Parkinsonism and Related Disorders 21 (2015) 46–49

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Epidemiology of Huntington's disease in Finland

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ARTICLE INFO

Article history:
Received 12 August 2014
Received in revised form
22 September 2014
Accepted 27 October 2014

Keywords:
Hereditary neurodegenerative diseases
Choreatic disorders
Clinical neurology
Neuroepidemiology

ABSTRACT

Object: To estimate the prevalence of Huntington's disease (HD) in Finland.
Methods: Persons diagnosed with HD from 1987 to 2010 were identified in the national registers and hospital records of the identified patients, and death certificates of the deceased subjects were obtained. Results of genetic analyses were obtained from the two national laboratories.
Results: Following the discovery of the Huntingtin gene (*HTT*), the rate of new diagnoses of HD has increased in Finland. We ascertained 207 patients with HD, 114 of whom were alive on 31 December, 2010 suggesting a minimum estimate of point prevalence of 2.12/100,000. The age at the time of diagnosis was 52.6 ± 12.1 years (mean ± standard deviation) and the duration of the disease was 8.5 ± 4.4 years among deceased patients. The length of the CAG repeats in the affected allele was 43.3 ± 3.5 repeats and the length was inversely correlated with the age at diagnosis ($\beta = -0.73$, $p < 0.001$). The number of diagnoses varied regionally, whereas the repeat length did not. The frequency of the high risk *HTT* haplogroup A was 39% in Finnish chromosomes abstracted from the 1000 Genomes database compared to 53% in other European samples ($p = 0.024$).
Conclusions: The annual rate of HD diagnoses and the age at diagnosis have increased. The prevalence of HD in the Finnish population is lower than that of other Caucasian populations, partly explained by the low frequency of *HTT* haplogroup A among the Finns.

1. Introduction

Huntington's disease (HD) is a neurodegenerative disorder that is manifested with motor symptoms, such as chorea, and is accompanied by psychiatric and cognitive dysfunction [1]. It is a monogenic disease with autosomal dominant inheritance and is caused by an expanded cytosine-adenine-guanine (CAG) repeat in the *HTT* gene coding for Huntingtin [2]. The affected trinucleotide repeat exhibits a tendency to expand further, especially when inherited from the father [3]. The disease usually becomes manifest between the ages of 30 and 50 years, but the onset of symptoms can occur at any age [4].

The overall prevalence of HD is 5.6/100,000 among Caucasian populations, however, with wide variation [5]. Recently, prevalence estimates as high as 12.3–13.7/100,000 have been reported [6,7]. The prevalence seems to be lower in Asian and African populations being, for instance 0.5/100,000 in Japan. Among Europeans, 95% of the affected chromosomes of patients with HD, but only 53% of chromosomes with a CAG repeat length in the normal range (<27), belong to a distinct haplogroup defined by single nucleotide polymorphisms in the *HTT* region [8]. The frequency of haplogroup A is similar in European and Asian populations, but the haplogroup A variants A1 and A2 conferring high risk of HD are not found in Asian populations, whereas they comprise 31% of haplogroup A in the general population in Europe.

The prevalence of HD in Finland has been reported in 1987 to be 0.5/100,000 [9]. The disease was deemed rare to the extent that this was considered a negative feature of Finnish disease heritage [10,11], an enrichment of rare monogenic diseases in the Finnish population that has been suggested to result from long-term genetic drift rather than founder effects [12]. The discovery of the *HTT* gene and the causative mutation in 1993 has improved the

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http://dx.doi.org/10.1016/j.parkreldis.2014.10.025
1353-8020/

diagnostics of HD and here we report the prevalence of this disease in Finland based on comprehensive screening of diagnoses made during the last 25 years.

2. Methods

2.1. Study design and data source

In order to identify patients with HD we searched the Finnish Hospital Discharge Register (FHDR) for patients with the diagnosis 3334A in the ninth revision of the International Classification of Diseases (ICD-9) or with the diagnosis G10 in ICD-10 between 1 January, 1987 and 31 December, 2010. This register is maintained by the National Institute for Health and Welfare (THL) and contains information on all hospital discharges. We also searched the Hospital Benchmarking Database maintained by THL for all outpatient appointments with the ICD-10 diagnosis G10 from 1 January, 1998 to 31 December, 2010. Patient records were then obtained for review in order to confirm the diagnosis. The dates of death of the ascertained HD patients and ICD diagnosis codes on death certificates were obtained from Statistics Finland, the national authority that compiles vital statistics. We also obtained information on all confirmed *HTT* repeat expansions from the two laboratories in Finland providing the analysis. The registry of HUSLAB (Helsinki, Finland) covered the years 1993–2010 and that of the Department of Medical Genetics, University of Turku (Turku, Finland) covered the years 1998–2010. In addition, we searched the patient records of persons with HD at the Family Federation of Finland in Helsinki, where genetic counseling of families with HD was centralized in the 1980s and 1990s.

A patient was included in the study if the review of patient records confirmed the clinical diagnosis of HD. The diagnosis was accepted if the patient had a motor phenotype suggesting Huntington's disease and an expansion of the CAG repeat in *HTT* or if the patient had a motor phenotype suggesting HD and a family history of Huntington's disease or a family history of motor symptoms suggesting HD. For the genetic diagnosis of Huntington's disease it was required that the repeat expansion in *HTT* was at least 37 CAG repeats. Because the data on the age at onset was incomplete, we used the date of diagnosis as an approximation of the time of onset. Patients were determined to have a definite maternal or paternal inheritance if a clinical or genetic diagnosis of HD had been given to the mother or father, respectively, or to their siblings or parents. A probable maternal or paternal inheritance was defined as a parent, a parent's sibling, or a grandparent exhibiting signs and symptoms consistent with HD but not having a clinical diagnosis.

