Predictive Testing of Minors for Huntington's Disease : The UK and Dutch Experiences.

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Abstract

A consistent feature of predictive testing guidelines for Huntington's disease (HD) is the recommendation not to undertake predictive tests on those <18 years. However, exceptions are made, but the extent of, and reasons for deviation from the guidelines are unknown. The UK Huntington's Prediction Consortium has collected data annually on predictive tests undertaken from the 23 UK genetic centres in the UK. DNA analysis for HD in the Netherlands is centralized in the Laboratory for Diagnostic Genome Analysis. In the UK, 60 tests were performed on minors between 1994 and 2015 representing 0.63% of the total number of tests performed. In the Netherlands, 23 tests were performed between 1997 and 2016. The majority of the tests were performed on those aged 17 and 16 years for both countries (57% and 23% for the UK, and 57% and 26% for the Dutch). Data on the reasons for testing were identified for 36 UK and 22 Dutch cases and included: close to the age of 18 years, pregnancy, currently in local authority care and likely to have less support available after 18 years, person never having the capacity to consent and other miscellaneous reasons.

This study documents the extent of HD testing of minors in the UK and the Netherlands and suggests that, in general, the recommendation is being followed. We provide some empirical evidence as to reasons why clinicians have departed from the recommendation. We do not advise changing the recommendation but suggest that testing of minors continues to be monitored.

Key words: Huntington's disease, Predictive testing, minors.

Introduction

Huntington's disease (HD) is a well-known neurodegenerative disorder with age dependent penetrance[1]. Predictive testing for HD became available in 1986[2] and was initially undertaken as part of research projects; however, guidelines for predictive testing were developed and first published in 1989 and 1990[3,4] and have since been updated twice[5,6,7]. In the earlier versions the guidance was not to test before the age of majority but, the latest update specifically states that "…the minimum age of testing be 18 years. Minors at risk requesting the test should have access to genetic counselling, support and information including discussion of all their options for dealing with being at risk." Elsewhere in that document there is a comment that the recommendations are "not intended as rigid rules but rather recommendations to guide and inform practice, based on current evidence and expertise"[7]. The debate and recommendation not to test minors are based on theoretical concepts with limited empirical evidence available[8-13]. In this report we document the extent of predictive testing for minors in the UK and the Netherlands, and comment on some of the reasons why clinicians have departed from the guidelines/recommendations.

Methods

Data Collection in the UK

In the UK, a Huntington's Prediction Consortium (UKHPC) was launched in 1989 to collect annually anonymised data on predictive tests for HD performed in the UK. This database has been described previously and has been used to present data on the uptake of predictive testing in the UK[14]. We analysed data from 1994 because that was the first full year for which predictive testing was available based on measurement of the CAG repeat length. Given the strong and consistent recommendation not to test those <18 years, the few cases where this had occurred were not included in that report. We have now used the UKHPC database to report on the extent of predictive

testing of minors in the UK. Some reasons for predictive testing were noted on the database but, in addition, the UK clinical genetic centres were asked to give more detail on the reasons why a test was undertaken on a minor. This exercise resulted in two additional cases being reported.

Data Collection in the Netherlands

DNA analysis for HD in the Netherlands is centralized in the Laboratory for Diagnostic Genome Analysis (LDGA), Department of Clinical Genetics (Leiden Medical University Center, Leiden, The Netherlands). All requests for pre-symptomatic testing of minors were identified from patients who had undergone DNA analysis for HD between January 1997 and December 2016. The referring clinical geneticists were asked to give more detail on the reasons for testing.

Results

There are 23 genetic centres in the UK but not all centres reported data for every year. In the period 1994-2015 there should have been 506 centre level annual reports (22 years x 23 centres) but in fact 476 (95%) were reported. Testing of minors was reported from 20 of the 23 UK genetic centres. There were 9616 tests recorded on the database with 9466 having an age of testing recorded. 63 tests were reported on patients <18 years but subsequently two entries were questioned and one entry was marked as already symptomatic. The extent of predictive testing of those <18 years in the UK is 60/9463 = 0.63%. An equivalent figure was not available for the Dutch data. The male/female ratio for the UK data was 21:39; similarly, the ratio of normal to abnormal results was 38:22. Neither ratio was significantly different from that seen in the UK adults having predictive tests[14]. The prior probability was 50% in 53 cases and 25% in 5 cases; in one case the prior probability was low because it was a re-test to confirm a previous pre-natal test result based on a linkage analysis and in a further case the prior probability was difficult to determine from the UKHPC database.

