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Treatment of Wilson Disease in Japan: An Insurance Claims Database Study

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1. Abstract

1.1. Background & Aims: Wilson disease (WD) is a rare hereditary disease of copper metabolism. For such rare diseases, analysis of health insurance claims databases allows data collection from large numbers of patients. The objective of this study was to evaluate the characteristics and treatment of patients with WD in Japan using the Medical Data Vision (MDV) database.

1.2. Methods: Participants were identified through the ICD-10 disease code for WD (E83.0) between 2011 and 2021. The index date was the date of the first documented claim. All reimbursement claims for WD-specific treatments, all-cause-hospitalisation, liver transplantation and in-hospital deaths following the index date were extracted.

1.3. Results: 1,952 patients with WD were identified, of whom 1,131 (57.9%) were analysed. The estimated prevalence of WD in 2021 was 5.96/100,000. The mean age of the analysis population was 55.4±25.2 years. In the year before the index date, 850 patients (75.2%) presented clinical manifestations potentially associated with WD. Following the index date, 830 patients (73.4%) were prescribed a WD-specific treatment. Clinical manifestations persisted after the index date (82.1% at Year 1 and 75.6% at Year 5), whether patients were prescribed a WD-specific treatment or not. During the post-index period, 106 patients (9.4%) died in hospital (mean age at death: 68.8 years).

1.4. Conclusion: Treatment rates for WD in Japan are higher than described elsewhere. Nevertheless, ~30% of patients were not receiving the recommended standard of care and ~75% still presented clinical manifestations of WD over time. These findings underline the need for more effective treatment paradigms for WD.

2. Introduction

Wilson disease (WD) is a hereditary, progressive, severely debilitating disease principally affecting the liver and the central nervous system [1]. The disease is caused by a defect of copper handling due to mutations in the ATP7B gene, localised on chromosome 13, and encoding the transport protein ATP7B, a copper-transporting ATPase [2, 3]. Loss-of function mutations in this gene lead to failure of excess copper elimination into the bile and tissue accumulation, mainly in the liver and brain, where it causes degenerative injury [4, 5].

Wilson disease is a rare condition and its worldwide prevalence has been estimated from clinical studies to lie between 1:30,000 and 1:50,000 (2 to 3.3 cases per 100,000) [6]. Genetic screening studies yield higher prevalence rates (13 – 15 cases per 100,000), potentially due to the large number of undiagnosed cases [7]. However, these genetic screening studies could also include computer-predicted pathogenic mutations in their analysis and their results are somewhat conflicting [6]. It has been suggested that the prevalence of WD may be higher in East Asian countries such as in Japan than in Europe and North America [8]. Although generally fatal if untreated, WD can be successfully treated by dietary and pharmacological interventions. It is generally accepted that when patients are diagnosed

early before irreversible organ damage has occurred, and when they are adherent to their treatment, most of them will be able to live a normal life [9, 10]. Copper chelating agents, in particular trientine and D-penicillamine, and zinc salts, which inhibit intestinal copper absorption, represent the mainstay of pharmacological management [10]. Practice guidelines for the management of WD from Europe, North America and Japan emphasise the need for uninterrupted lifelong treatment to prevent symptom emergence or progression, unless liver transplantation, which can provide a cure, is undertaken [11-14]. We have recently performed a longitudinal study of patients with WD identified in the French national health insurance database in order to describe patient characteristics, disease burden and treatment patterns [15]. An unanticipated finding of this study was that less than fifty percent of patients with an ICD code for WD received treatment corresponding to the standard of care recommended in practice guidelines during the study period. A similar finding has also been reported in an insurance claims study in South Korea, in which only 34.9% of patients were receiving a specific treatment for WD [16]. The objectives of the present study were to identify patients with WD in a large Japanese insurance claims database and to document treatment patterns and associations of treatment with disease burden.

