a risk factor for neurological worsening (OR 6.94), with a cut-off level of 18.15 pg/mL (sensitivity 80%; specificity 72.5%). Further prospective longitudinal studies are needed to verify these observations; however, sNfL seems to be the first quantitatively measured objective biomarker that can predict neurological worsening in WD patients. Ziemssen *et al*. [27] additionally documented that advanced initial neurological deficits (higher UWDRS scores indicating more severe neurological deficits) and changes in brain MRI are also associated with early neurological deterioration. The results suggested the need for new definitions based on biochemical and neuroradiological biomarkers, such as initial sNfL levels and neuroradiological scores. Initial sNfL levels and neuroradiological scores (using a WD-specific brain MRI semiquantitative scale) would be expected to improve after initiating anti-copper treatment. If there is no improvement during the first 6 months, particularly in sNfL, and if neurological deterioration occurs, this could be considered to reflect natural disease progression. In cases where improvements and deterioration coexist, drug-related worsening or lack of compliance could be considered and verified through copper metabolism assessment [56].

Less frequently reported in the literature include links between early deterioration and the use of concomitant drugs blocking dopaminergic neurotransmission, chronic liver disease, splenomegaly, leukopenia and thrombocytopenia, and drooling [30].

Risk Factors for Late Neurological Deterioration in WD

Late neurological deterioration in WD is usually related to treatment non-compliance [1–4]. Risk factors for non-compliance include ADRs leading to drug discontinuation, which occur in up to 30% of patients on DPA, ZS, and TN [1–4]. Also, educational level may impact compliance with treatment since patients with upper secondary/post-secondary and higher education are more often compliant with treatment compared to primary school or vocational education. The importance of patient education about WD and its treatment (including ADRs) as well as involving their families in patient management is crucial [2]. Treatments for WD are generally taken 3 times per day and exploring once-daily solutions may promote better compliance and therefore better outcomes.

Another cause of late neurological deterioration is copper deficiency in the course of WD overtreatment [52]. This is a rare complication of chronic treatment of WD, usually with ZS and without adequate control of copper metabolism. In the literature, there are 20 WD patients reported so far with copper deficiency in the course of WD (10 males and 10 females). The mean time from anti-copper initiation to copper deficiency symptoms was 15.7 $\pm$ 11.7 years. The most frequent clinical symptoms are hematological (leukopenia and neutropenia) and neurological (sensory axonal neuropathy, posterior cord myelopathy, white matter demyelination, and epileptic seizures or

