Epidemiology, treatment and burden of Wilson disease in France: A 10-year analysis of the national health insurance database

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Introduction

Wilson disease (WD) is a rare and inherited disorder of copper metabolism caused by mutations in the copper transporter ATP7B gene, which leads to toxic accumulation of copper in liver and brain. Left untreated, WD can be fatal. Symptoms most often first present in adolescence of early adulthood.

Medical treatment currently relies on copper chelators (D-penicillamine or trientine) or zinc. Poor treatment adherence is frequent and may result in severe complications.

In the present study, we evaluated retrospectively for a period of 11 years Wilson disease burden in a large cohort of WD patients from the Nationwide French social security (SNDS) database.

Materials and Methods

Data were extracted in the SNDS database for an 11-year period from January 1st, 2009, to December 12th, 2019, inclusive. The database contains information on all reimbursed health care expenditure (hospitalizations, consultations, laboratory tests, prescriptions, etc.) by beneficiaries of French national health insurance.

Patients were eligible for the study if they were a beneficiary of the General Regimen and had at least one medical claim for a hospitalization with the ICD-10 diagnostic code for WD (E83.0*: copper metabolism disorder) on the hospital discharge summary, or were listed as eligible for ALD (long term disability) status for WD. “Clinical manifestations” of WD refers to any reported hepatic, neurological or psychiatric conditions potentially attributable to WD, identified via ICD-10 codes or ATC codes of specific delivered medications.

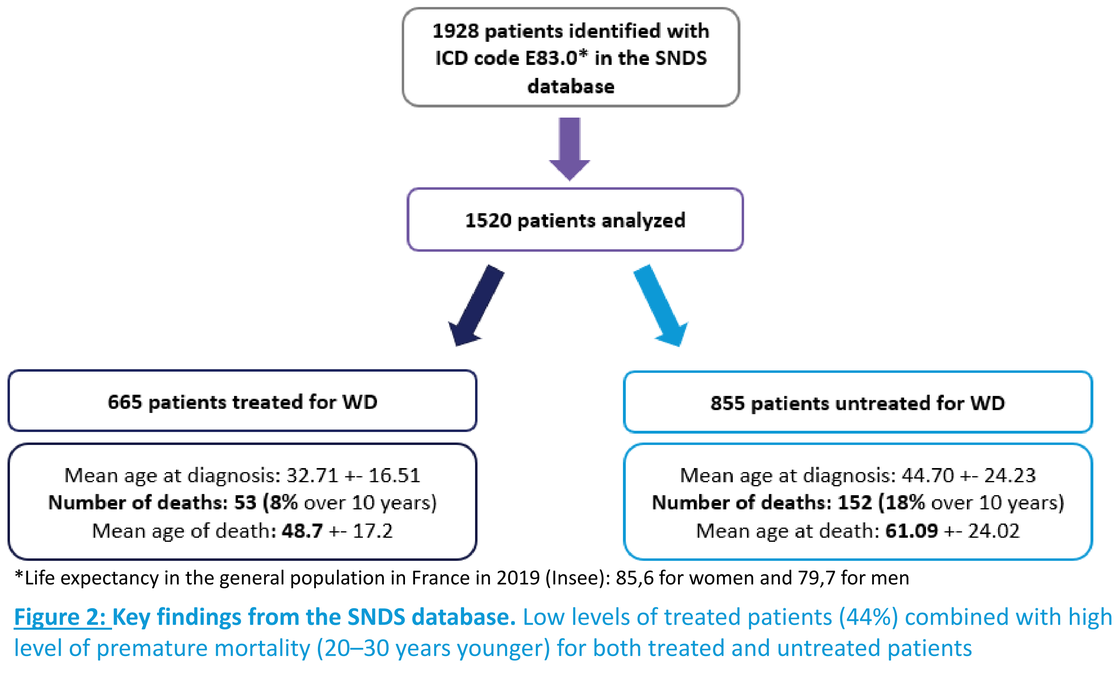
Results

Table 1 Patient characteristics at inclusion.