3. Materials and Methods

This was a retrospective longitudinal study of patients with a reimbursement claim associated with WD in Japan, conducted in the Medical Data Vision (MDV) hospital insurance claims database. Data were extracted for all patients with such a reimbursement claim between 1st April 2011 and 31st December 2021. The index date was defined as the date of the first claim associated with WD. The pre-index period was defined as the twelve-month period preceding the index date. Patients were followed until the end of the study period (31st December 2021), or until they died, if this occurred before. The total study period thus lasted from 1st April 2010 to 31st December 2021 (Figure 1).

3.1. Data Source

The MDV database is a private database which compiles all healthcare resource consumption from 2008 in participating hospitals using the Japanese Diagnosis Procedure Combination (DPC) fixed-payment reimbursement system. It currently covers over 419 facilities, representing more than twenty percent of acute-care hospitals using DPC in Japan, and includes data on an accumulated 32 millions patients of all ages. Both inpatient and outpatient medical services are documented. Reasons for hospitalisation are identified by a diagnostic code based on the International Classification of Diseases, 10th Edition (ICD-10), together with a specific identifier related to the Japanese vernacular name. However, patient identifiers are hospital-based so individuals cannot be tracked across hospitals if they visit different facilities. The individual hospital facility and department in which the patient was hospitalised are documented.

The database contains anonymous information on demographics (age and gender), medical department accessed, diagnosis, medication, surgery, procedures and laboratory tests [17]. Mortality information is limited to in-hospital deaths.

3.2. Participants

Patients with WD were identified through the relevant ICD-10 and Japanese vernacular name codes. First, all patients with at least one claim associated with ICD-10 code E83.0 (disorders of copper metabolism). This group includes several different Japanese vernacular name codes as subclasses, and we included only those with the specific code for Wilson disease (8830765). Patients with no documented healthcare reimbursement during the one-year pre-index period were excluded.

3.3. Data Extraction

Information was extracted from the database on age and gender at the index date. Hepatic, neurological and psychiatric signs and symptoms potentially attributable to WD were identified for each year preceding and following the index date through the relevant disease and medication codes in the database. Prescriptions of specific WD treatments (D-penicillamine, trientine or zinc acetate) were documented through the appropriate ATC codes for each year preceding and following the index date. All hospitalisations were identified and the length of stay determined. For patients who died, the date and age at death were documented.

3.4. Prevalence Calculation

The crude prevalence of WD was determined as the number of patients with WD identified in the database for a given year, divided by the total number of insurees for the same year. The standardised prevalence was calculated by weighting the crude prevalence rate according to the age and gender distribution in the whole Japanese population.

3.5. Statistical Analysis

The study is purely descriptive and no statistical hypotheses were tested. For certain analyses, two subgroups of patients were compared. These consisted of patients with at least one documented prescription of a WD-specific treatment during the study period ('with prescription' subgroup) or of patients without such prescriptions ('without prescription' subgroup). Continuous variables are presented as mean values with their standard deviation (SD) or median values with their interquartile range (IQR). Categorical variables are presented as frequency counts and percentage.

3.6. Ethics

The study complied with all relevant international and national legislation on medical research and data privacy. In particular, it complied with the Declaration of Helsinki (Fortaleza Revision, 2013) and with the Japanese Act on the Protection of Personal Information (Act

No. 57, 2003 and subsequent revisions). Furthermore, since all data was anonymized prior to extraction, the Japanese Pharmaceuticals and Medical Devices Agency guidelines for conducting pharmacoepidemiological research using medical databases, which specify when ethics approval and informed consent are required, did not apply.

4. Results

4.1. Study Participants

Between 1st April 2011 and 31st December 2021, 1,952 patients with at least one claim with an associated ICD-10 code for copper metabolism disorders (E83.0) and a Japanese vernacular name code for Wilson disease (code 8830765) were identified in the MDV database. Of these, 1,131 patients (57.9%) were analysed. The remaining 821 patients were excluded since they had no claims identified during the twelve-month pre-index period. The mean follow-up duration in the analysis population was 20.2 months (median: 12.0 months). Based on the total number of insurees in the MDV database in 2021 (11,719,754 individuals) and the total Japanese population of 124.8 million, the standardised prevalence of WD in Japan in 2021 was estimated to be 5.96 cases per 100,000.

