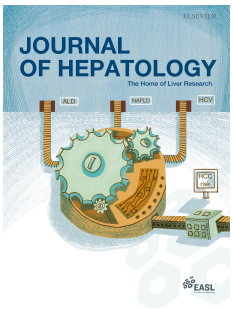

Early Neurological Worsening in Wilson's Disease: the need for an evidence-based definition

Tomasz Litwin, MD, PhD, Anna Członkowska, MD, PhD, Lukasz Smolinski, MD, PhD

PII: S0168-8278(23)04932-2

DOI: https://doi.org/10.1016/j.jhep.2023.06.009

Reference: JHEPAT 9221

To appear in: *Journal of Hepatology*

Received Date: 14 June 2023

Accepted Date: 15 June 2023

Please cite this article as: Litwin T, Członkowska A, Smolinski L, Early Neurological Worsening in Wilson's Disease: the need for an evidence-based definition, *Journal of Hepatology* (2023), doi: https://doi.org/10.1016/j.jhep.2023.06.009.

Early Neurological Worsening in Wilson's Disease: the need for an evidence-based definition

Tomasz Litwin, MD, PhD [1,*] Anna Członkowska MD, PhD [1], Lukasz Smolinski, MD, PhD [1]

[1] Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

***** Correspondence: Tomasz Litwin, MD, PhD, Institute of Psychiatry and Neurology, Second Department of Neurology, Sobieskiego 9, 02-957 Warsaw, Poland. Tel: +48 22 4582537; fax: +48 22 8424023; E-mail: tomlit@medprakt.pl

Running title: Early neurological deterioration in WD

Word count: 798 (with references)

Conflict of interest: The authors declare no conflict of interest

Financial disclosure: All financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, grants, patents received or pending, royalties) with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the submitted publication have been completely disclosed.

We have no financial interests relevant to the submitted publication.

Funding: No funding has been provided for the research

To the Editor

We read with great interest the article by Mohr et al.(1) on neurological worsening in Wilson's disease(WD) and would like to share our views. In WD, which is a treatable metabolic disorder, the hepatic symptoms improve typically 2 to 6 months after anti-cooper treatment is started, but the improvement in neurological symptoms may take up to 3 years (1-5). Unfortunately, based on our current systematic review up to 21.8% of patients with the neurological presentation at diagnosis experience a neurological worsening during the first 6 months of treatment(2). This early neurological worsening is sometimes referred to as drug-related or "paradoxical" although there is no direct evidence to support a casual relationship between treatment and worsening(1-2,4) (apart high starting dose of d-penicillamine)(3). Neurological worsening occurring later than 6 months after treatment start (late worsening) is typically attributed to non-compliance, which occurs in up to 30% of patients with WD(1,5).

In the 1980s, the early neurological worsening was reported in as many as half of all patients with WD receiving d-penicillamine(3); this observation made physicians reluctant to use the drug in patients with neurological symptoms. However, later studies, including some with a prospective design, reported a lower frequency of the early neurological worsening: 11% - 15% among all patients and up to 32% among those with the neurological presentation(2). In a retrospective chart review, among 128 patients with the neurological presentation of WD, Mohr, et al. found the early neurological worsening in 26%(1), which is almost in line with previous work (4) as well as with our systematic review - 21.8%(2). However, Mohr et al. looked for the early worsening during the first 3 months of treatment compared to 6 months in most previous studies(1).

It would be easier to compare different studies if we agreed on a definition of the early neurological worsening in WD. We suggest that the definition should be based on objective neuroimaging and biochemical markers of brain injury, which could help distinguish between

a treatment-related worsening and a natural course of the disease. Currently, in clinical trials, the distinction between the two is based on a subjective judgment of the investigator (5). The available evidence indicates that the change in the concentration of neurofilament light chain in serum(4) or in the rate of brain atrophy(2) after treatment initiation could help establish an objective timeframe for the definition of the early neurological worsening in WD. For example, if these two biomarkers normalize or at least plateau as late as 12 months after treatment start, should we still regard the cases of worsening occurring before that time as drug-related or paradoxical? We think not because such evidence would rather support a natural progression of the disease. Therefore, we need to investigate prospectively if and when biomarkers of brain injury in WD normalize after treatment start to be able to decide on when a neurological worsening in WD is drug-related. We suspect that the natural progression of the disease, regardless of treatment, could explain a substantial proportion of cases of early neurological worsening because the severity of neurological impairment at treatment start is the best predictor of such a worsening(2). In addition, judging whether a patient has a neurological worsening based solely on a subjective judgment is flawed, particularly when assessed retrospectively. We therefore need to agree on what change in impairment constitutes a worsening: an increase of at least 4 points on the Unified Wilson's Disease Rating Scale part III, of at least 1 point on part II(4-5), or more than 20% in the total score (2). Finding an evidence-based definition of the early neurological worsening is also clinically relevant because this outcome should be assessed in drug trials in WD(2, 5).

References:

[1] Mohr I, Pfeiffenberger J, Eker E, Merle U, Poujois A, Ala A, Weiss KH. Neurological worsening in Wilson disease – clinical classification and outcome. Journal of Hepatology 2023; doi:org/10.1016/j.hep.2023.04.007.

[2] Antos A, Czlonkowska A, Smolinski L, Bembenek J, Przybylkowski A, Skowronska M, Kurkowska-Jastrzebska I, Litwin T. Early Neurological Deterioration in Wilson's Disease: A Systematic Literature Review and Meta-Analysis. Neurological Sciences 2023; DOI: 10.1007/s10072-023-06895-6.

[3] Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol 1987; 44: 490–493.

[4] Ziemssen T, Smolinski L, Czlonkowska A, Akgun K, Antos A, Bembenek J, Kurkowska-Jastrzebska I, Przybyłkowski A, Skowrońska M, Rędzia-Ogrodnik B, Litwin T. Serum neurofilament light chain and initial severity of neurological disease predict the early neurological deterioration in Wilson's disease. Acta Neurol Belg 2023; 123: 917-925.

[5] Weiss KH, Askari FK, Czlonkowska A, Ferenci P, Bronstein JM, Bega D, Ala A, Nicholl D, Flint S, Olsson L, Plitz T, Bjartmar C, Schilsky ML. Bis-choline tetrathiomolybdate in patients with Wilson's disease: an open-label, multicentre, phase 2 study. Lancet Gastroenterol Hepatol 2017; 2: 869–876.