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Adherence to treatment, a challenge even in treatable metabolic rare diseases: A cross sectional study of Wilson's disease

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Abstract

Wilson's disease (WD), a rare genetic disorder responsible for copper accumulation in the body, is fatal if left untreated. Although there are effective treatments, adherence to treatment tends to be low. We evaluated the medication adherence of 139 patients using the Morisky scale. Adherence was correlated with age at diagnosis and at inclusion in the study, the form of the disease, the treatment, the duration of treatment, delivery and storage problems, depression, anxiety, the level of education, and the biological data. 32.4% of the patients had low adherence; their levels of exchangeable copper were significantly higher than those of the patients with high or medium adherence ($P = .049$). The average age of the patients at the time of the study was significantly higher in those with high adherence than in those with medium or low adherence ($P = .043$). 75.9% of the patients with high adherence had a neurological form and 26.7% of the patients with low adherence were asymptomatic ($P = .0090$). The duration of treatment was significantly longer in the patients with high adherence than in those with medium or low adherence ($P = .0192$). The type of treatment (chelators or zinc) had no impact on the level of adherence. Forty-four percent of the patients experienced problems dispensing and storing medications. Despite the availability of effective treatments for this rare disease, adherence problems occur with Wilson's disease in particular in asymptomatic patients. Although different factors are involved, sustained multidisciplinary management on a case-by-case basis is necessary.

KEYWORDS

chronic disease, compliance, D-penicillamine, exchangeable copper, medication adherence, persistence, Wilson's disease, zinc salts

1 | INTRODUCTION

Wilson's disease is an autosomal recessive disease responsible for copper accumulation. It begins with hepatopathy and, in the absence of medical treatment, progresses to multisystem affliction mainly affecting the cornea (Kayser-Fleischer rings) and the brain (Parkinsonism, dystonia, tremor, dysarthria, and neuropsychological disorder). The diagnosis is most often made in adolescents and young adults,[1] after the onset of hepatic and/or

neurological symptoms. It can also be diagnosed during family screening in asymptomatic patients.

Although exceptional for a rare genetic disease, there are effective treatments for Wilson's disease (WD), provided they are started early and followed throughout life, including in asymptomatic patients. These treatments comprise copper chelators (D-penicillamine and trientine salt) or zinc salts, taken orally and several times a day. At the time of the study, trientine 2HCl required cold storage and was the only trientine salt available in France. Zinc acetate and trientine 2HCl were dispensed at hospital pharmacies. Low adherence leads to progressive worsening of the clinical condition, and interruption of treatment can lead to a fulminant worsening of the disease and even death.[1,2] Strict adherence to the drug treatment is, therefore, an essential management element, as is the case for all chronic disease treatments.[3] Adherence, which represents the degree to which the patient's behavior matches the medical recommendations,[4,5] is a well-studied and problematic phenomenon in high-prevalence chronic pathologies such as diabetes and hypertension, as well as diseases with a more moderate prevalence such as HIV, for example.[6,7] Several degrees of adherence to medical instructions are used in the literature, in particular concerning drug intake.[8] Despite the numerous studies in regard, the problem remains elusive.

In the context of rare diseases, studies regarding adherence are rare,[2,9] as for most rare diseases, there are no effective treatments. A first prospective study conducted by our team in Paris (France) on this topic that involved 39 Wilsonian patients at the National Reference Centre for Wilson's Disease (CRMR) showed that, as is the case with all chronic pathologies, adherence was difficult in WD.[6,10-12] Only 15.4% of the patients with symptomatic or asymptomatic Wilson's disease strictly adhered to their treatment.[13] In a recently published Polish study, adherence in symptomatic patients was found to be 74.1%.[2]

In light of these surprising results regarding a population followed by a multidisciplinary team trained in the pathology, we wanted to explore this issue in more depth with a larger population. The main objective of the WILOBS study was to confirm the occurrence of adherence difficulties in Wilsonian patients by determination of the rate of adherent patients using the validated French version of the Morisky scale[14] (Figure S1). The eight-item Morisky Medication Adherence scale (MMAS-8) is a structured self-reported measure of medication-taking behavior.[15-17] We sought to identify the main factors involved in adherence. More generally, this study aimed to improve the clinical and the psychological management of patients encountering adherence difficulties and to anticipate possible difficulties in all patients with Wilson's disease.

