OPEN ACCESS Freely available online

ADVANCES IN RARE DISEASES

Evaluating diagnosis and management gaps in wilson disease: results from a qualitative patient survey

Tamir Miloh[1]*, Mary Graper[2], Michael Schilsky[3]

1Baylor College of Medicine, Houston, Texas, **2**Wilson Disease Association, New York, **3**Yale University School of Medicine, New Haven, CT

Abstract

Wilson disease (WD) is a rare genetic disorder causing copper accumulation affecting many organs, primarily the liver and Central Nervous System (CNS). Critical to preventing disease progression are early diagnosis and intervention. A 21-question survey was distributed within the Wilson Disease Association patient network. The aim was to assess clinical presentation, time to accurate diagnosis and current challenges with management. 97 of 877 patients responded (11%), 93% from the United States. Average age was 46 and 53% were male. Presenting symptoms were predominantly hepatic or neurologic (33% and 34%). At symptom onset, 35% consulted their Primary Care Provider (PCP). Diagnosis was primarily confirmed by a gastroenterologist/hepatologist (52%). Time from presentation to diagnosis was <1 year (68%), 1-5 years (22%) and >5 years (10%). One-third of patients reported being misdiagnosed. Patients presenting with CNS symptoms were misdiagnosed almost twice as often as patients presenting with liver symptoms (48% and 28%). As first-line therapy, 58% were prescribed D-penicillamine (D-Pa) and 35% were prescribed trientine. At the time of the survey, 19 patients remained on trientine for >4 years and 10 on D-Pa. Change in therapy was mainly due to side effects of medication (23%). General challenges with therapy included dietary restrictions (55%), cost of therapy (39%), dosing frequency (35%), product storage (27%), and side effects (24%). The rate of misdiagnosis with WD is high, especially in patients with CNS symptoms. There is a need to address patient reported challenges including improved recognition of signs and symptoms and early diagnosis.

Keywords: Wilson Disease, Central Nervous System, Hepatic, Parkinsonism

Citation: Miloh T, Graper M, Schilsky M (2018) Advances in Rare Diseases. Evaluating diagnosis and management gaps in wilson disease: results from a qualitative patient survey, Adv Rare Dis. 4:1. doi:10.12715/ard.2014.3.1

Received date: August 04, 2018; **Accepted date:** September 22, 2018; **Published date:** September 28, 2018

Competing Interests: : Mary Graper is the Vice President of Scientific Affairs on the Board of Directors, Wilson Disease Association and Member of Advisory Board for Kadmon; received Honorarium.

Dr. Tamir Miloh is on the Medical Advisory Board for Wilson Disease Association, advisor for Kadmon and Alexion.

Dr. Michael Schilsky is the Medical Advisory Chair for the Wilson Disease Association, advisor for Kadmon, Wilson Therapeutics, GMPO, and Vivet, and is a speaker for Gilead. He has received grant support from the Wilson Disease Association, Wilson Therapeutics, and GMPO.

Sources of funding: The authors have declared that no source of funding exists

*E-mail: tamiloh@texaschildrens.org

Introduction

In the United States, a disease is considered rare when it has a prevalence of less than 200,000. On this basis, there are estimated 5,000-8,000 rare diseases, and affecting over 400 million people in the world. The majority of these are genetic, commonly manifesting in childhood and continuing across the lifespan [1].

Wilson disease (WD) is a rare (1:30,000) autosomal-recessive inherited disorder of copper metabolism at the level of the ATP7B copper transporter, resulting in copper accumulation in different organs. Copper accumulation affects the liver, and later the central nervous system [2]. Hepatic symptoms may include elevated liver enzymes, chronic hepatitis, and cirrhosis with end stage liver disease or acute liver

failure. Neurologic manifestations include dysarthria, Parkinsonism, tremor, dystonia, chorea, and ataxia as well as cognitive, behavioral and psychiatric changes [3]. Kayser-Fleischer (KF) rings may be seen in the eyes. Due to its autosomal recessive inheritance and lack of symptom presentation in the early phase, family screening/history of first degree relatives in pre-symptomatic patients is of the utmost importance and should be performed in all cases. A delay in diagnosis, inadequate treatment or non-adherence may lead to progressive copper accumulation and worsening of symptoms [2,4,5]. A study in diagnosis, treatment and outcomes showed that patients who have an earlier diagnosis at a pre-cirrhotic stage and who receive adequate care have a better long-term prognosis and a reduced need for liver transplantation [6].