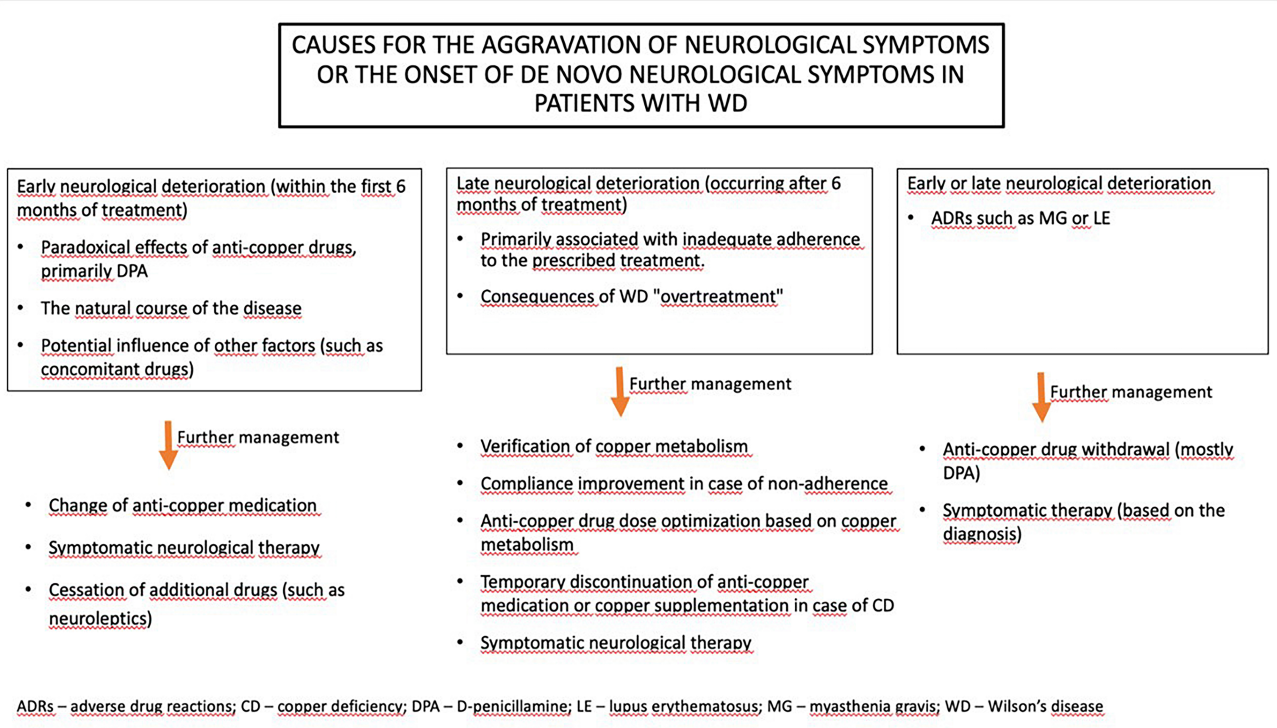

Fig. 1. Neurological deterioration in WD — the diagnosis and management algorithm. (PowerPoint, Office Professional Plus 2019, Microsoft (Redmond, WA, USA).

epilepsy *de novo*) [52]. According to the American Association for the Study of Liver Disease (AASLD), copper deficiency could be suspected when daily copper excretion is <20 μg/24 hours (<0.3 μmol/24 hours) with ZS therapy or <100 μg/24 hours (<1.6 μmol/24 hours) with chelators if associated with low serum total copper and low ceruloplasmin levels; however, cut-offs for serum copper and ceruloplasmin are not provided [1,2,52]. In the literature, there are several case reports of WD patients who neurologically worsened, with numbness, progression of gait disturbances, and increased prevalence of falls, in whom initially the anti-copper treatment was escalated. After verification of copper metabolism, treatment should be temporarily stopped and copper supplementation may be considered. With copper deficiency, hematological symptoms usually recover after normalization of copper metabolism and neurological symptoms usually improve, but they can persist. It is therefore important to be aware of copper deficiency in cases of late neurological deterioration, particularly in those mostly treated with ZS, as treatment intensification may cause irreversible neurological worsening [1,2,52].

Some cases of late deterioration, but also some early neurological deterioration, may be an ADR of the anti-copper drug (mostly DPA) causing aggravation of neurological symptoms or even neurological symptoms *de novo*, of which clinicians involved in WD management should be aware [1,2,4,65,66]. ADRs include the autoimmune-related complications of DPA-induced myasthenia gravis (MG) and lupus erythematosus (LE). DPA-induced MG in WD patients occurs relatively rarely (only eight cases have been described in the literature so far); however, MG symptoms — progressive muscular weakness with ptosis, dysphagia, dysarthria, and fatigue — may mimic neurological WD deterioration, and further anti-copper drug escalation can worsen the MG symptoms [1,2,66]. MG usually occurs 2–12 months after DPA introduction, but in some cases, MG symptoms may arise after several years. The DPA-induced MG diagnosis is based on neurological signs, an electrophysiological examination, positive serum antibodies against acetylcholine receptors (AChR-Abs) or muscle-specific kinase (MuSK-Abs), a positive edrophonium test and reversal of MG symptoms after DPA cessation (which usually occurs in a few weeks, but may take longer) [66]. The course of DPA-induced LE may mimic severe infection; however, arthralgia leading to immobilization, even in the case of body temperature normalization, may additionally be treated as neurological worsening. The diagnosis of LE is based on international criteria: (1) at least one clinical and serological LE symptom; (2) exposure to an LE-inducing drug (e.g., DPA); (3) no history suggestive of LE before the introduction of a potentially LE-inducing drug; (4) exclusion of other disorders; and (5) resolution of LE after suspected drug cessation. Treatment of DPA-induced LE includes cessation of DPA, with introduction of ZS or TN, and symptomatic treatment (including steroids) until the LE symptoms disappear [65].