2 | METHODS

2.1 | Population

This cross-sectional study was carried out between December 19, 2014 and November 27, 2015, and participation was offered to all Wilsonian patients consulting at the CRMR (Lariboisière Hospital, Paris). The inclusion criteria were: Wilson's disease confirmed with a Leipzig score ≥ 4, patients over 14 years of age, disease treated for at least 1 year, and autonomy in taking treatment and signing of consent forms. The non-inclusion criteria were: patients under guardianship or trusteeship, duration of treatment less than 1 year, patients not living in France and whose drugs were issued abroad, a history of a liver transplant, a severe neurological disability incompatible with taking psychological tests, and non-French speaking patients.

2.2 | Ethics approval and consent to participate

All of the patients signed a written consent form. The study received a favorable assessment from the Ethics Evaluation Committee for Biomedical Research Projects in North Paris (No. 14-030/IRB 00006477).

2.3 | Data studied

Based on the literature[18] and our clinical experience, the following factors were collected: gender, the level of education, the age at diagnosis and at inclusion, the presence of relatives at home, the form of the disease, the existence of another family member with Wilson's disease, the treatment, the duration of treatment, the occurrence of problems with dispensing and storing medicines, feeling of being sufficiently informed regarding the disease, talking about the disease with relatives, and cancelation or postponement of consultations in the past 2 years. Depressive and anxious symptoms were assessed using the Hospital Anxiety and Depression Scale, which is a self-administered questionnaire that distinguishes three levels of depression or anxiety: no symptoms (≤ 7), mild symptoms (8-10), and moderate to severe symptoms (≥ 11).[19]

2.4 | Adherence assessment

Adherence was assessed using the Morisky scale, which distinguishes three levels of adherence: high (8), medium

TABLE 1 Characteristics of the patients included

	Total	Low persistence	Medium persistence	High persistence	*P*-value
Population n (%)	139 (100%)	45 (32.4%)	65 (46.8%)	29 (20.9%)	
Gender n (%)					.2482
Male	69 (49.6%)	19 (42.2%)	32 (49.2%)	18 (62.1%)	
Female	70 (50.4%)	26 (57.8%)	33 (50.8%)	11 (37.9%)	
Age at diagnosis Mean ± SD (years)	21.7 (11.8)	18.7 (8.4)	23.5 (11.9)	22.3 (15.1)	.1045
Age at inclusion Mean ± SD (years)	39.0 (13.7)	34.4 (10.1)	39.7 (13.8)	44.9 (16.1)	.0043
Phenotype n (%)					.0090
Neurologic	72 (51.8%)	16 (35.6%)	34 (52.3%)	22 (75.9%)	
Hepatic	45 (32.4%)	17 (37.8%)	22 (33.8%)	6 (20.7%)	
Asymptomatic	22 (15.8%)	12 (26.7%)	9 (13.8%)	1 (3.4%)	
Relative with WD in the family					.6029
Yes n (%)	76 (54.7%)	27 (60.0%)	35 (53.8%)	14 (48.3%)	
No n (%)	63 (45.3%)	18 (40.0%)	30 (46.2%)	15 (51.7%)	
Feeling of being sufficiently informed about the WD					.1825
Yes n (%)	129 (92.8%)	42 (93.3%)	58 (89.2%)	29 (100.0%)	
No n (%)	10 (7.2%)	3 (6.7%)	7 (10.8%)	-	
Education n (%)					.078
Higher education	68 (48.9%)	25 (55.5%)	34 (52.3%)	9 (31.0%)	
Upper/post-secondary education	39 (28.1%)	11 (24.4%)	14 (21.5%)	14 (48.3%)	
Vocational education	32 (23.0%)	9 (20.0%)	17 (26.2%)	6 (20.7)	
Dialog with the entourage about Wilson's disease					.3370
Yes n (%)	117 (84.2%)	39 (86.4%)	56 (85.5%)	22 (75.9%)	
No n (%)	22 (16.5%)	6 (13.6%)	9 (14.5%)	7 (25.9%)	

