GE – Portuguese Journal of Gastroenterology

Editorial

GE Port J Gastroenterol 2025;32:75–77
DOI: 10.1159/000542402

Received: October 20, 2024
Accepted: October 22, 2024
Published online: November 5, 2024

Building Clinical and Research Delivery Networks: A Blue Print for Multidisciplinary Management and Consensus in Wilson Disease

Aftab Ala[a] James Liu Yin[a] Michael L. Schilsky[b]

[a]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK; [b]Division of Digestive Diseases and Transplant and Immunology, Yale University Medical Center, New Haven, CT, USA

Keywords
Network · Wilson disease · Multidisciplinary management

Redes de disseminação clínica e de investigação – um diagrama para consensos e abordagem multidisciplinar na Doença de Wilson

Palavras Chave
Redes · Doença de Wilson · Multidisciplinar

Calinas et al. [1] present an overview of the current state of Wilson disease (WD) management in Portugal. Due to the varied clinical presentations of WD, as in many other countries, the management of the condition utilizes a number of different specialities, which do not have consensus on management strategies [2]. Their aim of creating a practical guide, which includes several different specialities to help standardize the approach to management of a very complex condition, must be commended. It will also help, as they state, to raise awareness about WD in Portugal since globally diagnosing this disorder remains a significant challenge in diagnosis and further management.

Their summary of current evidence and reported presentations highlights well the huge variation in WD that is found both clinically and in the literature. Across all three different categories of clinical phenotype that include neurology, hepatology, and psychiatry, there are a plethora of reported symptoms ranging from common to the rarer. This range of symptoms makes creating comprehensive guidance difficult since it is not possible to account for every situation. Historically, consensus guidance was based on case-reports and retrospective work, but more recently there has been a drive towards prospective clinical trials. However, many areas of patient care are still reliant on older data with case series, and many articles still lack sufficient statistical power for conclusive recommendations due to their cohort size. The heterogeneity of WD combined with a limited number of prospective studies makes forming evidence-based recommendations for diagnosis and management challenging due to some areas of uncertainty and controversy. While the authors have presented their findings and advice in a structured and practical way with acknowledgement of limitations, there are some areas which benefit from further discussion.

It is widely accepted that there can be disease progression in WD; this is usually a combination of factors including compliance with medication and incorrect administration of medication [3]. Nevertheless, a minority of patients with hepatic involvement, who despite reported compliance, normal liver function tests and what appears to be adequate chelation treatment still have progression of disease [4]. It is unclear whether the

karger@karger.com
www.karger.com/pjg

Correspondence to:
Aftab Ala, aftab.ala1@nhs.net

disease in these individuals is progressive despite treatment, or, the more likely issue, that the current measures of disease stability are not accurate enough to detect changes that indicate that therapy may need to be altered. This reinforces the need to develop new and more sensitive techniques that might not only detect but predict progression; a candidate for this is accurately measured bioavailable copper levels in the circulation discussed below. Future work must demonstrate correlation of changes in bioavailable copper with disease activity and importantly for patient outcomes. Additionally, in these individuals with disease progression, we must be open-minded and recognize that there may be concurrent disease that is driving disease progression and be on the lookout for this. Guidance being produced should therefore ideally not only assimilate current practice but be adaptable to new possibilities.

