

Juvenile Huntington's disease: a population-based study using the General Practice Research Database

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ABSTRACT

Background: The juvenile form of Huntington's disease (HD) is a rare disorder. There are no population-based estimates of either its incidence or prevalence in any population in the world. The present study was undertaken to estimate the frequency of juvenile HD in the UK and to examine the range of pharmacological treatments used in its management.

Method: The records of individuals under the age of 21 who had recorded diagnoses of HD were retrieved from the General Practice Research Database from 1990 through 2010. From these data estimates of incidence and prevalence were made as well as the specific treatments used in the treatment of its physical and psychological manifestations.

Results: 12 incident and 21 prevalent patients with juvenile HD were identified. The 21 prevalent cases included the 12 incident cases. The minimum population-based estimate of incidence is 0.70 (95% CI 0.36 to 1.22) per million patient-years. The minimum estimate of prevalence is 6.77/million (95% CI 5.60 to 8.12) per million patient-years. Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

Conclusions: In the UK, juvenile HD is an extremely rare and complex disorder. The prescribing data demonstrate that the clinical management of juvenile HD is undertaken with no formal evidence base for the efficacy or safety of the treatments used. Research into the safety and efficacy of appropriate therapies is urgently required to offset the haphazard nature of prescribing. Multinational collaboration will be necessary to enrol sufficient numbers. Exploratory studies, though, should begin now.

INTRODUCTION

Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder associated with abnormal movements, psychiatric disturbances and cognitive decline.^{1 2} HD segregates as an autosomal trait located in chromosome 4p16.3. The HD gene encodes the huntingtin protein.² The HD abnormality is an expanded CAG repeat on exon 1 of the HD gene leading to the corresponding

ARTICLE SUMMARY

Article focus

This population-based study, using primary care data, was designed to

- Estimate the incidence and prevalence of juvenile Huntington's disease (HD) in the UK.
- Examine the range of pharmaceutical treatments used in its management.

Key messages

- The minimum estimate of the incidence of juvenile HD is 0.70 (0.36–1.22) per million patient-years.
- The minimal estimate of the prevalence of juvenile HD is 6.77 (5.60–8.12) per million patient-years.
- Patients were frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

Strengths and limitations of this study

- The study, based on primary care data for the UK as a whole, provides the first population-based estimates of incidence and prevalence of juvenile HD.
- The study indicates that the pharmacological treatments used for the management of juvenile HD are used in the absence of a formal evidence base.
- The study's major limitation is the extent to which, because of the stigma associated with the condition, primary care physicians are reluctant to include an HD diagnosis in patients' records.

expression of an expanded polyglutamine repeat in the huntingtin protein. Alleles with 40 or more CAG repeats invariably give rise to HD provided that individuals live a normal lifespan.¹

The juvenile form of HD is characterised by an onset in childhood or adolescence. Alleles with 60 or more CAG repeats usually result in the juvenile HD although it may occur in patients with less than 60 repeats. In adult HD the movement disorder is typically chorea. In juvenile HD the movement disorder, rather than chorea, is primarily tremor, bradykinesia and dystonia.^{3–5} In

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juvenile HD cerebellar signs, epilepsy, myoclonus and spasticity may also occur. As in adult HD, psychiatric disturbances and cognitive decline are also present^{4 5} but seizures are very unusual.

Although there have been various published estimates of the incidence and prevalence of adult HD there has been no attempt to estimate the population-based incidence, or prevalence, of the juvenile form. This study was designed to obtain an estimate of the incidence and prevalence of juvenile HD using the General Practice Research Database (GPRD) as well as to examine the range of specific treatments used in its management.

METHODS

Study design and setting

The GPRD is a computerised database containing anonymised electronic patient records from UK primary care. It covers around 6% of the UK population at any one time and both its unique features, as well as the high quality of the data contained within it, have been described elsewhere.⁶ The database is now included under the umbrella of the Clinical Practice Research Datalink that brings together data from across the UK's National Health Service.