The impact of adherence to therapy has also been shown to be extremely important in preventing clinically overt disease progression in pre-symptomatic patients. A study evaluating the long-term effectiveness of treatment in adherent pre-symptomatic patients showed a significantly higher likelihood of remaining symptom-free, with overall survival increased to the same rates as the general population [5].

The introduction of two chelators, D-penicillamine (DPA; dimethyl cysteine) and trientine (triethylene tetramine dihydrochloride) as oral de-coppering agents has changed the natural history of WD. DPA was approved by Food and Drug Administration (FDA) in 1956 and was fraught with tolerability issues, leading to a high rate of discontinuation. As a result, trientine, approved by the FDA in 1969, was developed for patients intolerant to DPA and thus received an arbitrary second-line treatment status. Both agents are effective chelators and are considered to be the standard of care. Current guidelines for treatment of WD favor trientine as the therapy of choice based on its tolerability profile, especially in newly diagnosed and pediatric patients [7,8]. Chelators are recommended for patients with or without symptoms, in whom clinical improvement can be seen after a few months of initiation of treatment, though patients may require 2-3 years of consistent de-coppering to normalize laboratory values [2,5]. Zinc, another WD treatment option, inhibits intestinal absorption of copper [2,7].

For patients with WD, treatment is life-long and success is highly predicated on the ability to adhere to medication regimen. Overcoming hurdles can lead the way towards effective disease management while avoiding undue burden for patients and their caregivers. To better understand opportunities to improve early and accurate diagnosis, timely management and treatment challenges, a qualitative survey of patients with WD to gain insights into the patient experience was undertaken. The aim of the survey was to assess patient-reported mode of diagnosis and challenges in the management and treatment.

Methods

Study design and objectives

The Wilson Disease Association (WDA) conducted a patient survey to assess patient-reported mode of diagnosis and challenges in management of WD.

Participants

A 21-question electronic survey was distributed to 877 patients with WD within the WDA patient network in 2016. Participation in the survey was voluntary and was conducted anonymously via SurveyMonkey®.

Survey endpoints

The questionnaire assessed topics in: primary symptoms prompting clinical evaluation, time from symptom onset to accurate diagnosis and appropriate treatment, proportion of patients who are misdiagnosed, specialties to which patients were referred, and disease burden including treatment challenges.

Statistical analysis

Survey results were analysed using descriptive statistics.

Results

97/877 of patients (11%) responded, and patients were largely from the US (93%). Average age was 46 years (range 6-75 y), and 53% were male.

Primary symptoms prompting clinical evaluation

Hepatic abnormalities and neurologic symptoms were the key drivers prompting patients to seek medical intervention in 33% and 34% of cases, respectively (Figure 1). Other signs and symptoms included routine blood tests showing elevated liver enzymes (28%) and psychiatric symptoms (21%). A smaller proportion of patients reported no symptoms and were identified through screening after family member was diagnosed with WD (15%) (Figure 1).

Central Nervous System (CNS)-related signs and symptoms were more commonly reported in males than females (55% vs. 45%) and most often included mental health-related comorbidities (52%) (Table 1A). Liver-related signs and symptoms were more commonly reported in females (56% vs. 44%) and often included comorbid CNS-related symptoms and/or elevated liver enzymes (22% and 22% respectively) (Table 1B). However, the gender differences observed in relation to CNS or liver related symptom presentation were not statistically significant.

Healthcare provider diagnosis

At the onset of symptoms, the highest proportion of patients (35%) consulted their primary care provider (PCP), 15% consulted their pediatrician, 16% their gastroenterologist, 10% their neurologist and 24% consulted with other physicians. Patients were most likely to have received a confirmed diagnosis from a gastroenterologist (33%), neurologist (23%),

Table 1A: Sub-analysis of patients reporting initial presentation with primarily CNS-related signs and symptoms (N=33) – patient response (mean percent) on gender, prevalence of comorbidities and HCP referrals, initial visits and diagnosis.

