BRIEF REPORT

Wilson's Disease in Finland: A Nationwide Population-Based Study

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ABSTRACT: Background: Data on the epidemiology and prognosis of Wilson's disease are scarce, and no clinical data are available from Finland.

Methods: All persons diagnosed and treated for Wilson's disease in Finnish hospitals in 1998 to 2017 were identified. Data were collected from national registries and patient charts.

Results: The point prevalence was 0.45/100,000 (95% confidence interval, 0.29–0.67) on December 31, 2017, but no more than 0.35/100,000 (95% confidence interval, 0.21–0.55) among native Finns. Annual incidence was 0.016/100,000 (95% confidence interval, 0.0093–0.026). Median age at diagnosis was 15.8 years (interquartile range, 8.3–32.2; range, 3.8–48.1 years). Upon presentation, liver damage was observed in 58%, neurological signs and symptoms (most often tremor and dysarthria) in 40%, and 32% of patients were asymptomatic. Patients had poorer long-term survival (hazard ratio, 2.92 for death; $P = 0.005$) compared with matched controls.

Conclusions: Wilson's disease is very rare in Finland. Patients have an increased risk of death indicating an unmet treatment need. © 2020 The Authors. *Movement Disorders* published by Wiley Periodicals LLC. on behalf of International Parkinson and Movement Disorder Society.

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Wilson's disease (WD) is a copper accumulation disorder affecting primarily the brain and the liver.[1] It is inherited recessively and hundreds of different mutations, all in the gene *ATP7B*, have been reported as causative.[2,3] However, there is an inadequately understood discrepancy between predicted genetic and actual clinical prevalence of the disease with the latter consistently reported to be lower than the former.[3] Underdiagnosis has been suggested, but reduced penetrance may also be a contributing factor.[4-8] Moreover, data on prognosis are scarce.[9,10]

Hepatolenticular degeneration was described in Finland among the first reports of the disease,[11] but clinical prevalence data are not available. A recent meta-analysis reported that the Finnish population had the lowest predicted genetic WD prevalence among the 7 investigated specific populations.[3] Here we aimed to investigate clinical WD in a nationwide, population-based setting.

Methods

Study Design and Data Source

We searched the Finnish Care Register for Health Care (CRHC), which contains information on all hospital discharges and outpatient visits in Finland, for patients treated with the diagnosis E83.0 in the 10th revision of the *International Classification of Diseases* between January 1, 1998, and December 31, 2017. Individual patient records of the identified patients were obtained for review to confirm the diagnosis and to collect clinical and genetic data. The dates and causes of death were obtained from the mandatory national registry maintained by Statistics Finland. Statistics Finland also provided anonymized data on randomly selected control subjects (N = 6600) matched for year of birth and sex for the survival analysis. We also obtained individual information from Fimea, the Finnish Medicines Agency, on the use of penicillamine and trientine, the use of which requires an explicit approval (valid for 1 year at a time) by Fimea for each patient.

The diagnosis was accepted if the patient met The European Association for the Study of Liver criteria for WD (score 4 or more on the scoring system developed at the 8th international meeting on WD).[12] We excluded 1 patient with rapid liver failure leading to transplantation who had been diagnosed with WD (fulfilling the criteria for established diagnosis) and treated as such but was found more than a decade later to harbor a mutation in the gene of DNA polymerase gamma, catalytic subunit (*POLG1*), leading to a revision of his diagnosis to mitochondrial recessive ataxia syndrome.

Statistical Analysis

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the distribution of continuous variables and subsequently Student's *t* test, the Mann-Whitney *U* test, or independent-samples Kruskal-Wallis test were used as appropriate. A 2-source capture–recapture analysis was performed using the CRHC data (the primary source, a) and Fimea data (the secondary source, b) to evaluate the completeness of ascertainment: N = [(a + 1) (b + 1) / (c + 1)] –1 (c, the number of cases common to both sources). Age-standardization was carried out using the direct method with the European Standard Population 2013 as reference. Poisson regression was used to analyze annual trends in the frequency of new diagnoses and linear correlation to analyze age-at-diagnosis trends. Survival from birth was analyzed using the Kaplan-Meier method and matched Cox regression. Median follow-up of survival was 32.3 years (interquartile range, 22.1–55.6 years). *P* values less than 0.05 were considered significant. IBM SPSS Statistics, version 25 (IBM, Armonk, NY) and SAS 9.4. (SAS Institute Inc., Cary, NC) were used for statistical analyses.

Results

WD was verified in 33 subjects (15 men). The capture–recapture analysis (25 patients found in both registries, 8 only in the CRHC and 3 only in the Fimea records) suggested a total WD population of 37 patients (95% confidence interval [CI], 36–38), indicating an ascertainment of 89%.

The point prevalence of diagnosed WD varied between the 0.25 (95% CI, 0.13–0.43) per 100,000 persons in 1998 and 0.45 (95% CI 0.29–0.67) in 2017. On December 31, 2017, there were 25 subjects alive with the diagnosis. The standardized prevalence was 0.46/100,000 persons. Because 7 of the living patients were immigrants (with permanent residence), the prevalence among native Finns was 0.35/100,000 (95% CI, 0.21–0.55).