(6 < 8), and low (<6).[15-17] The blood levels of exchangeable copper, which measures the toxic unbound copper, and serum transaminases were assayed at the time of inclusion. These indicators are key elements in the follow-up of patients with Wilson's disease, in particular for assessing adherence with treatment: a high level of exchangeable copper and/or transaminases is a good marker of low adherence.[20]

2.5 | Execution of the study

The test was administered during an interview with a psychologist at the CRMR following the medical consultation and the patients' blood test. It lasted 1 hour on average.

2.6 | Statistical analyses

The results are presented for the total population and for the three subgroups defined according to the level of adherence of the subjects. The biological data (exchangeable copper and hepatic enzymes) were studied for the three groups of adherence and by grouping the patients with medium and low adherence. The univariate statistical analyses depended on the nature of the variables analyzed. For the qualitative variables (number of subjects, number of missing values, and percentage of each modality calculated on the responses expressed), the Chi^2 test was applied, except when the theoretical numbers were less than 5, in which case the Yates continuity correction or Fisher's exact test was used. For the quantitative variables (number of subjects, number of missing values,

TABLE 2 Processing and regularity of CRMR follow-ups

	Total	Low persistence	Medium persistence	High persistence	*P*-value
Current treatment					.0748
D-Penicillamine	49 (35.3%)	15 (33.3%)	23 (35.4%)	11 (37.9%)	
Trientine 2HCl	22 (15.8%)	11 (24.4%)	7 (10.8%)	4 (13.8%)	
Zinc acetate	52 (37.4%)	11 (24.4%)	31 (47.7%)	10 (34.5%)	
Zinc sulfate	15 (10.8%)	8 (17.8%)	4 (6.2%)	3 (10.3%)	
D-Penicillamine + Zinc sulfate	1 (0.7%)	-	-	1 (3.4%)	
Duration of treatment					.0192
Mean ± SD (years)	17.9 (11.3)	16.2 (9.6)	16.7 (11.5)	23.1 (12.4)	
Medication delivery and storage issues					.1213
Yes n (%)	61 (43.9%)	23 (51.1%)	30 (46.2%)	8 (27.6%)	
No n (%)	78 (56.1%)	22 (48.9%)	35 (53.8%)	21 (72.4%)	
Sense of being sufficiently informed about Wilson's disease					.1825
Yes n (%)	129 (92.8%)	42 (93.3%)	58 (89.2%)	29 (100.0%)	
No n (%)	10 (7.2%)	3 (6.7%)	7 (10.8%)	-	
Consultations missed by the patient in the last 2 years					.4320
Yes n (%)	9 (6.5%)	5 (11.1%)	3 (4.6%)	1 (3.4%)	
No n (%)	130 (93.5%)	40 (88.9%)	62 (95.4%)	28 (96.6%)	
Consultations postponed by the patient in the last 2 years					.0861
Yes n (%)	48 (34.5%)	17 (37.8%)	26 (40.0%)	5 (17.2%)	
No n (%)	91 (65.5%)	28 (62.2%)	39 (60.0%)	24 (82.8%)	

TABLE 3 Depression and anxiety symptoms assessed by the HADS scale

	Total	Low adherence	Medium adherence	High adherence	*P*-value
Depressive symptoms n (%)					.8191
NA	2	1	-	1	
Absent	110 (80.3%)	36 (81.8%)	52 (80.0%)	22 (78.6%)	
Doubtful	17 (12.4%)	5 (11.4%)	7 (10.8%)	5 (17.9%)	
Present	10 (7.3%)	3 (6.8%)	6 (9.2%)	1 (3.6%)	
Anxiety symptoms n (%)					.4762
NA	2	1	-	1	
Absent	82 (59.9%)	24 (54.5%)	39 (60.0%)	19 (67.9%)	
Doubtful	28 (20.4%)	8 (18.2%)	15 (23.1%)	5 (17.9%)	
Present	17 (12.4%)	9 (20.5%)	7 (10.8%)	1 (3.6%)	