Age (years)	39.5 ± 22.0
Mean ± SD	38 [22 – 56]
Median [IQR]	233 (15.3%)
<16 years old	
Gender (n,% female)	732 (48.2%)
ALD status[1]	624 (41.1%)
For Wilson’s disease	699 (46.0%)
Other	359 (23.6%)
None	
Disease manifestations at inclusion[1]	1019 (67.0%)
Any of the following	742 (48.8%)
Hepatic	453 (29.8%)
Neurological	562 (37.0%)
Psychiatric	

[1] Categories are not mutually exclusive.

Figure 1: Patients characteristics at inclusion



*Life expectancy in the general population in France in 2019 (Insee): 85,6 for women and 79,7 for men

Figure 2: Key findings from the SNDS database. Low levels of treated patients (44%) combined with high level of premature mortality (20–30 years younger) for both treated and untreated patients

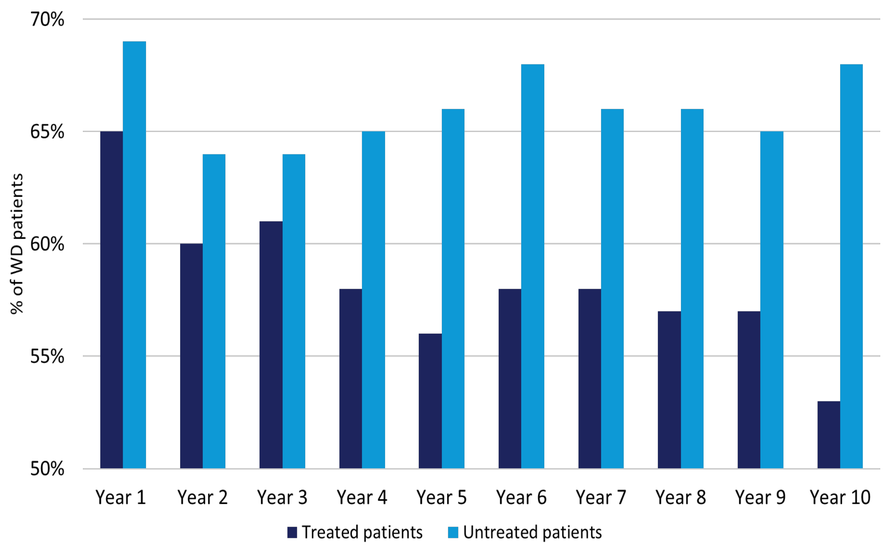


Figure 3: Clinical manifestations evolution in treated and untreated patients. While treated patients seems to improve, still half of them present clinical manifestations 10 years post diagnosis

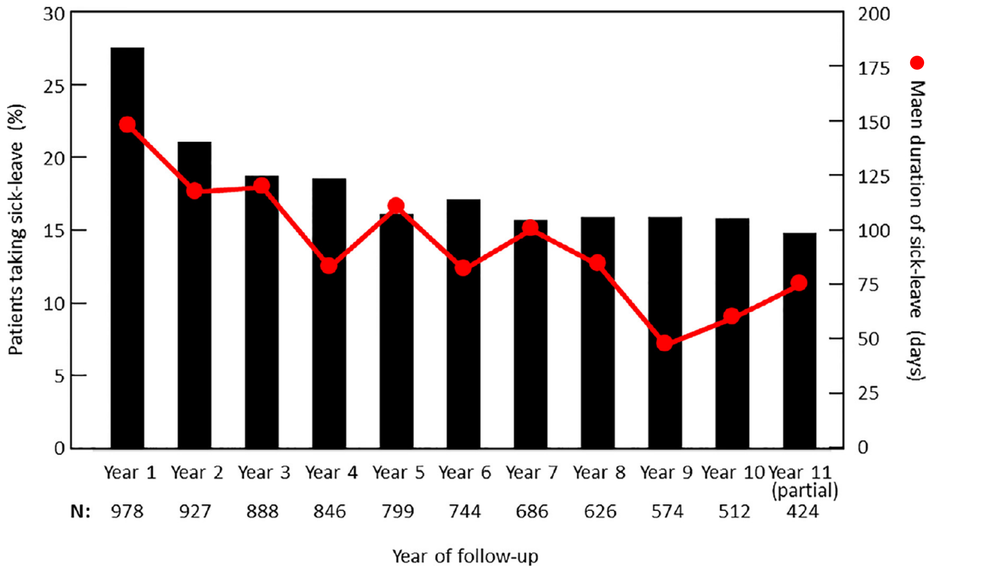


Figure 4: Change in sick-leave over time. Black columns: proportion of patients taking sick-leave; red symbols: mean duration of sick-leave per year for patients taking sick leave. Data are presented for the sub-population of patients of working age (18 to 64 years inclusive).

