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ARTICLE

Predictive genetic testing in Huntington's disease: should a neurologist be involved?

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Abstract

International guidelines on Huntington's Disease recommend neurological examination in the predictive testing trajectory. Experiences and personal wishes of persons at risk of Huntington's Disease regarding this topic have never been evaluated. The objective was to provide an overview of the experiences of Dutch at-risk persons, opting for predictive testing, in consulting a neurologist before and after DNA analysis. Persons who were counseled in four Dutch clinics between 2017 and 2019 were retrospectively or prospectively approached for a questionnaire which listed topics as experiences with consultation and personal wishes. From 71 participants, 44 participants visited a neurologist. 41 participants indicated their visit to a neurologist as positive (93.2%). The majority of participants ($n = 59$) desired consulting a neurologist. Thirty-two participants indicated consultation shortly after (Desired After Group) and twenty-seven before DNA analysis (Desired Before Group) as personal wish. The Desired Before Group consisted of a significantly higher number of participants who actually consulted a neurologist before predictive testing ($n = 26$) compared with the number of participants who actually consulted a neurologist after DNA analysis in the Desired After Group ($n = 11$) ($p < 0.001$). The Desired After Group ($n = 19$) had a significantly higher number of Huntington's disease gene expansion carriers compared with the Desired Before Group ($n = 5$) (p 0.003). Participants are content with consultation. However, persons without the gene expansion still feel the need to get in touch with a neurologist. Therefore, offering a consultation with a neurologist before DNA analysis might be beneficial for all.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by involuntary movements, psychiatric disorders, and cognitive deterioration. HD results from an unstable and expanded CAG trinucleotide repeat in the Huntingtin gene on chromosome 4 [1]. A CAG repeat size of 36 or more is associated with HD [2]. Most patients develop symptoms and signs in adulthood with a mean onset of 40 years of age.

Persons at risk are those from an HD family who do not know their genetic status. They have the availability to opt for predictive DNA testing. If predictive testing shows an expanded CAG repeat (>39), this person will develop HD in time (HD gene expansion carrier, HDGEC). A CAG repeat of 36 to 39 gives reduced penetrance which means that the clinical symptoms might not appear. The main reasons for persons at risk to get predictive testing are: prepare for the future, wanting to inform their children and family planning [3–8].

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There are several departments of Clinical Genetics offering predictive testing in the Netherlands. Four of these, Leiden University Medical Center (LUMC), Maastricht University Medical Center (MUMC+), Radboud University Medical Center (Radboudumc), and University Medical Center Groningen (UMCG) participated in the study. A person at risk for HD who visits one of these four clinics is informed by a clinical geneticist about the possibilities of predictive testing. In LUMC persons at risk are also assessed by a neurologist with HD expertise. The neurologist takes the medical history and performs a neurological examination. In MUMC+, Radboudumc, and UMCG persons at risk are as a routine not assessed by a neurologist in the counseling phase. They are offered to consult a neurologist with HD expertise, appointments are made at patient's request before or after the predictive testing trajectory.

The international guidelines of the Huntington Association and the World Federation of Neurology Research Group on Huntington's chorea of 1994 and the revised version of 2013 posits that neurological examinations (if possible) are considered important to establish a baseline evaluation of each person (paragraph REC 6.2). This however is not a requirement for participation in predictive testing [9, 10]. At the moment there is a diverse use of neurological examination around predictive testing: some persons at risk are assessed by a neurologist before their predictive test as a part of the procedure while others are only offered a neurologic examination before or after the test procedure [4, 7, 11].

No data are available if a neurological consultation contributes to the psychological well-being of persons at risk for HD or HDGECs. The results of PREDICT-HD and TRACK-HD showed that even in pre-manifest HDGECs subtle motor, cognitive and behavioral changes can be observed, before clinical diagnosis according to the current criteria of HD-onset [12–19]. If fear for the disease onset is the reason for predictive testing, consulting a neurologist might have a positive contribution and even be stress reducing if there are no signs of the disease. On the other hand, a neurological examination might also arouse fear of finding signs of the disease.

The experiences of persons at risk of HD in consulting a neurologist in the predictive testing phase have never been systematically evaluated. The guidelines advise a neurological examination, during the preliminary investigation phase of predictive testing. It is our aim to provide an overview of the experiences of Dutch persons at risk of HD in consulting a neurologist before or after DNA analysis. Furthermore, we would like to be able to make a recommendation if and at what moment in the testing procedure the judgment of a neurologist is desirable.

Subjects and methods

This is a partially retrospective and prospective cohort study in at-risk persons who visited one of the four genetic counseling clinics in the Netherlands. Ethical approval was collected from the local ethics committee of each of the four university hospitals.

At-risk persons who visited the genetic counseling clinics of LUMC, MUMC+, Radboudumc, and UMCG between 1st January 2017 and 31st July 2019 were approached by mail to participate in this study and fill in an online questionnaire. They received a code to login online. Informed consent was also given online. Both HDGECs and participants with a normal DNA test result were included, as well as those who finally decided not to undergo the predictive test. Those who were legal incapable or under 18 years of age were excluded from participation.