The mean age of the analysis population at the index date was 55.4 ± 25.2 and 138 patients (12.2%) were children aged <16 years (Table 1). Men were somewhat over-represented (54.6%; N = 617). A high proportion of patients had a documented claim for clinical manifestations potentially associated with WD in the years preceding the index date, when a disease code for WD was first documented (Figure 1). For example, five years prior to the index date, 49.7% of the 189 patients with data available had a claim for hepatic manifestations, 32.3% had a claim for neurological manifestations and 16.4% had a claim for psychiatric manifestations (Figure 1; Table 1).

Table 1: Comparison between patients with and without prescription claims

	All patients N = 1,131	Patients without prescription claims N = 301	Patients with prescription claims N = 830	p
Age at index date	n = 1,131	n = 301	n = 830	
Mean ± SD	55.4 ± 25.2	45.9 ± 25.2	58.8 ± 24.2	<0.0001
Median [IQR]	63 [40 – 75]	47 [24 – 66]	67 [47 – 76]	
<16 years (n, %)	138 (12.2%)	46 (15.3%)	92 (11.1%)	0.06
Gender	n = 1,131	n = 301	n = 830	
Men, (n, %)	617 (54.6%)	167 (55.5%)	450 (54.2%)	0.71
Women (n, %)	514 (45.5%)	134 (44.5%)	380 [45.8%)	
Prior symptoms at Year -1	n = 1,131	n = 301	n = 830	
Hepatic symptoms	698 (61.7%)	141 (46.8%)	557 (67.1%)	<0.0001
Neurological symptoms	484 (42.8%)	90 (29.9%)	394 (47.5%)	<0.0001
Psychiatric symptoms	308 (27.2%)	54 (17.9%)	254 (30.6%)	<0.0001
At least one of the above	850 (75.2%)	663 (79.9%)	187 (62.1%)	<0.850

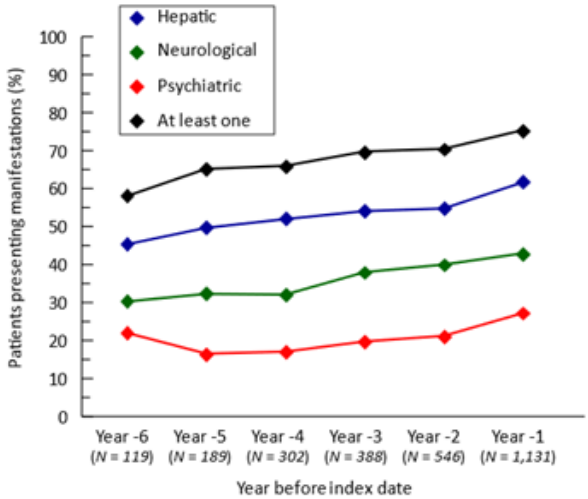

Figure 1: Clinical Manifestations prior to the index date

4.2. Treatment Prescription

830 patients (73.4%) were prescribed a WD-specific treatment (copper chelator or zinc salt) at least once after the index date during the study period ('with prescription' group). Of these, 827 (73.1%) were prescribed the treatment in the year immediately following the index date. The treatment most widely prescribed was zinc acetate (N = 770; 68.1%); D-penicillamine (N = 66; 5.8%) and trientine (N = 26; 2.3%) were prescribed in <10% of patients. Compared to the remaining 301 patients constituting the 'without prescription' group, patients from the 'with prescription' group were older (p <0.0001) (Table 1) and more frequently had a claim for WD-compatible symptoms in the year before the index date (Table 1). There was a small gender imbalance in favour of men in both groups.

The mean follow-up duration for the patients in the 'with prescription' group was 19.6 months, compared to 22.0 months in the 'without prescription' group (median values: 12.6 and 10.7 months respectively). The interval between two consecutive prescriptions was very similar for all WD-specific treatments. The mean interval ranged from 27.7 ± 45.7 days for trientine to 32.8 ± 97.3 days for D-penicillamine and the median interval from 8 [IQR: 3 – 22] days for zinc acetate to 11 [4 – 29] days for D-penicillamine.

