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Early neurological worsening in patients with Wilson's disease

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ABSTRACT

Background: Early neurological worsening during treatment initiation for Wilson's disease (WD) is an unresolved problem. Our aim was to establish the frequency and outcome of early neurological worsening in patients with WD.

Methods: We analyzed 143 symptomatic patients diagnosed with WD between 2005 and 2009. Early neurological deterioration was based on worsening on the Unified Wilson's Disease Score Scale, scored at baseline through 6 months or occurrence of new neurological symptoms. Reversibility of worsening was followed up to 24 months.

Results: Early neurological worsening was observed in 11.1% (16/143) and involved only patients with neurological signs at diagnosis. Mean time to worsening from treatment initiation was 2.3 ± 1.9 months. Neurological deterioration was completely reversible in 53% (8/15) and partially in 13% (2/15) of patients over 9.2 ± 5.2 months. Patients who experienced early deterioration had significantly more severe baseline neurological deficit, higher prevalence of thalamic (66% vs 29%) and brain stem (73% vs 33%) lesions seen on baseline magnetic resonance imaging, and more often used concomitant dopamine receptor antagonists (46% vs 5%). Disease duration, treatment type (D-penicillamine or zinc sulfate), type of neurological manifestations, initial copper metabolism results, and liver function parameters did not differ between evaluated groups.

Conclusions: Neurological worsening at the beginning of anti-copper therapy may occur in over 10% of WD patients. Special attention should be paid to those with severe initial neurological manifestations, advanced brain injury and using dopamine receptor antagonists. Type of anti-copper therapy did not show clear association with early neurological worsening.

1. Introduction

Wilson's disease (WD) is a genetic disease involving copper metabolism disturbances that result in copper accumulation in many tissues with secondary damage to affected organs (e.g., liver and brain) [1–3]. WD is also one of the few genetic disorders that can be successfully treated with pharmacological agents, such as chelators that induce urinary excretion of copper or zinc salts that inhibit copper absorption in the digestive tract [1–16]. Clinical improvement is observed during treatment in the majority of WD patients. However, there are also cases of neurological worsening, often severe and irreversible, that occur soon after initiation of WD treatment [1,2,9–17]. This has been reported mainly in patients starting therapy with chelators but some recent papers describe similar frequency of worsening on zinc salts [10,18,19]. The reason for this phenomenon is not fully understood [1,2]. One proposed explanation is rapid mobilization of copper from tissue with transient elevation of blood and cerebrospinal fluid (CSF) levels of toxic free copper [9,13,15–17]. In contrast to early deterioration, late neurological deterioration in WD is associated mainly with poor adherence [20,21]. In the literature there are no data about potential predictors of early deterioration or association between applied treatment and outcome in WD patients who experienced neurological deterioration. Thus, the aim of our study was to analyze the occurrence and outcome of early neurological worsening in newly treated, symptomatic WD patients and to establish the clinical and laboratory factors that may affect progression.

2. Materials and methods

2.1. Patients

This is a retrospective analysis of prospectively collected data of all consecutive adult patients newly diagnosed with symptomatic WD in the 2nd Department of Neurology, Institute of Psychiatry and Neurology

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Warsaw between January 2005 and December 2009. The study was approved by the local ethics committee of the Institute of Psychiatry and Neurology, Warsaw, Poland. The WD diagnosis was based on clinical symptoms, abnormal copper metabolism, genetic examination and confirmed using international criteria [22]. The disease was considered symptomatic if a patient had clinical signs of WD at the time of diagnosis or earlier. The hepatic symptoms and signs were assessed according to clinical data and laboratory results. The neurological examination followed a detailed pattern, as described previously [19].

The included WD patients were divided into two groups according to the presence of neurological symptoms at diagnosis, and then further subdivided into groups with and without early neurological deterioration. All patients were treated with either D-penicillamine (DPA) or zinc sulfate (ZS), which are the only anti-copper agents available on the Polish market [18,19]. There was no protocol for choosing the first line therapy drug and attending neurologist had no clear preference of one drug over the other. The decision was usually made after discussing with patients regimens, side effects, pregnancy planning and costs of both treatments [19]. To account for this source of bias we additionally compared severity of baseline neurological dysfunction between DPA and ZS.

2.2. Detailed clinical assessment

Hepatic assessment consisted of a structured interview and additional laboratory examination. Each patient was asked questions about fatigue, weight loss, leg edema, jaundice, abdominal swelling, hematemesis, hemorrhages, and fulminant liver failure. Laboratory examinations included serum aminotransferases (upper normal limit for alanine was 40 IU/L), bilirubin, international normalized ratio (INR), albumin and abdominal ultrasonography (USG). Baseline hepatic involvement was classified as follows: 1) lack of hepatic signs or symptoms; 2) mild injury (increased level of aminotransferases or bilirubin or INR, but without significant sonographic changes in liver parenchyma; 3) moderate injury (increased levels of aminotransferases or bilirubin or INR < 2.4 combined with enlargement of liver or spleen in USG; 4) severe injury (INR > 2.4, and/or USG changes in liver echogenicity; and 5) very severe injury (acute liver failure, hepatic encephalopathy) [19].