A genetic analysis had been recorded in 17 patients (52%). The most frequently observed pathogenic mutation was c.3207C > A (p.His1069GIn) (Table 1).

Altogether, 17 new diagnoses had been made in Finland in 1998–2017 (Supplementary Fig. 1), yielding an annual incidence of 0.016/100,000 person-years (95% CI, 0.0093–0.026). The median age at the time of diagnosis was 15.8 years (interquartile range, 8.3–32.2; range, 3.8–48.1 years), with 10 patients diagnosed during the first 2 decades of life and none after 49 years of age. Upon presentation, liver damage was observed in 10 (58%) patients and neurological signs and symptoms (most often tremor and dysarthria; Table 1) in 7 (40%) patients. Five patients (32%) were asymptomatic and diagnosed through family screening.

Of the identified 33 patients, penicillamine had been used in 21 (64%), trientine in 10 (30%), and zinc in 21 (64%) patients. Liver transplantation had been

TABLE 1 The genotypes (known for 17 patients) and observed neurological signs and symptoms at the time of diagnosis

Genotype	N	Symptom/Sign	No. (%)
Homozygote: c.3886G > A, p.(Asp1296Asn)	3	Tremor	4 (24)
Homozygote: c.3207C > A, p.(His1069Gln)	1	Dysarthria	3 (18)
Homozygote: c.4021G > C, p.(Gly1341Arg)	1	Walking impairment	3 (18)
Homozygote: c.1639delC, p.(Gln547Argfs*22)	1	Parkinsonism	2 (12)
Compound heterozygote: c.865C > T, p.(Gln289*) and c. 1708-1G > A p. (?)	2	Seizures	2 (12)
Compound heterozygote: c.3207C > A, p.(His1069Gln) and c.3818C > A, p.(Pro1273Leu)	1	Chorea or athetosis	1 (6)
Compound heterozygote: c.3207C > A, p.(His1069Gln) and c.3646G > A, p.(Val1216Met)	1	Cognitive impairment	1 (6)
Compound heterozygote: c.3207C > A, p.(His1069Gln) and c.2866-2A > C, p.(?)	1	Dystonia	0
Compound heterozygote: c.3207C > A, p.(His1069Gln) and c.2336G > A, p.(Trp779*)	1	Myoclonus	0
Compound heterozygote: c.3207C > A (p.His1069Gln) and c.2866-14T > G, p.(?)	1	Hyperreflexia	0
Compound heterozygote[a]	4	Autonomic dysfunction	0

[a]No further data on mutation characteristics had been recorded.

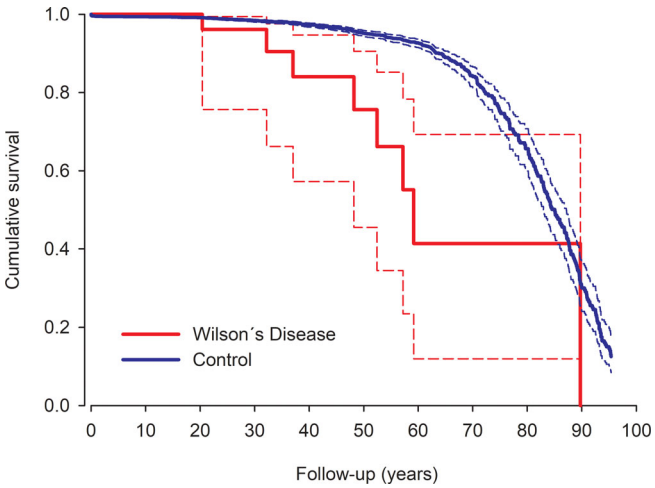

FIG 1 Survival of patients with Wilson's disease (N = 33) and age-matched and sex-matched controls (N = 6600) from birth in Finland. [Color figure can be viewed at wileyonlinelibrary.com]

performed for 5 patients (15%). The patients were usually followed-up primarily by paediatricians or gastroenterologists and seldom by neurologists. Patients with WD had poorer survival during the follow-up with a hazard ratio of 2.92 (95% CI, 1.39–6.15; $P = 0.005$) for death compared with matched controls (Fig. 1). There was no survival difference between men and women with WD ($P = 0.29$). Eight patients had died with a mean age of death at 49.5 years (standard deviation, 21.1). In 4 cases, the main cause of death was a malignancy (1 of each: liver, pancreas, bronchus, and breast).