Some comments on the reasons for testing were recorded on the database but additionally centres were contacted to provide more detail on the reasons for the predictive test. This resulted in the description of two cases not recorded on the database. Reasons for testing 36 cases from the UK and 22 from the Netherlands are summarised in Table 1. The age structure of predictive tests undertaken on minors in the UK and the Netherlands is shown in Fig 1; it can be seen that that most tests of minors were performed on those aged 16 and 17 years (23% and 57% respectively for the UK and 26% and 57% for the Netherlands).

One of the additional cases reported from the UK was a boy with a maternal family history of HD and paternal family history of seizures. He had an unremarkable birth history but developed neonatal seizures at 5 days. By the age of 4 years he had evidence of developmental delay and intention tremor. An MRI scan showed normal basal ganglia but a small cerebellum was questioned. He had brisk lower limb reflexes and by the age of 5 years juvenile onset HD was considered. He was tested for HD and the result was normal.

In the Dutch data, the male/female ratio was 8:11; the ratio of normal to abnormal results was 18:5. The former ratio was the same as seen in a series of Dutch adults having predictive tests from 2005-2011 (102:141, unpublished data). The latter ratio however was significantly different from the data in adults: in a group of 107 individuals aged 18-40 years having predictive tests the ratio was 55:52. The prior probability was 50% in 21 cases and 25% in one case. In one case the prior probability was low because of an intermediate allele in the mother.

Discussion

The current guidance advising against predictive tests for HD of minors is based on theoretical concerns and expert opinion of experienced practitioners[7]. We have provided some empirical evidence for the extent of the predictive testing of minors in the UK as 0.63%. In both the UK and the Netherlands, the most common reason for testing a minor was that the young person was close to 18 years and counselling sessions had been undertaken. Testing was also performed in a small number of cases in relation to a pregnancy. One small category of cases relates to a "looked after" young person in foster care, or some other form of institutional care, when more support may be available to them as a minor rather than waiting until he/she is 18 years when less support might be available. It has to be acknowledged that it is impossible to know if the young person would still request predictive testing after having left the "care" environment. We also noted cases where the young person had another condition (Down syndrome or autism) which meant that the ability to consent was impaired, and was expected to remain so irrespective of the age of testing; therefore, the basis for the testing was an assessment of the best interests of the young person. An unusual scenario which occurred more than once was that juvenile HD had occurred in the family and testing of a sibling was undertaken <18 years. Each such case has to be assessed individually.

Another scenario which occurred more than once was that all sibs in a sibship requested to be tested pre-symptomatically at the same time, including one or two minors. Repeated attempts to exclude the minors from such "group based" testing were made but this led to strong feelings of isolation and not being part of the family dynamics. For the sake of the family system, predictive testing was undertaken in those cases after a careful counselling procedure.

We have reported one diagnostic test performed because the possibility of juvenile HD was raised. It was not reported to the database because it had been performed as a potentially diagnostic test but it illustrates that challenging scenarios occasionally arise in at-risk patients with neurological or behavioural problems. Such a "diagnostic" test could be predictive, and difficult to interpret, if the CAG repeat expansion was not in the range clearly associated with juvenile onset disease.

In the Dutch series, not only were results skewed to abnormal, but in addition, half of expanded CAG repeat lengths were in the high range (48-56 repeats), associated with younger age at onset. In several files it was mentioned that the parent was young when he or she developed symptoms of HD. Given the early age of onset in their parent, offspring may feel a greater urge to know their own status at a younger age than offspring of a parent whose onset was in their mid-forties or later. They (or their caregivers) may also experience subtle changes in behaviour and executive functions at a younger age, and consequently question whether such changes represent the onset of symptoms at a younger age. This was the case in two minors in the Dutch series, who presented behavioural problems at the time of their request.