Participants

For the purposes of this study juvenile HD was defined as onset before the age of 21 years. The source population was therefore all patients, under 21 years of age, registered with general practices contributing to the GPRD, between 1990 and 2010. Eligible cases were defined as any person, under the age of 21 years, with one or more diagnoses of HD or Huntington's chorea in their medical record. The last date for each record was the earliest of either the date of death, the date of patients' deregistration from the practice if still alive, the date the patient achieved the age of 21 years, the date the practice left the GPRD, or the end of the observation period (2010). The Read codes used to identify cases in the database were F134.00 (Huntington's chorea) and Eu2200 (dementia in HD).

Biases

In order to ensure that incident cases were not wrongly identified as prevalent ones, two additional criteria for inclusion as incident cases were applied: (1) they must have been registered with the practice for 12 months or longer by the date the diagnosis was recorded and (2) they had to have had at least one other recorded contact, with the practice, during the preceding 12-month period.

Prescription data

The medicines prescribed for incident and prevalent patients were also retrieved from the GPRD. Medications commonly prescribed for children and adolescents, and not specific for those with juvenile HD (including antibiotics, antifungal agents, emollients and routine

vaccinations) were not examined further. Specific treatments for the symptoms and signs of juvenile HD were analysed in detail. Those treatments prescribed more than twice for a particular patient were categorised as 'regular' treatments.

Statistical methods

Incidence was calculated from the numbers of incident cases (as defined above under biases), within 5-year age-bands, in relation to the total number of patient-years within the same age-band. Prevalence was calculated, for each year during the study period (1990–2010), from the numbers of patients with recorded juvenile HD divided by the total numbers of patients aged less than 21 years during that year. For estimates of both incidence and prevalence binomial 95% CIs were calculated.

RESULTS

Main findings: incidence

There were 12 records (4 females, 8 males) of patients fulfilling the criteria for inclusion as incident cases of juvenile HD. Their ages, at diagnosis, ranged from 5 to 20 years (median 15 years). The overall incidence was 0.70 (95% CI 0.36 to 1.22) per million patient-years. The estimates of incidence in 5 year age-bands (table 1) ranged from 0 (95% CI 0 to 1.1) per million patient-years at age 0–4 years, to 1.26 (95% CI 0.46 to 2.74) per million patient-years at aged 15–20 years.

Eight of the 12 incident cases had records of potential prodromal diagnoses, suggestive of juvenile HD, up to 3 years before a formal diagnosis of HD was entered into their records. These included sleep disorders (3 cases), psychiatric referrals (2 cases), movement disorders (2 cases) and referral for genetic counselling (1 case). The remaining cases had no obvious prodromal reported diagnoses.

Main findings: prevalence

There were 21 records (8 females, 13 males) of individuals contributing to the database, aged less than 21 years, with a diagnosis of HD. They provided a total of 116 patient years within the database. These 21 prevalent cases included the 12 incident cases. The average annual prevalence of juvenile HD, between 1990 and 2010, was 6.77/million (95% CI 5.60 to 8.12/million) but fluctuated year by year (table 2).

Table 1 Incidence estimates of juvenile Huntington's disease in the UK

Age group (years)	Incident cases	Population (patient years)	Incidence per million patient-years (95% CI)
0–4	0	4097551	0 (0 to 1.1)
5–9	3	4156414	0.7 (0.2 to 2.1)
10–14	3	4115431	0.7 (0.2 to 2.1)
15–20	6	4762455	1.3 (0.5 to 2.7)

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Table 2 Prevalence estimates of juvenile Huntington's disease in the UK