Abbreviation: NA, not adapted.

mean, and SD), when the distribution was close to normal (Shapiro-Wilk test not significant), a Student *t*-test or an analysis of variance was performed. Otherwise, non-parametric tests were used (Wilcoxon, Kruskal-Wallis). A multivariate multinomial regression was performed to complete the descriptive analysis. The variables used in the multivariate analysis were those with a *P*-value less than .05 in the univariate analyses. Data management and the descriptive analyses were performed using the SAS V9.4 software (North Carolina). The multivariate

analysis was performed with R V3.5 software (Vienna, Austria).

3 | RESULTS

Participation in the study was offered to 164 patients, of whom 139 agreed to participate. Twenty-five patients refused, of whom 14 stated that they were not interested in this study and 11 stated that they did not have the time to participate. Of the 139 patients included, 70 were women (50.4%). The proportion of asymptomatic patients was 15.8%, while 32.4% had hepatic impairment and 51.8% had hepato-neurological impairment. Of note, 35.3% of the patients were treated with D-penicillamine, 15.8% with trientine 2HCl, 37.4% with zinc acetate, and 10.8% with zinc sulfate. One patient received dual therapy (D-penicillamine + zinc sulfate). The mean duration of treatment was 17.9 ± 11.3 years (1-52).

High adherence was noted for 20.9% of the patients (n = 29), 46.8% (n = 65) had medium adherence, and 32.4% (n = 45) had low adherence (Table 1). The ALT levels were significantly higher in the low-adherence group than in the group combining medium and high adherence (60.6 vs 42.61 IU/L [$P = .035$]). The levels of ASAT were not significantly different between the two groups ($P = .15$). The levels of exchangeable copper were significantly higher in the low-adherence group than in the group combining medium and high adherence (0.80 vs 0.67 μmol/L; $P = .049$).

The mean age at diagnosis was 21.7 years, and it was comparable between the three groups. The mean age at inclusion was significantly higher for those with high adherence (44.9 years) than for those with medium adherence (39.7 years) and with low adherence (34.4 years; $P = .043$; Table 1).

Having another member of the family who was afflicted did not affect the level of adherence ($P = .6029$). The level of adherence varied according to the clinical phenotype: the patients with high adherence were mainly patients with a neurological form (75.9%; $P = .0090$) while 26.7% of the patients with an asymptomatic form had low adherence (Table 1).

The patients were mainly treated with D-penicillamine or zinc acetate (35.3% and 37.4%, respectively). The type of treatment had no impact on the level of adherence but the reasons for a poor adherence changed over time. Of the 19 patients with poor adherence treated with zinc salt, 6 of them (31.5%) declared having intestinal issues. Of the 11 patients with poor adherence treated with trientine, 8 (72.7%) have problems getting the medication or with its cold storage. The duration of treatment was significantly longer for the patients with high adherence, at 23.1 years of treatment compared to 16.2 years and 16.7 years for the patients with low or medium adherence, respectively, ($P = .0192$). Nearly 44% of the patients experienced problems with dispensing and storing drugs: 51% of the patients in the low-adherence group and 28% in the high-adherence group (Table 2).

The vast majority of the patients stated that they were sufficiently informed regarding the disease (92.8%) and that they talked about the disease with their friends and family (84.2%), without this having an impact on the level of adherence.

The level of education did not modify the level of adherence ($P = .078$; Table 1). The patients with high adherence rarely missed or postponed their consultations (3.4% and 17.2%, respectively), while nearly 40% of the patients with low or medium adherence had postponed a consultation at least once (Table 2).

Eighty percent of the patients had a depression score and 60% had an anxiety score, which corresponds to an absence of symptoms, with no differences between the three groups (Table 3).