Survey Question	Answer Choices	Patient Responses (N=33)
Gender	Male	55%
	Female	45%
Comorbidities	Mental health-related signs and symptoms	52%
	Liver-related signs and symptoms	21%
	Routine Blood Tests Abnormalities	15%
	Other	3%
Q5: What type of medical provider did you first visit for these symptoms?	Primary Care Provider	30%
	Neurologist	27%
	Pediatrician	12%
	Other	22%
	Gynecologist	6%
	Psychiatrist	3%
Q6: What type of provider confirmed your diagnosis of Wilson disease?	Neurologist	58%
	Other	21%
	Gastroenterologist	12%
	Hepatologist	9%

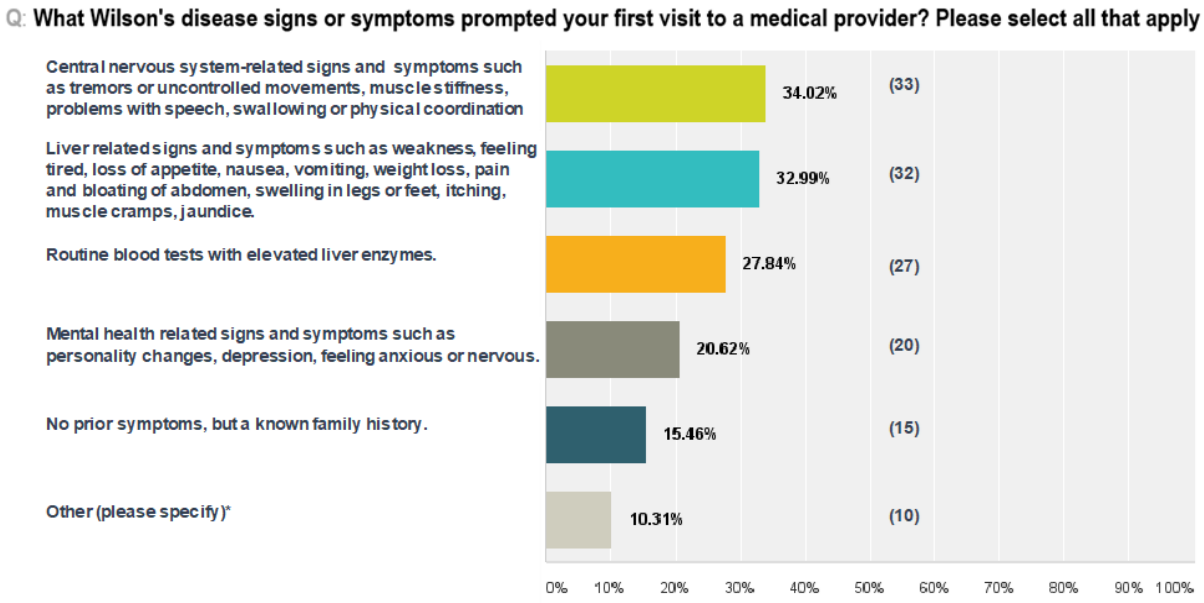

Figure 1: Multitude of symptoms at initial presentation.

Table 1B: Sub-analysis of patients reporting initial presentation with primarily liver-related signs and symptoms (N=32) – patient response (mean percent) on gender, prevalence of comorbidities and HCP referrals, initial visits and diagnosis.

Survey Question	Answer Choices	Patient Responses (N=32)
Gender	Male	44%
	Female	56%
Comorbidities	CNS-related signs and symptoms	22%
	Routine Blood tests with Abnormalities	22%
	Mental health-related signs and symptoms	16%
	No prior symptoms	3%
Q5: What type of medical provider did you first visit for these symptoms?	Primary Care Provider	50%
	Pediatrician	16%
	Gastroenterologist	16%
	Other	15%
	Ophthalmologist	3%
Q6: What type of provider confirmed your diagnosis of Wilson disease?	Gastroenterologist	44%
	Hepatologist	19%
	Other	16%
	Neurologist	12%
	Pediatrician	9%

hepatologist (19%), or other (25%). Following their initial diagnosis of WD, most patients reported being managed by a hepatologist (41%), gastroenterologist (29%), PCP (10%), or other (20%). The majority of the patients were seen by their health care professional on a bi-annual basis (55%). A lower proportion of patients were seen on an annual basis (39%) (Table 2).