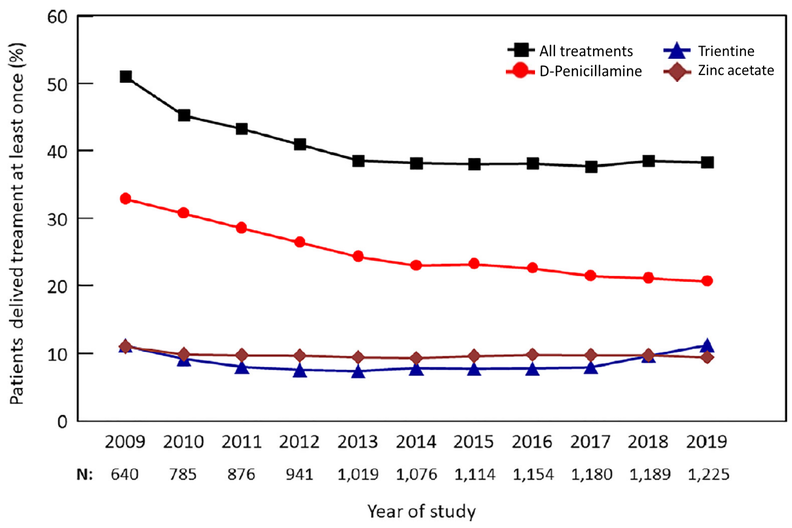


Figure 5: Treatments for Wilson's disease delivered over the course of the study

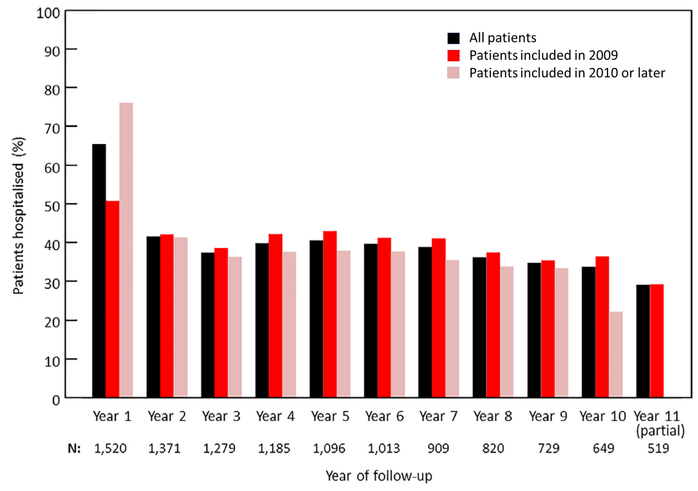


Figure 6: Hospitalizations over the follow-up period

Discussion and Conclusion

High disease burden in this nationwide French cohort with WD (ICD-10 diagnostic code for WD (E83.0*: copper metabolism disorder):

- 56% patients did not receive standard of care medication for WD
- 17.1% of patients received a disability pension over the study period
- 27.2% took sick leave for half a year on average during the year following index date. The whole analyzed patient population took sick leave for a mean 16.1 days/patient in 2017, ie more than twice than the general French population (7.2 days in 2017).
- 75% incident patients were hospitalized during the year following the index date and 34 to 42% were hospitalized each year throughout the 10-year follow-up period.
- 67% of patients had ≥1 clinical manifestation (symptom and/or treatment consistent with WD) during the index date year, and 56% still did 11 years post index
- Significant mortality rate: overall 13.8% over the 10-year study period and significant premature mortality with a mean age at death of 58, 49 or 61 years, for all, treated and non-treated WD patients, respectively, as compared to the general French population*

These results are at odds with published literature and suggest that WD patients are not only undertreated despite available medications, but also that disease burden is significantly underestimated, and that survival is significantly reduced in WD; refined survival analyses and determination of individual causes of death are ongoing.
WD management and treatment need further improvement and disease awareness to reduce Wilson disease burden.