Neurological evaluation was based on a structured interview with questions about salivation, dysphagia, speech, writing, gait disturbances, bradykinesia, and involuntary movements. Neurological manifestations were classified using a system (rigidity-tremor, tremor, dystonic, parkinsonism) applied in our department since 1960 [19]. According to our protocol, all patients with neurological symptoms were scored in the following two domains of the Unified Wilson's Disease Rating Scale (UWDRS) [23,24]: part II, activities of daily living (0, completely independent; 39, completely dependent); and part III, neurological deficits (0, no deficit; 143, maximum). The assessment with the UWDRS was done at diagnosis (i.e., treatment initiation) and again at 3, 6, 12, 18, and 24 months, or earlier in the case of neurological deterioration.

Early neurological worsening was defined as any deterioration in UWDRS part II or deterioration of at least 4 points in UWDRS part III during the first 180 days from onset of therapy [19]. The reversibility of neurological deterioration was defined as follows: 1) complete, improvement of UWDRS scores compared to baseline results; and 2) partial, improvement in patient UWDRS scores compared to early neurological worsening results (the worst recorded score), but still worse than at baseline. Furthermore, for specific clinical analysis, the WD patients were divided into two groups according to the presence or absence of early neurological worsening. The early deterioration group was analyzed according to the timing of neurological worsening since WD therapy began, as well as neurological deterioration reversibility during 24 months of observation. In addition, both groups (i.e., with and without early neurological deterioration) were analyzed according to selected clinical and laboratory variables. We accounted for the initial clinical manifestation of WD (with or without neurological symptoms); the severity of initial neurological deficits (assessed in UWDRS parts II and III); concomitant treatment (during initiation of WD treatment or retrospectively up to 1 month before the diagnosis was established) with dopaminergic receptors blocking agents (neuroleptics/anti-emetics); gender, age at diagnosis, disease latency (time between first symptom and treatment initiation), type of WD treatment, type of neurological presentation at diagnosis, and severity of baseline liver disease.

2.3. Brain magnetic resonance imaging (MRI) analysis

Routine brain MRI was performed in all WD patients at the time of diagnosis. The conventional MR imagers with standard head coils and implementation of routine brain protocols were used. The MR images were qualitatively evaluated by a neuroradiologist not involved directly in the study (WC) for abnormalities in putamen, globus pallidus, caudate nuclei, cerebellum, thalamus, and brain stem. The WD lesions were assessed as hypointense in T1-weighted sequences and hyperintense in T2-weighted sequences (or, rarely, hypointense). The presence of atrophic changes (dilatation of lateral ventricles, widening of sulci and cisterns) was divided into cortical brain atrophy, cerebellar atrophy, and ventricle widening and visually assessed subjectively in T1-weighted sequences. The presence or absence of brain pathology was scored as "0", no abnormality, and "1", changes in signal intensity or presence of atrophic changes (as previously described) [25,26]. The localization of brain MRI WD pathology was analyzed according to the possibility of neurological deterioration.

2.4. Laboratory analysis

Analyzed laboratory findings included copper metabolism (serum ceruloplasmin, copper, urinary copper excretion), hematology (white cell count and platelets) and liver functions test (LFT) (serum alanine and aspartate aminotransferases, gamma glutamyl transpeptidase, alkaline phosphatase, albumin, total bilirubin and international normalized ratio) obtained at the time of WD diagnosis. Comparisons were made between groups with and without early neurological deterioration, as well as between baseline and time of worsening within the group that experienced neurological deterioration. Depending on applied treatment, we also report individual values of daily urinary copper excretion or zinc excretion and serum zinc levels, which may to some extent be a marker of compliance [1,2].

2.5. Statistical analysis

Calculations were carried out using Statistica v.10 (Stat Soft Inc. 2011, Tulsa OK, USA). Data were presented as number with percentage or mean with range and standard deviation. Comparisons were made using the two-tailed Fisher's exact test or the Mann–Whitney *U* test, as appropriate. We considered $P < 0.05$ statistically significant.

3. Results

3.1. Clinical data

Of the 143 newly diagnosed, symptomatic WD patients we identified 16 who experienced early neurological deterioration (16/143; 11.1%). All those cases occurred in the group of patients with at least some neurological signs and symptoms at the time of WD diagnosis (16/70; 22.8%). Therefore, the final analysis includes only patients with initial neurological presentation. One patient with early worsening was lost to follow-up for external reasons and therefore excluded from the analysis (Fig. 1).

The mean duration from initiation of WD treatment to early worsening was 2.3 ± 1.9 months (range: 0–6 months), and the mean