One of the key areas of development within the field of WD mentioned above is the measurement of bioavailable copper in the circulation. Current standard tests such as serum copper and caeruloplasmin are known to be poor markers of true bioavailable copper levels. The estimated "non-caeruloplasmin bound copper" is universally accepted as an inaccurate measurement due to the flaw in calculating the amount of copper in caeruloplasmin, leading to a result which is zero or negative in value in almost half of individuals, therefore rendering it clinically un-interpretable. Twenty four-hour urinary copper excretion has been in use for diagnosis and treatment monitoring of WD since the first use of penicillamine in the 1950s and its more widespread use in the 1960s [5]. Additionally, there are data for the use of penicillamine induced urine copper excretion for the diagnosis of WD (penicillamine challenge testing) that was validated in paediatric patients. There has been a significant shift in focus over the last decade to move away from using just the urinary copper excretion in isolation, and moving to pairing it with methods of measuring circulating bioavailable copper. As mentioned by the authors, serum exchangeable copper (CuEXC) and the relative exchangeable copper (REC) were adopted by many different international centres. There are a number of manuscripts describing the use of REC for WD diagnosis [5–7]. In the upcoming European Association for the Study of Liver WD guidelines, REC was recognized as a potentially useful diagnostic tool. However, while there are increasing data on the use of CuEXC and REC in clinical practice with good results, there remain some questions on its use. The CHELATE trial, the first head-to-head trial for WD treatment, was not granted the use of REC as an endpoint in the study, which led to the development and use of a novel method for measuring bioavailable copper that combined

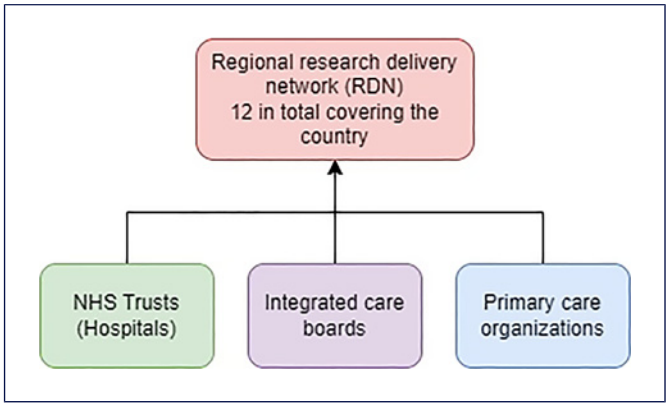

Fig. 1. Twelve NIHR Regional Research Delivery Networks (RDN) are formed from local services across England and encompassing all NHS services including hospitals, integrated care board, and primary care organizations. These same services will also refer patient to trientine centre/WD centres of excellence forming the clinical network. These twelve RDNs are co-ordinated from a single network coordinating centre with overall oversite from the Department of Health and Social Care (DHSC).

liquid chromatography and mass spectroscopy [8]. The underpinnings of this technique were published by Solovyev et al. [9], using inductively coupled plasma spectroscopy to accurately measure copper in chromatographically separated fractions. However, the availability of this equipment and conditions needed for sample processing may limit access to this testing.

An important key issue highlighted in this article is the assortment of specialities who may be involved in the care of WD patients. The authors recognize that there are multiple pathways to enter into care for different presentations of WD, and these can lead to less comprehensive care if there is no communication between specialists. To address this issue of having complex presentations with varied symptoms in patients across a range of ages, the best approach to the diagnosis and management of this condition would be to have dedicated centres with a concentration of expertise and a commitment to a multidisciplinary approach to care. Ideally, this would utilize joint clinics, or if not possible, facilitated communication between personnel that may include clinical biochemists, hepatologists, neurologists, psychiatrists, clinical nurse specialists, and other allied health care professionals. This concept of specialist centres is already in place in many countries, such as the USA and UK, where there is a system of accreditation by patient organizations of "centres of excellence" in WD. In France, there is also an extensive network for WD which links larger and smaller centres across the country, helping to

address diagnostic challenges and access to more specialized care and testing. This has been shown to be highly effective in France, where the assays for CuEXC were developed and utilized in clinical practice for a number of years. In Denmark, all WD is focused in a single centre, which has the necessary expertise.

Networks are an important part of treating a rare disease, both in clinical practice and research. Again, France is exemplary in having a robust clinical network for care and research for WD patients. In England, all public hospitals fall under the umbrella of NHS England and so there is an aspect of collaboration that is unique to this health service. There is ongoing work on central collation and integration of data from across different areas. The ability of the system to allow this may well provide crucial data to the understanding of disease progression. There also exists a WD special interest group which is a subset of the larger liver association (British Association for the Study of the Liver – BASL), helping bring together clinicians including allied health professional, patient organizations, and researchers across a range of specialities. In the wider setting, the UK/NIHR (National Institute for Health and Care Research) research delivery network (RDN) is a body that helps co-ordinate and support studies and is an important key factor in bringing together patients in less commonly seen conditions (Fig 1). It also plays in important role in supporting health care professionals in accessing resources with clinical and administrative support for studies.