4.3. Clinical Manifestations Over Time

Over the five years following the index date, the proportion of patients who presented clinical manifestations (symptoms or symptomatic treatments) potentially attributable to WD remained relatively stable (82.1% at Year 1 and 75.6% at Year 5), with the exception of psychiatric manifestations, for which the proportion of patients presenting them declined from 29.3% at Year 1 following the index date to 16.5% at Year 5 (Figure 2). When the two groups of patients with and without prescriptions were compared, certain differences were observed, notably for neurological and psychiatric manifestations. In these two groups, the proportion presenting clinical manifestations at the index date and during Year 1 was higher in the 'with prescription' group than in the 'without prescription' group. Thereafter the proportion fell in the 'with prescription' group and rose in the 'without prescription' group so that, at Year 5, the proportion was higher in the latter group (Figure 2). For example, in the 'with prescription' group, the proportion presenting neurological manifestations fell from 48.9% in Year 1 to 33.3% in Year 5, whereas the proportion rose from 35.9% to 57.1% in the 'without prescription' group. For psychiatric manifestations, the corresponding figures were 32.2% at Year 1 and 12.8% at Year 5 in the 'with prescription group' and 21.3% at Year 1 and 22.5% at Year 5 in the 'with prescription group'. The proportion of patients with hepatic manifestations remained relatively stable over time in both groups.

4.4. Hospitalisations

During the pre-index period, the mean number of hospitalisations per patient was 1.10 ± 1.65 and the mean length of stay was 23.9 ± 39.7 days (median: 12 [IQR: 5 – 27] days). The proportion of patients hospitalised and the mean number of hospitalisations per patient were higher in the 'with prescription' group patients than in the 'without prescription' group, whereas the mean length of stay was similar (Table 2). Following the index date, a total of 694 patients (61.4%) were hospitalised at least once during the follow-up period, and this proportion was significantly higher in the 'without prescription' subgroup (Table 2).

Twelve patients (nine in the 'with prescription' group and three in the 'without prescription' group) were hospitalised for liver transplantation during the follow-up period, for a mean duration of 25.3 ± 21.2 days (median: 20 days [range: 2 to 67 days]).