Twenty-two single nucleotide polymorphisms in the *HTT* region defining haplogroup A and the haplogroup A variants A1 and A2 conferring high risk of Huntington's disease [8] were identified in the 93 genomes from the Finnish population and are available in the data provided by the 1000 Genomes Project.

The study was approved by the ethics committee of the Hospital District of Southwest Finland (19/180/2010) and national authorization was given by the THL (STM/3375/2010). In addition, some of the hospital districts stipulated regional permits, which were obtained accordingly.

2.2. 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 of the Kruskall–Wallis test were used when appropriate. Differences in *HTT* haplogroup frequencies between populations were evaluated using Fisher's exact test. The 95% confidence interval (95% CI) for prevalence was calculated as described [13]. Correlation was tested with the linear regression analysis. *P*-values less than 0.05 were considered significant. IBM SPSS Statistics, Version 22, (IBM SPSS, Chicago, IL, U.S.A.) was used for statistical analyses.

3. Results

We identified 399 persons with the ICD codes indicating HD. Review of patient charts, death certificates, and results from genetic analyses confirmed Huntington's disease in 207 subjects (men, 97) (see Appendix). The mean annual number of new diagnoses was 2.7 (1981–1990), 7.1 (1991–2000), and 10.7 (2001–2010) (see Fig. 1). On 31 December, 2010 there were 114 subjects with an HD diagnosis, giving a point prevalence of 2.12/100,000 (95% CI: 1.77–2.54) and an age-adjusted prevalence of 2.09/100,000 standardized to European Standard Population 2013 (see Fig. 2). Age-specific prevalence was highest in subjects aged 60–64 years (6.5/100,000, 95% CI: 4.2–9.5). Furthermore, differences were found in the prevalence between the provinces (see Fig. 3 and Appendix) with Åland as an outlier.

The mean age at the time of diagnosis was 52.6 ± 12.1 years (range, 14–82 years) and this age increased during the three decades to 44.3 years ($N = 27$) from 1981 to 1990, 51.9 years ($N = 71$) from 1991 to 2000, and 55.4 years ($N = 107$) from 2001 to 2010 ($P = 0.001$). The mean duration of the disease was 8.5 ± 4.4 years (range, 0.6–23.8 years) among the 104 deceased patients.

The clinical diagnosis of HD had been confirmed by analysis of the CAG repeat length in the case of 162 patients, while 45 patients had been diagnosed on the basis of clinical features and family history of usually autopsy-proven or genetically diagnosed HD. The mean number of the CAG repeats in the affected allele was 43.3 ± 3.5 (median 43; range, 37–61) (see Appendix). The distribution of the repeat length in these patients was similar in different parts of the country ($P = 0.60$). The length of the CAG repeat in the expanded allele was inversely correlated with the age at diagnosis ($\beta = -0.73$, standard error 0.18, $P < 0.001$) and so was the length of the wild type repeat ($\beta = -0.20$, standard error 0.29, $P = 0.01$). The median length of CAG repeat was 43 among the 61 patients with definite or probable paternal inheritance (mean, 44.1 ± 4.2) and also among the 66 patients with definite or probable maternal inheritance (mean 43.2 ± 2.7, $P = 0.58$).

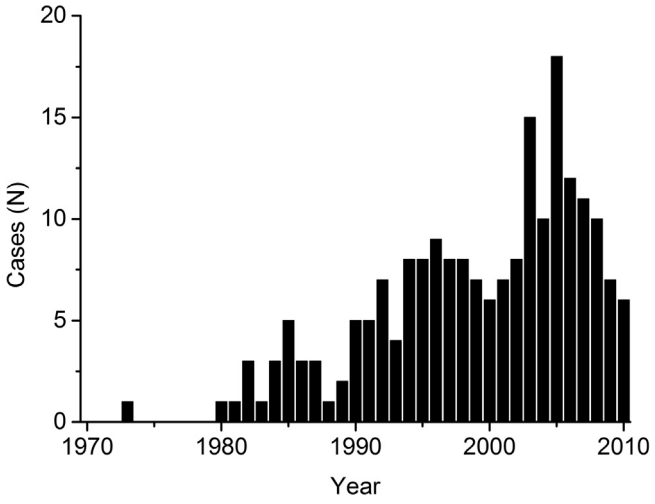

Fig. 1. The number of HD diagnoses in Finland between the years 1973 and 2010. The figure shows the annual number of clinically diagnosed new cases with HD identified by database search and chart review.

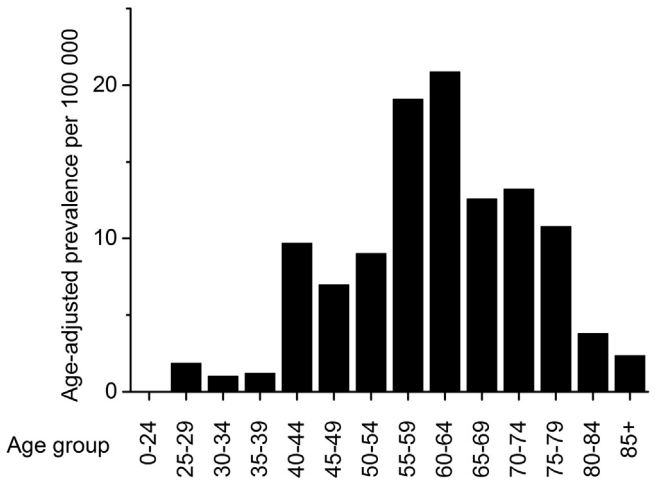

Fig. 2. Age-adjusted prevalence of HD. The prevalence figures are based on the number of patients that had the diagnosis of HD and that were alive on 31 December, 2010. The prevalence was age-adjusted to the European Standard Population 2013.