When responders presented with CNS-related signs and symptoms, they were most likely to visit their PCPs (42%), of which 12% were pediatricians, followed by a neurologist (27%). Confirmation of diagnosis was most often made by the neurologist (58%) (Table 1A).

When responders presented with liver-related signs and symptoms, they were most likely to visit their PCPs (66%), of which 16% were pediatricians, followed by a gastroenterologist (16%). Confirmation of diagnosis was most often made by the gastroenterologist (44%) or hepatologist (19%) (Table 1B).

Time to accurate diagnosis

A delay between the onset of symptoms and confirmation of diagnosis was not uncommon, with 32% of patients reporting more than 1 year from symptom onset to confirmation of diagnosis, and 10% of patients experiencing a diagnostic delay of greater than 5 years. For the patients who were diagnosed within 1 year (68%), a diagnosis was obtained within 3 months (31%), within 3-6 months (23%) or within 6 months to 1 year (14%) (Table 3A).

Of the patients with more prevalent CNS-related symptoms (34%), a confirmed diagnosis was obtained within 1 year (54%), within 3 years (24%) or greater than 3 years (21%) (Figure 1A). Of the patients with more prevalent liver-related symptoms (33%), a confirmed diagnosis was obtained within 1 year (63%), within 3 years (22%), or greater than 3 years (15%) (Figure 1B).

Table 2: Patient response (mean percent) of initial presentation, diagnosis and primary management of WD by HCP specialty and rate (mean percent) of HCP visitation.

Survey Question	Answer Choices	Patient Responses (N=97)
Q5: What type of medical provider did you first visit for these symptoms?	Primary Care Provider	35%
	Gastroenterologist	17%
	Pediatrician	16%
	Neurologist	10%
	Hepatologist	8%
	Other	8%
	Ophthalmologist	3%
	Gynecologist	2%
	Psychiatrist	1%
Q6: What type of provider confirmed your diagnosis of Wilson disease?	Gastroenterologist	33%
	Neurologist	23%
	Hepatologist	19%
	Other	17%
	Geneticist	4%
	Pediatrician	4%
Q9: Once diagnosed, what type of medical provider do you visit for the primary treatment of your Wilson disease?	Hepatologist	41%
	Gastroenterologist	29%
	PCP	11%
	Neurologist	9%
	Pediatrician	5%
	Other	5%
Q16: How often do you visit your Wilson disease treatment provider?	Once a week or once a month	6%
	Once every 6 months	55%
	Once a year	39%

Figure 1A: CNS-related symptoms sub-analysis: time to confirmed diagnosis.

Figure 1B: Liver-related symptoms sub-analysis: time to confirmed diagnosis.

Table 3A: Patient response (mean percent) of time to proper diagnosis.

Survey Question	Answer Choices	Patient Responses (N=97)
Q7: How long did it take from your first symptom to your confirmed diagnosis of Wilson disease?	Less than 3 months	31%
	Between 3-6 months	23%
	Between 6-12 months	14%
	Between 1-3 years	18%
	Between 3-5 years	4%
	Between 5-10 years	5%
	More than 10 years	5%

Misdiagnosis

A large proportion of patients reported being misdiagnosed (33%). Psychiatric disorders and other liver disease (in many cases, hepatitis) were identified as the leading misdiagnoses (Table 3B).

Table 3B: Patient response (mean percent) of misdiagnosis.

Survey Question	Answer Choices	Patient Responses (N=97)
Q10: Was your Wilson disease ever misdiagnosed?	No	67%
	Yes	33%

Patients with CNS-related symptoms demonstrated the highest rate of misdiagnosis (48%), with a period of 1 to 3 years from symptom onset to correct diagnosis. Patients presenting with liver-related symptoms were most likely to receive a confirmed diagnosis in less than 6 months (50%) and were almost half as likely to receive an incorrect diagnosis (28% vs. 48%) (Figures 1C and 1D).

