Management of Wilson Disease: The Quest Continues

Wilson's disease (WD) is a recessively inherited disorder of copper metabolism, caused by a mutation in the *ATP7B* gene at chromosome 13, with resultant accumulation of copper in various organs, predominantly in the liver, brain, cornea, heart and the kidneys.[1] The global prevalence of WD is estimated to be 1 in 30,000–100,000.[2] There are no community-based incidence and prevalence studies from India; however, the prevalence seems to be higher than the global estimates.[3] Typical clinical symptoms and signs, decreased serum ceruloplasmin level and presence of Kayser–Fleischer ring on slit-lamp examination lead to a suspicion of WD, which is confirmed by genetic testing.[4] Zinc salts reduce the absorption of dietary copper from the intestine, while copper chelators such as dimercaprol, d-penicillamine and trientine decrease the blood copper levels. These drugs form the mainstay of treatment in these patients.[5] Even under regular therapy, development of new neurological abnormalities is observed in around 19% and further worsening of neurological symptoms is seen in more than 24% of patients.[6]

Since the discovery of use of D-penicillamine in WD by Walshe in 1956, it has remained the standard therapy in WD. Among the various side effects of D-penicillamine (fever, rash, lupus-like reaction, gastric symptoms, bone pain, pancytopenia, proteinuria, retinitis, hepatotoxicity, renal impairment, neurological worsening), worsening of neurological symptoms (dystonia, tremors, gait disturbances) is the most worrisome, leading to a pre-emptive undertreatment of these patients.[7] Neurological deterioration is defined by >10% worsening in baseline Burke–Fahn–Marsden (BFM) score or appearance of any new neurological manifestation.[8] Brewer *et al.*,[9] in a retrospective study, showed that initiation of d-penicillamine resulted in paradoxical worsening in up to 50% and half of them do not improve to baseline even after discontinuation of the drug. They hypothesised that D-penicillamine may mobilise massive stores of hepatic copper to the blood and brain, leading to the neurological manifestations. Non-adherence to copper-restricted diet, poor compliance to medications, inadequate drug dosage and rapid escalation of chelation therapy are the possible causes of continued neurological worsening of patients on D-penicillamine. Neurological worsening has also been reported with trientine, ammonium tetrathiomolybdate and zinc.[5,10] Severe neurological manifestations, advanced brain damage and use of dopamine receptor antagonists at the time of initiation of D-penicillamine, are considered to be risk factors for neurological deterioration in patients of WD.[10]

In the current study, the prevalence of neurological worsening with D-penicillamine was estimated to be 22%, as compared to studies from various centres over the past two decades, which estimate a prevalence between 10% and 75%.[5,8,9,11] The neurological worsening in the current study was observed mostly within 8 to 12 weeks of treatment initiation which is in consonance with published literature.[8,9,11]

In a majority of the patients with penicillamine-induced neurological worsening, symptoms remit with planned down-titration of the drug, while in some it needs to be replaced with alternative medications. In rare instances (<3%), the neurological worsening is irreversible with shows relentless progression.[5]

Medici *et al.*[12] observed that zinc monotherapy leads to improvement in 75% of patients with neurological deterioration in WD. In the current study, no significant variation was found in the clinical and functional status among the various regimens used to manage patients with WD having neurological deterioration after initiation of D-penicillamine (zinc monotherapy, trientine monotherapy, a combination of zinc and slow escalation of D-penicillamine or a combination of zinc and trientine therapy). Out of the 27 patients with neurological deterioration, 24 of them showed improvement in the neurological symptoms.[11] Xiao-Qun Zhu *et al.*[13] observed that a combination therapy of Dimercaptosuccinic Acid (DMSA) and Zinc effectively improved the neurological symptoms in patients with WD, who had a history of neurological deterioration with D-penicillamine. Overall, 85% had improvement over 1–2 years of treatment, 12% had stabilisation of their neurological symptoms, while the remaining 3% continued to deteriorate. Future studies are required to establish the validity of this combination therapy in such patients. The current study provides further insight into the management of children and adolescents with neurological deterioration following initiation of D-penicillamine in WD.

With restricted availability and cost constraints of trientine in India, keeping in mind the fact that around 70% WD patients show improvement with D-penicillamine, the most rational approach in WD is to initiate penicillamine in low doses and escalate gradually. Despite the lack of consensus for management of patients with WD developing neurological deterioration on initiation of D-penicillamine therapy, withdrawal of D-penicillamine with Zinc monotherapy and a copper restricted diet, currently seems to be a rational initial approach. This can be followed by addition of trientene in non-responders. Prospective studies with appropriate design and adequate sample size should be planned to understand the underlying pathophysiology and to develop effective therapeutic strategy to manage and minimise the chances of neurological worsening in WD on treatment.

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References

1. Harada M. Pathogenesis and management of Wilson disease. Hepatol Res 2014;44:395–402.
2. Brewer GJ. Neurologically presenting Wilson's disease: Epidemiology, pathophysiology and treatment. CNS Drugs 2005;19:185–92.
3. Chu N-S, Hung T-P. Geographic variations in Wilson's disease. J Neurol Sci 1993;117:1–7.
4. Schilsky ML. Wilson disease: Clinical manifestations, diagnosis, and treatment. Clin Liver Dis (Hoboken) 2014;3:104–7.
5. Aggarwal A, Bhatt M. Advances in treatment of Wilson disease. Tremor Other Hyperkinet Mov (N Y) 2018;8:525.
6. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: A cohort study. Gut 2007;56:115–20.
7. Mohr I, Weiss KH. Current anti-copper therapies in management of Wilson disease. Ann Transl Med 2019;7:S69.
8. Kalita J, Kumar V, Chandra S, Kumar B, Misra UK. Worsening of Wilson disease following penicillamine therapy. Eur Neurol 2014;71:126–31.
9. 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;44:490–3.
10. Litwin T, Dzieżyc K, Karliński M, Chabik G, Czepiel W, Członkowska A. Early neurological worsening in patients with Wilson's disease. J Neurol Sci 2015;355:162–7.
11. Kumar M, Murugan TP, Lionel AP, Thomas MM, Yoganathan S. Management of Children and Adolescents with Wilson Disease and Neurological Worsening Following d-penicillamine Therapy: A Single-centre Experience. Ann Indian Acad Neurol 2022;25:698-702.
12. Medici V, Trevisan CP, D'Incà R, Barollo M, Zancan L, Fagiuoli S, *et al*. Diagnosis and management of Wilson's disease: Results of a single center experience. J Clin Gastroenterol 2006;40:936–41.
13. Zhu X-Q, Li L-Y, Yang W-M, Wang Y. Combined dimercaptosuccinic acid and zinc treatment in neurological Wilson's disease patients with penicillamine-induced allergy or early neurological deterioration. Biosci Rep 2020;40:BSR20200654.

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