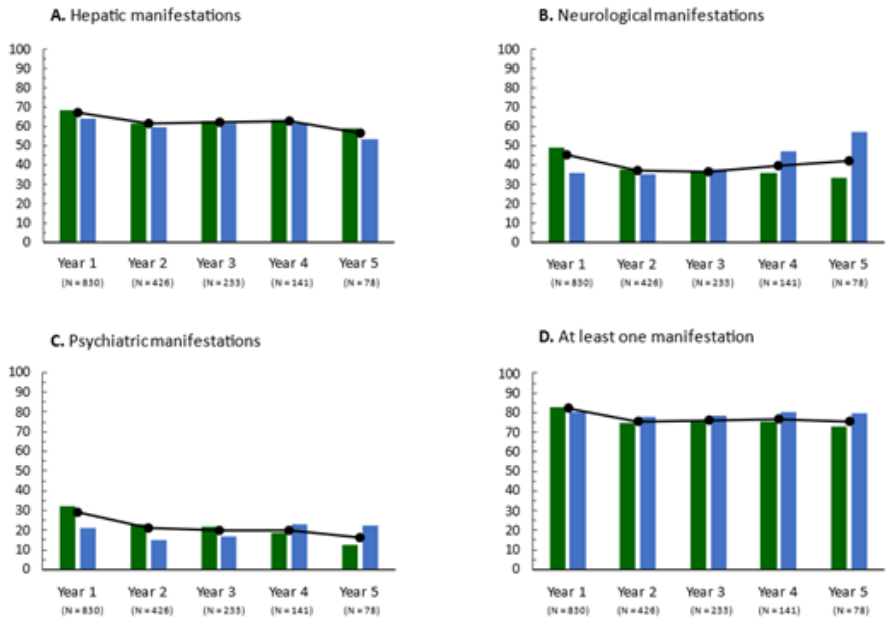

Figure 2: Clinical Manifestations by year following the index date

Table 2: Hospitalisations

	All patients N = 1,131	Patients with prescription claims N = 830	Patients without prescription claims N = 301	p
Number of hospitalisations during pre-index period				
Mean ± SD	1.10 ± 1.65	1.28 ± 1.71	0.62 ± 1.39	<0.0001
Median [IQR]	1 [0 – 1]	1 [0 – 2]	0 [0 – 1]	
Length of stay (pre-index period)				
Mean ± SD	23.9 ± 39.7	23.9 ± 40.1	23.4 ± 37.4	0.87
Median [IQR]	12 [5 – 27]	12 [5 – 28]	12 [4 – 25]	
Patients hospitalised during follow-up period n (%)	694 (61.4%)	561 (67.6%)	133 (44.2%)	<0.0001

4.5. Mortality

During the post-index period, 106 patients (9.4%) died in hospital. This proportion was higher (p = 0.006) in the 'with prescription' group (10.8%; n = 90) than in the 'without prescription' group (5.3%; n = 16). The mean age at in-hospital death was 68.8 ± 14.6 years (median 70 [IQR: 60 – 80] years) and did not differ between the 'without prescription' (mean age: 64.3 ± 17.1 years) and 'with prescription' groups (69.6 ± 14.1 years).

5. Discussion

In this study of a large Japanese health insurance claims database (MDV), we identified at least 1,952 insurees with WD over an eleven-year period. It is probable that this is an underestimate of the prevalence of WD in the Japanese population, since 821 patients with a claim associated with WD were excluded from the analysis for methodological reasons (no claim identified during the twelve-month pre-index period). Since approximately one-quarter of the Japanese population of 125 million are insured through the MDV, the estimated prevalence of WD for 2021 (the most recent year for which data are available) is at least 5-6 cases per 100,000.

Initial surveys performed in Japan more than thirty years ago reported prevalence rates between 3.3 and 6.8 cases per 100,000 [18-20], and our estimate is consistent with these findings, although lower than the 12 – 20 cases per 100,000 estimated through genetic screening [21]. Our estimated prevalence rate for WD is similar to that reported from an analysis of the South Korean insurance claims database (3.9 cases per 100,000) [16], but over twice as high as the estimate reported previously from an analysis of the French insurance claims database (2.2 cases per 100,000) [15] and other clinically-based estimates reported recently from Europe [22-24]. Our data supports previous finding that the prevalence of WD may be higher in East Asia than in other regions of the world [25].

At the index date, the mean age of the patients was 55 years old and 75% were ≥40 years old. The advanced age of the patients at the first documentation of WD in the MDV database is surprising, since symptoms of WD generally appear in the late teens or early twenties [4]. However, WD may also be diagnosed late, either due to initial misdiagnosis or to a long silent disease period [26, 27]. Delayed diagnosis is an important risk factor for disease progression [28]. However, there is no evidence from previous case series that the onset of symptoms of WD would be later in Japan than in other regions of the world [8, 29]. In the study from the South Korean insurance claims database, WD was first documented at a mean age of 26 years [16]. Similarly, the mean age at diagnosis in 929 patients referred to the national Polish reference centre was under thirty years [25], as it was in patients included in our previous study of the French national insurance database [15]. One possible explanation is that since the MVD is only one of several Japanese insurance claims databases, patients may have been diagnosed when insured elsewhere prior to entering the MDV database. Since patients are not frequently hospitalised (>75% hospitalised only once during the follow-up period, albeit for rather a long duration), it may take time for the WD label to appear in the database. Consistent with this idea, a majority of patients had clinical manifestations suggestive of WD several years before the index date, with 65% having at least one of these manifestations five years before the index date and 50% presenting hepatic manifestations. The presence of clinical manifestations suggestive of WD prior to the diagnosis of WD, and their management with symptomatic treatments has also been reported in the South Korean study [16], highlighting the significant issues of misdiagnosis and late diagnosis with this disease.