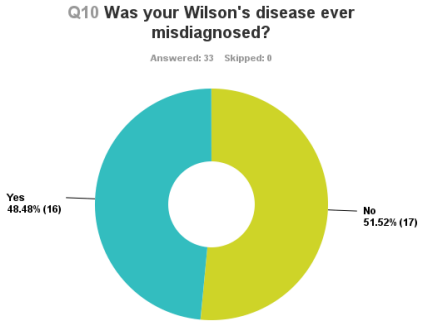

Figure 1C: CNS-related symptoms sub-analysis: misdiagnosis.

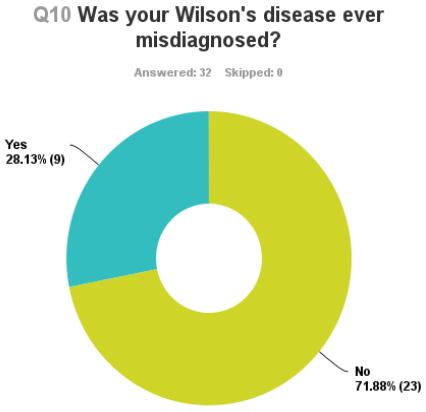

Figure 1D: Liver-related symptoms sub-analysis: misdiagnosis.

Table 4: Patient response (mean percent) of initial treatment, reason for treatment change and daily dosing frequency.

Survey Question	Answer Choices	Patient Responses (N=97)
Q11: Once diagnosed with Wilson disease what was your initial treatment?	DPA	59%
	trientine	35%
	Zinc	29%
Q13: Have you ever had to change your Wilson disease treatment for any of the following reasons?	No Change	45%
	Medication Side Effect	23%
	Other	13%
	Cost	12%
	Worsening of Symptoms	6%
Q14: How many times a day do you take your medication for Wilson disease?	BID	40%
	TID	36%
	QD	15%
	QID	4%

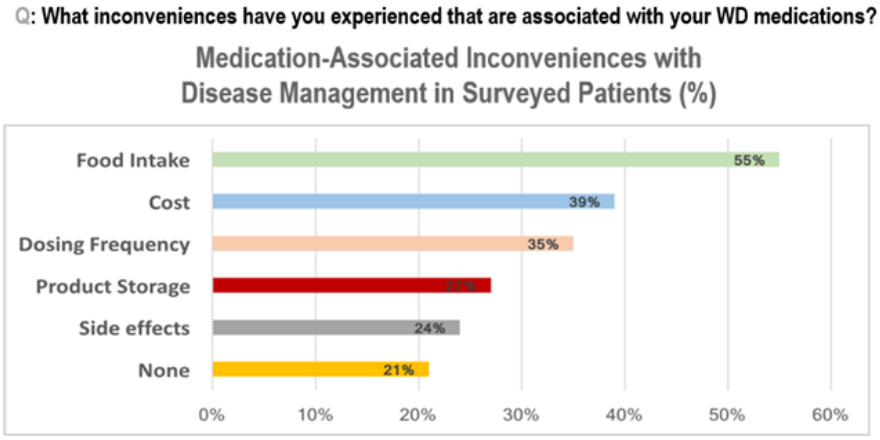

Figure 2: Patient reported inconveniences associated with WD medications.

Patient-reported treatment experience

Upon diagnosis, 59% of patients were prescribed DPA, while 35% were prescribed trientine as their first-line therapy. After 4 years of therapy, a greater number of patients remained on or converted to trientine (n=19) compared to DPA (n=10). Side effects were identified as the leading cause for medication changes or discontinuation (23%). Additional reasons included cost of therapy (12%) and worsening of symptoms (6%).

Medication were administered once daily (15%), twice daily (40%), or three times daily (36%) (Table 4). Patient-reported inconveniences associated with taking medication included food intake scheduling (55%), cost of therapy (39%), dosing frequency (35%), product storage (27%) and side effects (23%) (Figure 2).

Discussion

The diagnosis of WD is complex due to the highly variable symptom presentation and their interpretation, leading to a high rate of misdiagnosis and, consequently, delayed referral to appropriate specialists. As a result, initiation of therapy is often postponed and disease progression ensues. Thus, the need for early patient recognition and prompt intervention is of paramount importance.