The use of these networks in different countries are examples of connecting different health care professionals together to improve the standard of care in a condition that is less commonly seen. It also helps introduce new techniques and access to testing to a wider area. These networks can be a building block to develop a wider international collaborative effort to bring more people together for better care in WD. Hopefully, the generation of this multidisciplinary guideline in Portugal will be the first step in its journey along this same route to bring the latest diagnostics and comprehensive evaluation and testing to bear to achieve best patient outcomes for their population of WD, and for the larger community caring for this disorder.

Conflict of Interest Statement

A.A.: advisory boards and grants – Univar, Orphalan, Vivet, Ultragenex, Arbomed, National Institute of Health and Care Research (NIHR), Wilson's Disease Support Group, UK (unpaid), and Wilson Disease Association (unpaid). A.A. is also the Chair of Wilson's Disease Special Interest Group of British Association for the Study of the Liver (BASL). M.L.S.: grant support – Vivet therapeutics, Orphalan, and Wilson Disease Association; advisory boards: Arbomed, DepyMed, Orphalan, and Wilson Disease Association (unpaid).

Funding Sources

This manuscript was not supported by any sponsor or funder.

Author Contributions

A.A. and J.L.Y. wrote the 1st and 2nd draft. J.L.Y. added the references and figures. M.L.S. and A.A. finalized the manuscript with J.L.Y. A.A. is the overall guarantor for the manuscript and corresponding author.

References

1 Calinas F, Cardoso H, Carvalhana S, Manuel Ferreira J, Goncalves C, Magalhães M. Practical and multidisciplinary review on Wilson disease: The Portuguese perspective. Port J Gastroenterol. 2024;1–17. https://doi.org/10.1159/000541208

2 European Association for the Study of the Liver. EASL clinical practice guidelines: Wilson's disease. J Hepatol. 2012;56(3):671–85. https://doi.org/10.1016/j.jhep.2011.11.007

3 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(1):115–20. https://doi.org/10.1136/gut.2005.087262

4 Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. Lancet. 2007;369(9559):397–408. https://doi.org/10.1016/S0140-6736(07)60196-2

5 Mariño Z, Molera-Busoms C, Badenas C, Quintero-Bernabeu J, Torra M, Forns X, et al. Benefits of using exchangeable copper and the ratio of exchangeable copper in a real-world cohort of patients with Wilson disease. J Inherit Metab Dis. 2023;46(5):982–91. https://doi.org/10.1002/jimd.12639

6 Woimant F, Djebrani-Oussedik N, Poujois A. New tools for Wilson's disease diagnosis: exchangeable copper fraction. Ann Transl Med. 2019;7(Suppl 2):S70. https://doi.org/10.21037/atm.2019.03.02

7 El Balkhi S, Trocello JM, Poupon J, Chappuis P, Massicot F, Girardot-Tinant N, et al. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis. Clin Chim Acta. 2011;412(23–24):2254–60. https://doi.org/10.1016/j.cca.2011.08.019

8 Schilsky ML, Czlonkowska A, Zuin M, Cassiman D, Twardowschy C, Poujois A, et al. Trientine tetrahydrochloride versus penicillamine for maintenance therapy in Wilson disease (CHELATE): a randomised, open-label, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol. 2022;7(12):1092–102. https://doi.org/10.1016/S2468-1253(22)00270-9

9 Solovyev N, Ala A, Schilsky M, Mills C, Willis K, Harrington CF. Biomedical copper speciation in relation to Wilson's disease using strong anion exchange chromatography coupled to triple quadrupole inductively coupled plasma mass spectrometry. Anal Chim Acta. 2020;1098:27–36. https://doi.org/10.1016/j.aca.2019.11.033