In one case the testing procedure departed from the protocol as the request came from a paediatric neurologist. The laboratory noticed this only after DNA analysis had been completed. After consultation, the results were sent to a clinical geneticist, who reported the results in the first contact with the family. In order to prevent recurrence of this difficult situation, the Dutch laboratory now keeps strictly to the rule that pre-symptomatic testing can only be ordered by a clinical geneticist and the reason for testing is checked with the referring clinician for all requests regarding minors (including apparently diagnostic ones).

The relatively small number of tests which have been undertaken, and the fact that the majority were performed on those aged 17 years, suggests that the guideline is generally being observed. It should be noted that both in the UK and the Netherlands a young person at age 16 years can be

presumed to have the capacity to consent [15, 16]. A significant weakness of this study is that we have no information on the longer term outcomes of the testing. Recording of cases by the UKHPC is voluntary, with a high reporting rate, but we cannot be sure that all cases in the UK are submitted. This information was extracted from a large data set and the accompanying notes on the reasons for testing are frequently brief.

In conclusion, we do not advocate that the guidelines are changed but rather that the practice of testing minors continues to be assessed carefully on a case by case basis. The reasons for testing outside the recommendation should be documented carefully. The practice of laboratories accepting referrals for HD predictive tests, and apparently diagnostic tests, on minors only from clinical geneticists appears reasonable.

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16. Artikel 447 Wet Geneeskundige Behandelingsovereenkomst (WGBO, the Act on the Medical Treatment agreement in the Dutch Law).

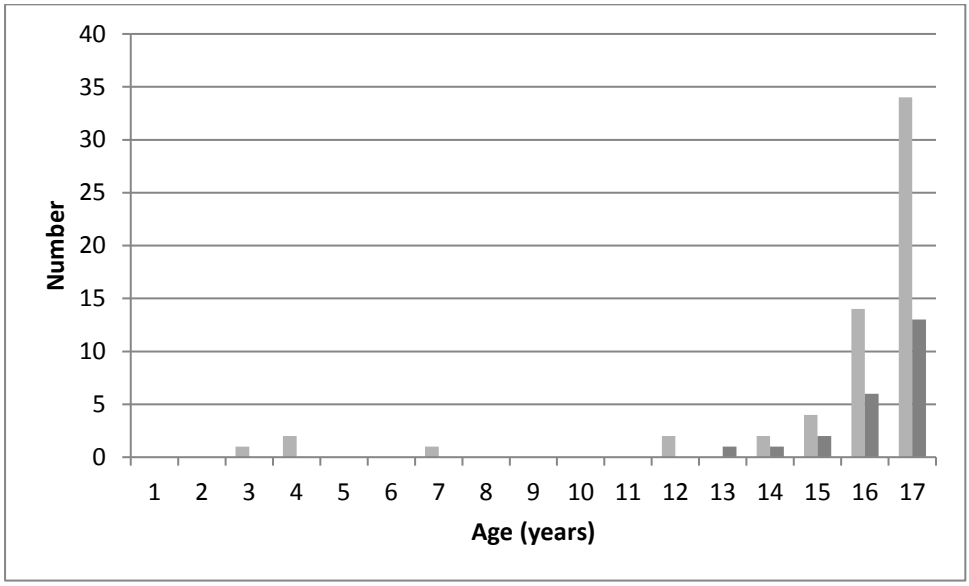
Table 1

Reasons for testing	**Number (UK and Dutch data combined)**
Close to age 18 years	25
Pregnancy	6
Currently in care and more support available <18 years	4
Person never having the capacity to consent	2
Siblings in the family with young onset HD	3
Persistent requests age 15 and 16 years	4
Mother had an intermediate result	2
? psychiatric symptoms	3
Confirm a prenatal test result based on linkage analysis	1
Estranged father with HD, mother had mental health problem and the young person had been told he/she would die.	1
Tested posthumously because mother wanted to make sense of the death which was due to another illness	1
Tested same time as mother	1
Diagnostic test but result normal	1
Tested together with siblings > 18 years (family wanted to go through the process as one)	3
Testing procedure not according to protocol (persistent request from minor was granted by child neurologist, results were given by clinical geneticist)	1

Figure 1

Age structure of 60 predictive tests undertaken in the UK 1994-2015

and 23 in the Netherlands 1997-2016



Legend to Figure 1

Light grey represents the UK predictive testing of minors

Dark grey represents The Netherlands testing of minors