With regard to treatment, 73.4% of patients were prescribed a WD-specific treatment during the study period, generally starting during the year following the index date. This rate is much higher than the rates reported in insurance claims database studies from South Korea 34.9% [16] and France (43.8%) [15]. In addition, persistence with treatment appears to be high, with a mean interval between two consecutive prescriptions of around one month throughout the follow-up period. Again, this contrasts with the situation in Europe, where poor treatment adherence or persistence has been regularly reported as an issue for effective treatment of patients with WD [30-32]. It should nonetheless be noted that the nature of the MVD database precludes assessment of adherence, so there is no information on whether patients took their treatment or not. However, they

may have benefited from treatment, since the proportion of patients prescribed a treatment who presented clinical manifestations suggestive of WD decreased following the index date whereas, in patients without prescriptions, this proportion rose over time. The specific WD treatment prescribed was zinc acetate in 92.8% (770/830) of patients prescribed a treatment and copper chelators in 11.1% (92/830) of them This pattern of use is the opposite of what has been reported in Europe, where D-penicillamine remains the mainstay of WD treatment [15, 25]. Zinc salts may be preferred in Japan due to their reported better tolerability profile. Another difference found between Europe and Japan was that patients under treatment were older than patients not prescribed WD-specific medication during the study period (difference of around twelve years in the mean age of the two groups) and more frequently presented clinical manifestations at the index date. In contrast, in the French insurance claims study, patients with prescriptions were around twelve years younger than those without [15]. However, in spite of the relatively high treatment rate in Japan, no specific WD treatment was documented for 26.6% (301/1131) of the patients during the study period. This is not consistent with current practice guidelines, which emphasise the need to treat all patients with WD early and for life [12, 14].

Only in-hospital deaths are available and the cause of death is not documented in the Japanese database. Overall, 9.4% of patients died during the follow-up. A higher proportion of patients in the 'with prescription' group died compared to the 'without prescription' group, but this is probably an artefact due to the difference in age (around 12 years) between the two groups; in addition, the mean age of death was similar in the two groups (69 years). This is lower than the life expectancy in the Japanese population as a whole, which was 84 years in 2020 [33]. This is in line with the reduced life expectancy associated with WD reported recently in three other countries [15, 16, 25]. However, since only in-hospital deaths are documented here, it is not possible to evaluate the impact of WD on life expectancy in Japan with any degree of precision.

The principal strength of the study resides in the substantial sample size for a rare disease (1,952 patients with WD identified and 1,131 patients analysed), the relatively long data collection period both prior to and following the index date, the consistent way that data are documented in the database, and the general coherence of the data with that reported from other sources. The study also has several some limitations, many of which are inherent to the way the MVD database is organised: (i) the is some enrolment bias due to the fact that the database principally covers relatively large acute-care hospitals, excluding a high proportion of other hospitals and all community clinics; (ii) since patient identifiers are hospital-specific, there is a risk of double-counting if a patient attended visits in more than one hospital; (iii) the date of diagnosis of WD is not documented, and diagnosis may thus have occurred prior to the index event; (iv) clinical manifestations such as tremor, which have been attributed to WD for the purpose of this analysis, are by no means specific for this condition; -(iv) Given the age of the patients documented in this study, some confounding from comorbidities cannot be excluded. (v) Only in-hospital deaths are documented, so that the mortality rate identified in this study is certainly under-estimated.

In conclusion, this insurance claims database study of 1,952 patients with WD in Japan has shown that treatment and estimated adherence rates are higher than those described in other countries. However, a significant proportion of patients were not receiving the recommended standard of care during the study period, and the majority of patients still presented clinical manifestations of WD over time, whether they were prescribed a specific WD treatment or not. the findings, together with converging lines of evidence from different countries and databases, further confirm the need to improve standards of care in this progressive, fatal disease, in which life expectancy is curtailed even when current treatments are available.

6. Funding

This study was funded by Vivet Therapeutics, Paris, France.

7. Conflict of Interest

TDL, BB and JPC are employees and shareholder of Vivet Therapeutics, a biotechnology company involved in the development of gene therapies for rare diseases including Wilson disease. CL and ZL are employees of Creativ-Ceuticals, a contract research organisation under contract with Vivet Therapeutics for the implementation and exploitation of this study.

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