There are no validated questionnaires regarding this subject. Therefore, a list of emerging topics was made: current age, gender, reason for predictive testing, consultation of neurologist, stage of the predictive process, and personal experiences with consultation and personal wishes.

Data were analyzed using the Pearson chi-square test, Fisher's exact test, *T*-test, Mann–Whitney *U* test or Pearson correlation, whichever is appropriate. Statistical analysis was performed using SPSS version 23. *P* values of <0.05 were considered as statistically significant.

Results

Two hundred and forty-five patients received an invitation to participate (Fig. 1). Seventy-one participants, of which 87.3% retrospectively, completed the questionnaire. The response rate was 29%. All, but three participants underwent predictive testing. Thirty-one participants had a repeat size >35 (43.7%). The main reasons for counseling are given in Table 1. Forty-four (62%) participants visited a neurologist before or after DNA analysis and twenty-seven (38%) did not visit a neurologist. The majority of the participants indicated their visit to a neurologist as positive ($n = 41$; 93.2%). Whilst more than one reason was given for being positive visiting a neurologist, 24 (58.5%) gave meeting the future treating neurologist as one of these, followed by the possibility to get informed about HD ($n = 20$; 48.9%). Thirty-two participants visited a neurologist before molecular testing (72.7%) (Table 1).

All participants ($n = 71$) were asked at what moment in the predictive testing phase they would have preferred to consult a neurologist. 67 participants answered the question. The majority ($n = 59$; 88%) opted for consulting a neurologist before or shortly after DNA analysis. Twenty-seven participants (45.8%) would prefer consulting a neurologist

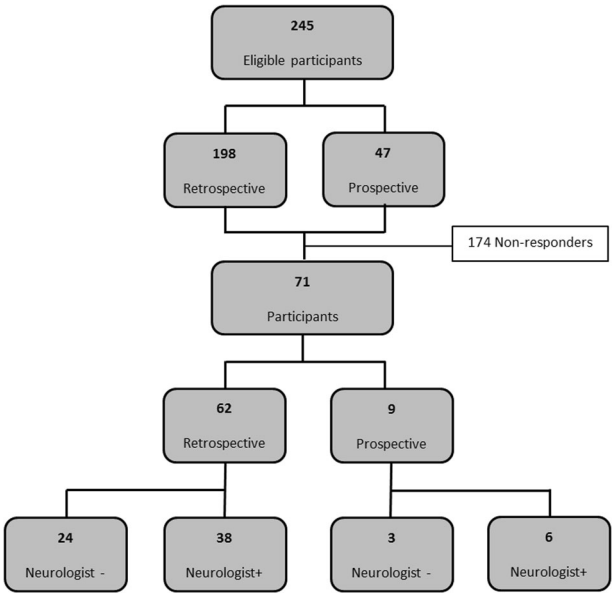

Fig. 1 Flowchart of inclusion. Neurologist− = no consult by a neurologist in predictive trajectory; neurologist+ = consult by neurologist in the predictive trajectory.

before DNA analysis (Desired Before Group). Twenty-six participants (96.3%) in the Desired Before Group actually consulted a neurologist before DNA analysis (Actual Before Group) and one did not (0.3%) (Actual After Group) (Table 2). The group ($n = 32$; 54.2%) who would prefer a consultation shortly after DNA analysis (Desired After Group), was more varied (Fig. 2). The Desired After Group consists of participants who want to consult a neurologist shortly after DNA analysis regardless the outcome of the analysis and those who wish to see the neurologist only in case they are HDGEC (Fig. 2). Eight participants did not want to visit a neurologist at all or in time when they or their relatives noticed symptoms and signs of HD.

The Desired Before Group and Desired After Group were compared with each other in order to evaluate the satisfaction of the participants with the provided care. The Desired Before Group consisted of a significantly higher number of participants who actually consulted a neurologist before predictive testing ($n = 26$) compared with the number of participants who actually consulted a neurologist after DNA analysis in the Desired After Group ($n = 11$) ($p < 0.001$) (Table 2). The Desired After Group had a significantly higher number of HDGECs (repeat length > 35) ($n = 19$) compared with the Desired Before Group ($n = 5$) (p 0.003). In the retrospective group, the number of participants with a repeat expansion (>35) ($n = 26$) was not significantly higher compared with those without a repeat expansion (<36) ($n = 33$) ($p = 1.0$). There were no significant differences in age between the Desired Before (mean 51.1; SD 14.5) and Desired After Group (mean 44.7; SD 14.1) (p 0.91).

Table 1 Baseline characteristics of patients .