Year	Prevalent cases	Numbers in GPRD aged less than 21 years	Prevalence per million (95% CI)
1990	1	248518	4.0 (0.1 to 22.4)
1991	1	304836	3.28 (0.1 to 18.3)
1992	1	350401	2.9 (0.1 to 15.9)
1993	5	376180	13.3 (4.3 to 31.0)
1994	5	406351	12.3 (4.0 to 28.7)
1995	6	434286	13.8 (5.1 to 30.1)
1996	6	524798	11.4 (4.2 to 24.9)
1997	6	605201	9.9 (3.6 to 21.6)
1998	6	708142	8.5 (3.1 to 18.4)
1999	7	850823	8.2 (3.3 to 17.0)
2000	6	946889	6.3 (2.3 to 13.8)
2001	6	1016667	5.9 (2.2 to 12.9)
2002	7	1075286	6.5 (2.6 to 13.4)
2003	8	1104342	7.2 (3.1 to 14.3)
2004	10	1133156	8.8 (4.2 to 16.2)
2005	8	1153294	6.9 (3.0 to 13.7)
2006	6	1176419	5.1 (1.9 to 11.1)
2007	7	1188555	5.9 (2.4 to 12.1)
2008	8	1184231	6.8 (2.9 to 13.3)
2009	3	1175793	2.6 (0.5 to 7.5)
2010	3	1167683	2.6 (0.5 to 7.5)

Prescription data

Prescription data for the treatment relevant to the symptoms and signs of juvenile HD among prevalent cases are summarised in [table 3](#). One patient had no prescriptions recorded during the observation period and six were prescribed products for intercurrent conditions (mainly antimicrobial agents, oral contraceptives, anti-asthma products and vaccines) which were assumed to be unrelated to HD.

Fourteen patients were prescribed regular treatments apparently for the specific management of their HD symptomatology. Simultaneous prescriptions of more than one therapeutic category were common. The products most commonly prescribed included antidepressants (particularly fluoxetine and citalopram), a wide variety of treatments for motor disorders (including baclofen, levodopa, amantidine and tetrabenazine), hypnotics, antipsychotics (risperidone and olanzepine) and anticonvulsants (especially valproate and clobazam). Because of the small number of patients it would be inappropriate to use these data to infer the relative frequencies of the phenotypic variations, in the clinical manifestations of juvenile HD. Nevertheless, the data correspond—at least qualitatively—to the phenotypic patterns observed in reports of juvenile HD.⁵

DISCUSSION

There have been a number of population-based studies of the prevalence of HD that have provided information

Table 3 Prescriptions for the specific management of patients with juvenile Huntington's disease

Therapeutic category	Number of patients having products prescribed (regular prescriptions*)
Antidepressants	8 (6)
Motor abnormalities	7 (5)
Hypnotics	7 (3)
Antipsychotics	6 (3)
Anticonvulsants	5 (5)
Anxiolytics	3 (0)
Food supplements	2 (2)
Wound dressings	2 (2)

*Regular prescriptions are those prescribed to a particular patient more than twice.

about the proportion of cases with the juvenile form of the condition.^{7 8} It is not possible to infer from these reports the prevalence of juvenile HD, because none provide estimates of the relevant population under 21 years of age. The estimates of incidence and prevalence of juvenile HD reported here are, therefore, the first to provide population-based epidemiological data on the frequency of this condition either in the UK or worldwide. The apparent increase in the incidence of juvenile HD with age, in [table 1](#), is intuitively appropriate. However, because of the small numbers involved it is impossible to be certain.

Our estimates of both the incidence and prevalence of juvenile HD, almost certainly underestimate the true frequency of juvenile HD. First, it is possible that some general practitioners chose not to record their patients' HD diagnoses for reasons of confidentiality. Second, the dates of onset of past diagnoses are not always reliably recorded. Past diagnoses may be recorded either without a date or as occurring at the date of registration. These cases were excluded from our analysis of incidence. Third, we report the dates of recorded diagnoses. Possibly, some patients diagnosed in adulthood began showing symptoms in childhood or adolescence. These cases were also excluded. Finally, the strict criteria we applied in defining incident cases might have resulted in omitting some who should have been assigned to this category. However, only two prevalent cases were excluded as incident cases (one aged 12 years and the other aged 19 years) because their records failed to include any other contact with the practice in the 12 months prior to the entry of a diagnosis of HD.

Extrapolated to the entire UK population our results suggest that at a minimum, there are 100 children and adolescents living with juvenile HD. This does not of course include patients, over the age of 20 years, during the period of the study, who were originally diagnosed as juvenile HD. Again, extrapolating to the UK as a whole, we estimate that 10 new cases are diagnosed annually.