Neurological Deterioration in WD — Management and Outcome

When finding neurological worsening in a patient with WD, a differential diagnosis work-up should be performed (Fig. 1) to explore the timing of the deterioration, copper metabolism assessment to verify treatment adherence as well as investigations to rule in/out copper deficiency and ADRs.

Copper metabolism assessment can exclude non-compliance as a cause of worsening. During anti-copper treatment, urinary copper excretion should be <100 µg/24 hours with ZS and 200–500 µg/24 hours with chelators, especially in long-term treated patients. In early WD, urinary copper excretion could be higher, up to 1000 µg/24 hours in the first year on chelators and up to 200 µg/24 hours with ZS [1–3]. In the case of early neurological deterioration with treatment compliance, the anti-copper drug should be switched to another drug to reverse the potential for drug-induced neurological worsening. Concomitant medications should also be checked, especially drugs with the potential to cause neurological deterioration (e.g., neuroleptics and drugs blocking dopaminergic transmission), and these should be stopped if possible. Extended observation over time is typically necessary to confirm the etiology of the deterioration [12]. Additionally, a detailed analysis of hematology and biochemistry may help diagnose copper deficiency (leukopenia and neutropenia), which can be managed with temporary anti-copper drug cessation and copper supplementation if required. Drug-induced MG or LE should be diagnosed and managed as above.

In a systematic review by Antos *et al*. [12] that analyzed the outcome of early neurological worsening, 24.2% of patients had symptoms that reversed completely and 27.3% had partial reversal. Symptoms did not improve by almost 40%, with some loss to follow-up. Data on the reversibility of late deteriorations are limited. In the case of copper deficiency, hematological symptoms are often reversible, but neurological symptoms have been reported to completely resolve in only 16% of cases, with only partial improvement in the rest [52]. ADRs causing neurological deterioration are generally reversible during the first few weeks after drug cessation and supplementary treatment where needed [65,67], underlining the importance of clinician awareness and prompt diagnosis [1–5].

The symptomatic treatment of neurological deterioration in WD is based on general treatment of neurological symptoms e.g., dystonia, tremor, parkinsonism, chorea, drooling, and dysphagia [53]. In addition, physiotherapy and speech therapy may be considered, according to general principles, and after discussion with the patient.

In cases of severe irreversible neurological deterioration, liver transplantation may be considered. In a study by Poujois *et al*. [28], liver transplantation resulted in major improvement in 8 out of 18 patients (44%) with severe persistent neurological deterioration and 1 additional patient experienced moderate improvement (5%), consistent with the general findings on reversibility observed by Antos *et al*. [12].

New treatment modalities are being developed that aim to have a low/no risk of neurological deterioration as well as to achieve better compliance through less frequent administration e.g., once-daily TN [60]. Although most of these new treatments are currently only at the preclinical stage, initial results (e.g., with methanobactin) are promising [60].

Conclusions

Neurological deterioration is a common occurrence in patients with WD and because of the potential for reversibility, all patients experiencing neurological deterioration should be carefully examined by an experienced neurologist, including physical and neurological investigations, brain MRI, serum hematology and biochemistry analysis, assessment of copper metabolism and urinary copper excretion, to provide the most comprehensive information for diagnosis and management.

Availability of Data and Materials

Not applicable.

Author Contributions

TL – performed the research, drafting and editing the manuscript, JB, AA, AC – conducted the research and performed the drafting and editing of the manuscript. All authors have read and approved the final version of manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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