The results of this survey present an opportunity for heightened disease awareness and vigilance among health care professionals (HCPs), especially among PCPs and pediatricians who are most often the first-line providers to encounter symptomatic patients. Additionally, the results highlight the greater risk of misdiagnosis among patients presenting with primarily neurological symptoms, demonstrating a need for

disease awareness among neurologists. Early diagnosis and prompt chelation, along with patient long term adherence, are critical to patient management success and can reduce the likelihood of developing irreversible neurological symptoms [9].

While WD management is lifelong, non-adherence is common and has been reported in more than 50% of patients especially among pre-symptomatic patients or those without overt symptoms [9,10]. Non-adherence may lead to acute hepatitis, hepatic failure, neuropsychiatric deterioration, and ultimately death [6]. Bi-annual monitoring of patient adherence is warranted (clinically, biochemically and radiologically) and should be done even more frequently among patients with suspected non-adherence [3].

Factors contributing to non-adherence in WD include medication side effects, complex dosing regimens, and the cognitive impairment which often accompanies WD. Medications may be associated with a range of side effects which may lead to abrupt patient discontinuation [2,6,11]. Therefore assessment for adverse effects is warranted, and alternate treatments should be offered in order to ensure continued treatment. A long-term study by Weiss et al., demonstrated that over a period of 13 years, DPA and trientine produce comparable clinical outcomes, but DPA versus trientine- treated patients had a higher rate of adverse events leading to premature discontinuation [11].

Management of WD can be fraught with multiple complexities including pill burden, dose regimen, dietary restrictions, and drug storage limitations. More specifically, chelating agents and/or zinc salts need to be taken apart from food (1 hour before or 2 hours after) and apart from other medications. Following a low copper diet may also present a challenge to some patients who need to be educated on high copper dietary choices that should be avoided. The dietary restrictions are more stringent within the first year of therapy and may be more difficult for younger children (as chocolate contains high copper). Furthermore, product storage that requires constant refrigeration may limit patient's freedom of traveling, impact adherence, and negatively affect overall quality of life.

This study is limited by the voluntary participation and therefore selection bias. It is retrospective in nature and dependent on patient subjective recollection. Our results highlight the need for accurate diagnosis, prompt intervention of WD, and vigilant long-term patient oversight. Addressing some of the challenges identified in this survey, along with advanced diagnostic techniques, may play a key role in treatment success and the prevention of clinical deterioration. While there are no randomized prospective head-to-head clinical trials in WD patients, selection of treatment should be determined on the basis of clinical experience and simplification of treatment regimen to allow patients to gain successful treatment outcomes.

Acknowledgement

We gratefully acknowledge the support of the Wilson Disease Association, without which the present study could not have been completed.

References

1. Baynam G, Bowman F, Lister K, Walker CE, Pachter N, Goldblatt J, et al. Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework. Adv Exp Med Biol. 2017;1031:55-94.
2. Aggarwal A, Bhatt M. Update on Wilson disease. Int Rev Neurobiol. 2013;110:313-348.
3. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015;14(1):103-113.
4. Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. J Neurol Neurosurg Psychiatry. 1992;55:692-696.
5. Dziezyc K, Karlinski M, Litwin T, Czlonkowska A. Compliant treatment with anti-copper agents prevents clinically overt Wilson's disease in pre-symptomatic patients. Eur J Neurol. 2014;21:332-337.
6. Beinhardt S, Leiss W, Stättermayer AF, Graziadei I, Zoller H, Stauber R, et al. Long-term Outcomes of Patients With Wilson Disease in a Large Austrian Cohort. Clinical Gastroenterology and Hepatology. 2014;12:683-689.
7. Roberts EA, Schilsky ML, American Association for Study of Liver D. Diagnosis

and treatment of Wilson disease: an update. Hepatology. 2008;47:2089-2111.

8. European Association for Study of L. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56:671-685.
9. Sabaté E. Adherence to long-term therapies: evidence for action: World Health Organization. 2003.
10. Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31:145-160.
11. Weiss KH, Thurik F, Gotthardt DN, Schafer M, Teufel U, Wiegand F, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol. 2013;11:1028-1035.