Discussion

In this population-based nationwide study, we found that the prevalence of clinically diagnosed WD in Finland was 0.45/100,000, which is only a third of global pooled average of estimates.[3] Moreover, the clinical prevalence was less than 20% of the predicted genetic prevalence of 2.37/100,000 (95% CI, 1.7–3.4) in Finland.[3]

There has been marked discrepancy between the predicted genetic prevalence and the reported clinical prevalence of WD in all investigated areas.[4-7] In all reported regions, the clinical prevalence has been clearly smaller than the generally predicted genetic prevalences.[3,8] Underdiagnosis has routinely been suggested as the culprit, but reduced penetrance also appears probable.[8] This is also suggested by the case of Sardinia, where the epidemiology of WD has been thoroughly studied. Although prevalence rates there have increased in successive clinical epidemiologic studies because of increased awareness and diagnostic activity, they remain much lower than genetic prevalence estimates.[7] Although Sardinia can be considered a genetic isolate with an exceptionally high prevalence, recent results from Ireland and France also suggest similar clinical–genetic epidemiological discrepancies.[4-6] Our results, drawn from data with complete nationwide coverage of more than 2 decades in a country with universal access to healthcare, are in line with these results. Furthermore, persons with 2 disease-causing mutations do not always display any alteration in their copper metabolism.[13] Indeed, a third of the patients in the current study were diagnosed when asymptomatic. Thus, it seems necessary to be cautious in interpreting the molecular analysis results of *ATP7B*, as suggested.[6,8,13] It is also necessary to remember that the genetic prevalence is a "birth prevalence," whereas all clinical prevalence estimates are limited by the time taken for diagnosis. Therefore, the genetic birth prevalence could be predicted to always overestimate the clinical prevalence for that reason.

Sardinia and Finland both are genetic isolates and outliers in European genetics.[14] They also appear to represent the opposite ends of the continuum in the epidemiology of WD. The prevalence of the disease among native Finns was no more than 0.35/100,000, only a fifth of the 1.38/100,000 pooled global average of estimates reported recently.[3] This marked difference is likely attributed to the unique genetic background of the population of Finland, which has caused an enrichment of some rare diseases, whereas others show decreased prevalence.[15]

Hepatic disease is the most common form of presentation in WD, and our results show that this is also the case in Finland.[1] We observed that 40% of Finnish patients had neurological signs or symptoms at disease onset, which is in line with the previous European reports.[5,9,16] However, not all patients had been examined by a neurologist so this proportion, and particularly those of specific neurological signs, may be an underestimation.

Our data showed that patients with WD have poorer long-term outcomes compared with the general population with an almost 3-fold hazard of death compared with matched controls. A previous study from Austria also reported that the 20-year survival of WD patients was lower (92%) compared with matched controls (97%).[9] A study from Hong Kong recently reported somewhat worse survival rates: 92.6% at 5 years and 89.5% at 10 years from diagnosis.[10] It is therefore apparent that the risk of death is markedly increased in patients with WD compared with the rest of population. Our data suggest that this difference begins to emerge already before 40 years of age.

This was a retrospective study relying much on registry data. Although the CRHC has been shown to be reliable,[17] some cases may have been missed because of erroneous coding. We also included only patients with a diagnosis of WD but were not able to capture those who may have deceased prior to clinical diagnosis. Thus, it is possible that our survival results underestimate the

mortality of persons with the disease. The immortal time bias up to the time of diagnosis in patients with WD in our analysis also has the same effect. Medical records were unavailable for 8%, but a detailed assessment of the profile of registry entries suggested that only 1 of these may have had WD. The capture–recapture analysis also suggested an excellent ascertainment of 89%, indicating that very few diagnosed patients were missed. Nevertheless, the small number of patients in the final sample means that a small number of missed patients could have markedly changed the results. Lastly, because less than half of the diagnoses had been genetically confirmed, it is possible that non-WD patients were included, as exemplified by the mitochondrial recessive ataxia syndrome patient initially misdiagnosed as WD, but it is also possible that undiagnosed WD patients were missed from the analysis.

In conclusion, WD is exceptionally rare in Finland. The hazard of death was nearly 3-fold higher in patients with the disease compared with healthy controls, indicating an unmet treatment need.

Data Availability

This article is based on third-party data. Access to data is regulated by Finnish law and the Finnish National Institute for Health and Welfare. The disclosure of data to third parties without explicit permission from the Finnish National Institute for Health and Welfare is prohibited. Only those fulfilling the requirements established by Finnish law and the Finnish National Institute for Health and Welfare for viewing confidential data can access the data. We confirm that the authors did not have any special access privileges that others would not have.

Ethics

This registry-based study was approved by the Finnish National Institute for Health and Welfare (1863/5.05.00/2017) and Statistics Finland (TK-52-1763-19). In addition, regional permits were required by some hospital districts, and they were obtained accordingly. Since the study involved no contact with patients, ethics committee approval was unnecessary. This was a retrospective register study, and thus no informed consent was required, and the participants were not contacted. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679, article 6 (1)(e) and article 9 (2)(j); Data Protection Act, sections 4 and 6).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

J.O.T.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
M.H.: 1B, 1C, 2C, 3B
V. Kytö: 1B, 1C, 2A, 2B, 2C, 3B
V. Kaasinen: 1B, 1C, 2C, 3B

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