Most of the potential prodromal diagnoses, reported for incident cases, were typical of the clinical features of

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juvenile HD, including motor disturbances and psychiatric problems. It is striking that three patients complained of sleep disturbances. This has not previously been reported in association with juvenile HD. Furthermore, hypnotics were prescribed to a significant proportion of juvenile HD patients.

The symptomatology of juvenile HD is complex and causes suffering in all domains of life. The range of pharmacological products prescribed (table 3) for our cohort of people with juvenile HD are similar to that recently reported by Robertson *et al.*⁹ Most of the treatments for the motor manifestations of juvenile HD are those shown to be effective in Parkinson's disease but none have ever been formally assessed in juvenile HD. Even though a wide range of other therapies are used, often simultaneously, there are no studies to guide the current trial-and-error 'experimental' approach to the treatment of juvenile HD. No studies of the effectiveness of antidepressants, antipsychotics or anticonvulsants have ever been done to assess the effectiveness of these treatments in juvenile HD. In particular, in view of current anxieties about the potential hazards of using antidepressants in children,¹⁰ clinical trials of the effectiveness of specific serotonin reuptake inhibitors, are especially urgent. The present investigation also suggests that there is a critical need to assess the comparative effectiveness of other treatment options in juvenile HD. Because the number of children and adolescents with juvenile HD are small, in any one country such as the UK, only multinational trials are likely to produce the most rigorous answers. Small exploratory studies should be initiated immediately to guide the design of larger trials as well as provide some early answers.

The humane and supportive care of children and adolescents with HD requires the availability of appropriate resources to be provided by the UK's health and social services. These resources are complex and multidisciplinary. It is incumbent on those planning the provision of such care that the needs of these young people—and their families—are met.

Contributors All the authors were involved in the design and analysis of the study. ID and SE were responsible for the extraction of the data and undertook the statistical analyses. MDR and NSW wrote the first draft of the paper which was then edited and approved by the other contributors. MDR is the guarantor.

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Competing interests LS is supported by a Senior Clinical Fellowship from the Wellcome Trust and ID by a fellowship from the Medical Research Council.

Ethics approval Ethical approval for the study was obtained from the GPRD's Independent Scientific Advisory Committee and from the London School of Hygiene and Tropical Medicine's Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi:10.5061/dryad.3v18v

REFERENCES

1. Novak MJ, Tabrizi SJ. Huntington's disease. *BMJ* 2010;c3109.
2. Wexler NS. Huntington's disease: advocacy driving science. *Ann Rev Med* 2012;63:1–22.
3. Van Dijk JG, van der Velde EA, Roos RAC, *et al.* Juvenile Huntington's disease. *Hum Genet* 1986;73:235–9.
4. Ribai P, Nguyen K, Hahn-Barma V, *et al.* Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Arch Neurol* 2007;64:813–19.
5. Quarrell OWJ, Brewer HM, Squitieri F, *et al.* *Juvenile Huntington's disease (and other trinucleotide repeat disorders)*. Oxford: Oxford University Press, 2009.
6. Herrett E, Thomas SL, Schoonen WM, *et al.* Validation and validity of diagnoses in the General Practice Research Database. *Br J Clin Pharmacol* 2010;69:4–14.
7. Morrison PJ, Johnston WP, Nevin NC. The epidemiology of Huntington's disease in Northern Ireland. *J Med Genet* 1995;32:5240530.
8. Quarrell O, O'Donovan KL, Bandmann O, *et al.* The prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. *PLoS Curr* 2012;4. doi:10.1371/418606b742ef3.
9. Robertson L, Santini H, O'Donovan KL, *et al.* Current pharmacological management in juvenile Huntington's disease. *PLoS Curr Huntington Dis*. <http://currents.plos.org/hd/article/current-pharmacological-management-in-juvenile-huntingtons-disease-2/> (accessed 30 Oct 2012)
10. National Institute for Health and Clinical Excellence. *Depression in children and young people: identification and management in primary, community and secondary care*. London: National Institute for Health and Clinical Excellence, 2005. <http://guidance.nice.org.uk/CD28> (accessed 30 Oct 2012).

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