The multivariate multinomial analysis focused on five variables: age, age at diagnosis, the form of the disease, the duration of treatment, and problems with delivery and storage. Two variables were significantly different between the low- and the high-adherence groups: the form of the disease (asymptomatic vs neurological) and problems with delivery and storage. An asymptomatic phenotype and problems with delivery and storage were associated with low adherence ($P = .01376$ and $P = .01507$, respectively).

4 | DISCUSSION

Our study shows that even with a rare metabolic disease that can be effectively treated with copper chelators or zinc salts, there are nonetheless significant problems with treatment adherence. Thirty-two percent of the patients had low medication adherence. This is close to the rates reported for more common chronic pathologies such as arterial hypertension and HIV infection[21,22] and higher than, for example, in type 2 diabetes,[23] or for other chronic neurodegenerative diseases such as Parkinson's disease.[24] Treatment adherence in Wilson's disease, which is a rare genetic disease, is problematic, as is also the case with more frequent chronic pathologies. While new treatments are still being sought for most rare and fatal genetic diseases, when they are available, they are nonetheless not always taken as prescribed.

This work confirms the results of our first study on the subject[13] and the study by Maselbas et al that showed that 27.6% of the patients were nonadherent.[25] In a

recently published Polish study, 25.9% of the symptomatic patients had low persistence.[2] However, adherence rates vary between studies. Different studies involve different types of measurement, none of which are completely reliable. In our study, we chose the Morisky scale to assess adherence, and thus divided our population into three groups. More nuanced than a binary observing/nonobserving categorization, this distribution corresponds to the description of different degrees of low adherence in the literature[8] and to our clinical observations. Indeed, in practice, patients are rarely strictly or poorly adherent. There are many intermediate behaviors regarding medication adherence, with significant variations from one individual to another but also for the same individual, for example over time.

Some authors also suggest measuring the treatments in the blood or even in the urine to ensure adherence.[7] The determination of the blood level of free copper or exchangeable copper appears to be a good indicator of adherence to treatment in Wilson's disease. In this study, it was significantly correlated with the level of adherence determined by the Morisky scale. Nonadherent Wilson's disease patients often retain a degree of cytolysis. This was confirmed by our study: the level of ALT was significantly correlated with the level of adherence.

Our study confirms that adherence is particularly difficult in the context of a silent disease,[26,27] including when it is a rare disease. For Wilson's disease, adherence differs depending on the phenotypic presentation. Patients with an asymptomatic form have more difficulty with adherence. The absence of bodily symptoms sustains the belief that one is not sick. Sustained and close support (consultations with the doctor, examinations) is not always warranted from a purely medical point of view. However, it appears to be particularly important for these patients in order to promote awareness of the disease and the need for good drug adherence. The study by Maselbas et al[2] did not show any difference in persistence to treatment in Wilson's disease according to the phenotypic presentation of the disease, but this study did not include asymptomatic patients.

The most severe patients, that is, those with a neurological form, were the most adherent. The literature indicates that adherence to treatment with chronic diseases tends to decrease over time.[28] By contrast, in this study, the adherence levels of the older patients at the time of the study and of those treated for a longer time were significantly better. A possible bias in this result is, however, that the oldest subjects with the longest treatment durations included in our study have been monitored in a reference center for a long time and thereby constitute an adherent population. Our study did not find that there was a statistically significant difference in adherence based on gender, although there were slightly more men in the group with high adherence, unlike what has been reported in other studies, such as that of Qvarnström et al in the context of arterial hypertension.[28]

Unlike the study by Maselbas, et al, there was not a difference according to the type of treatment but according to the logistical problems inherent to the treatments.[2] Patients who had problems with storage or delivery of the medications had low adherence compared to those without these difficulties. In the context of Wilson's disease, this mainly involves dispensing of zinc acetate or trientine 2HCl at hospital pharmacies, which generally have limited opening hours and are often far from the patient's home, a monthly delivery of the medication, and a need to keep the trientine 2HCl cold. This was a specific French situation at that time. These difficulties, in the context of a chronic pathology requiring treatment several times a day for life, constitute a major constraint. This is reminiscent of the difficulties with planning for patients with a neurological form of the disease,[29] for whom obtaining a new package of drugs each month can be challenging. This is in addition to the constraints such as the need to take the treatments 2 to 3 times a day and away from meals, which have been described as being detrimental to adherence.[30,31]