Number of participants	71
Age (SD) (years)	47.8 (15.4)
Female/male	38/33
Retrospective	62 (87.3)
Repeat >35	31 (43.7)
Main reason for counseling	
Family planning	8 (11.3)
Fear of developing disease	24 (33.8)
Future planning	9 (12.7)
For the next generation	22 (31)
Fear of having HD	7 (9.9)
Missing	1 (1.4)
Consultation neurologist	
Yes	44 (62)
No	27 (38)
Time of consultation	
Before DNA test	32 (72.7)
After DNA test	12 (27.3)
Consultation neurologist	
Symptoms HD discussed	35 (79.5)
Neurological examination showed	28 (63.6)
– No abnormalities	19 (67.9)
– Non-specific abnormalities	3 (10.7)
– HD symptoms	6 (21.4)
Experience consultation neurologist	
Positive	41 (93.2)
Neutral	3 (6.8)
Negative	0
Reasons positive experience visit neurologist[a]	
Information about HD/ask questions	20 (29.4)
Information about research	9 (13.2)
Relief there were no signs of HD	15 (22.0)
Get acquainted with neurologist	24 (35.3)

Data are *n* (%) or *n* (SD).

HD Huntington's disease.

[a]More than one reason was given in some cases.

Table 2 Actual versus desired visit to neurologist.

	Desired visit neurologist		
Actual visit neurologist	Before DNA	After DNA	Total
Before DNA	26	6	32
After DNA	0	11	11
No consultation	1	15	16
Total	27	32	59

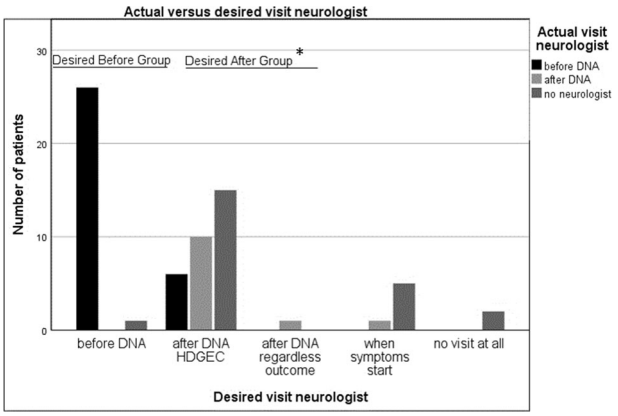

Fig. 2 Time of desired visit neurologist versus actual visit. *The Desired After Group consists of participants who want to consult a neurologist shortly after DNA analysis regardless the outcome of the analysis and those who wish to see the neurologist only in case they are HDGEC. HDGEC Huntington's Disease Gene Expension Carrier.

Discussion

The international guidelines of the Huntington Association and the World Federation of Neurology Research Group on Huntington's chorea of 1994 and the revised version of 2013 state that neurological examinations (if possible) are considered important to establish a baseline evaluation of each person. The guidelines state that the examination should be done before predictive testing.

We describe the experiences of persons at risk of HD with consulting a neurologist in the predictive testing phase. The main reasons to undergo DNA analysis in the Netherlands are comparable to the literature [3–8]. The majority of the participants who visited a neurologist felt positive about their visit to a neurologist. The participants who consulted a neurologist before DNA analysis were significantly more satisfied with the offered care compared with those who consulted a neurologist after DNA analysis.

However, our results also show that HDGECs were more likely to prefer a consult after DNA analysis, whereas participants without a repeat expansion were more likely to prefer a consult before analysis. On the one hand, those without a repeat expansion may wish to get the opportunity to ask questions about HD or get acquainted with an HD specialist. On the other hand, HDGECs might fear a consultation with a neurologist will reveal symptoms or signs of HD.

The majority of the subjects participated retrospectively and there were no significant differences between HDGECs and non HDGECs.

There are some limitations to this study. The number of participants is small, which might make statistical analysis less valid. There is also a chance of selection bias, meaning those who were not content with the offered care or would not wish to see a neurologist, did not participate. Most of the persons were included retrospectively, which might have induced recall bias.

Neurological examination is not a requirement for participation in predictive testing. Previous literature states that in case the applicant clearly does not wish to consider that he is possibly affected and that he might perhaps need a neurological consultation, we should appreciate such as a psychological defense [3]. However, our results show that our participants who consulted a neurologist were positive about the consult. Participants felt it was even comforting to be acquainted with an HD specialist who will treat them (in the future). With numerous trials evaluating disease-modifying therapies it becomes more and more important to define disease onset as early as possible. However, it is even more important to keep HDGECs informed about these trials and offer them the possibility to participate in register studies such as Enroll-HD. In this way they have a higher and better chance to participate in future disease-modifying therapy trials.

We conclude that most participants would like to consult a neurologist before or after DNA analysis. In our study persons without the gene expansion for HD clearly feel the need to have the opportunity to get in touch with a neurologist. As we are not able to distinguish pre-manifest HDGECs from non-expansion carriers in the beginning of the predictive testing procedure, offering a neurological consult in the pre-manifest testing procedure before DNA analysis might be beneficial for all.

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Compliance with ethical standards

Conflict of interest Raymund Roos is an adviser of UniQure at the time this study was conducted. The other authors declare that they have no conflict of interest.

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