Various studies have shown that depression and other psychiatric disorders are factors involved in low adherence.[32,33] The patients in our study did not exhibit anxiety-depressive symptoms. Thus, patients can also have low adherence in the absence of a psychiatric disorder. It is not necessarily a pathological phenomenon. We can, however, hypothesize that very depressed patients do not attend referral centers.

The presence of another family member with the same disease does not change the level of adherence. Reach's study shows that there is not always a beneficial effect on adherence when confronted with other patients who have become symptomatic.[34] On the contrary, it can generate significant anxiety and promote a form of denial. The difference in status and feelings (asymptomatic patients vs a symptomatic family member) or the quality of the relationship with the family member in question may also come into play. The connection with the doctor and the team is of great importance, including for low-adherence patients. If they get along well, this can allow them to talk about their low adherence, which is always a delicate subject, or to come back to the team after a sometimes-long interruption of follow-ups.

In our study, 90% of the patients monitored in a referral center where there was regular and up-to-date information stated that they were sufficiently informed regarding the disease and the treatments. This nonetheless did not prevent low-adherence behavior. Similarly,

in our study, we did not find any correlation between the level of education and the level of adherence. Conversely, the study by Maselbas et al[25] showed that low-persistent patients had a lower level of education than persistent patients. These results were qualified, however, by the unresolved question of whether high adherence determined the education level or, conversely, whether the education level determined high adherence. While it is often considered to be a factor of high adherence, the intellectual and cognitive dimension is not the only one involved nor does it reflect the psychological reality.[27,32] While it was not statistically significant, there was, however, a difference in postponed and missed consultations depending on the level of adherence. Adherence does not only comprise drug intake but also regular monitoring in consultation.[35] Multidisciplinary care and regular monitoring of such patients[13] are essential.

The main limitation of our study was the recruitment from a reference center specializing in Wilson's disease. The number of patients with Wilson's disease in France is estimated to be 906, and approximately 600 are monitored at referral centers.[36] These patients receive specific and close monitoring. The second limitation is the blind spot that occurs in any study on adherence: the least adherent patients miss the follow-ups and they, therefore, tend not to be included in studies of the subject. The rate of low adherence is, therefore, certainly even higher than that found in studies. Unfortunately, our current study was not built to reassess patient adherence after counseling but to measure it at definite time. A follow-up on the participants shall be proposed to re-evaluate morbidity and mortality and their relation to adherence.

In conclusion, our study confirms the occurrence of adherence difficulties for patients with Wilson's disease, in particular for those with an asymptomatic form of the disease. This warrants close monitoring of such patients, despite the absence of symptoms. Having treatments available from community pharmacies and which does not required storage in a fridge (which is the case with the new salt of trientine 4HCl recently available in some European countries) should help promote adherence and, therefore, limit the risk of clinical worsening of the disease. The identification of adherence factors remains difficult and the results are often contradictory. Low adherence appears to be a multifactorial and non-homogeneous problem for which multidisciplinary and case-by-case management must be considered.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Elodie Jacquelet, Aurelia Poujois, Marie-Christine Pheulpin, Adèle Demain, France Woimant: Designing and conceptualization of research studies. **Elodie Jacquelet, Aurelia Poujois, Adèle Demain, Nadège Tinant**: Conducting experiments. **Elodie Jacquelet, Aurelia Poujois, Marie-Christine Pheulpin, Adèle Demain, Nadège Tinant, Nathalie Gastellier, France Woimant**: Analyzing data. **Elodie Jacquelet, Aurelia Poujois, Adèle Demain, France Woimant**: Writing the first draft of the manuscript. **Aurelia Poujois, Marie-Christine Pheulpin, Nadège Tinant, Nathalie Gastellier, France Woimant**: Critical revisions of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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