Huntington's disease: cognition and apathy

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Chapter 6
Huntington's disease gene expansion carriers are aware of their degree of apathy

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Abstract

Huntington's disease (HD) is characterized by motor and behavioral symptoms, and cognitive decline. Apathy is a common behavioral symptom and its severity is related to disease progression. It has been suggested that HD gene expansion carriers are unaware of signs and symptoms of the disease, which might also account for their awareness of their own level of apathy. Therefore, the aim is to investigate the level of agreement on the degree of apathy severity between HD gene expansion carriers and their proxies using a self-report questionnaire. In total 109 REGISTRY participants (31 pre-motormanifest, 49 early motormanifest, and 29 late motormanifest) and their proxies completed the Apathy Evaluation Scale (AES). The Wilcoxon signed-rank test was used to assess whether HD gene expansion carriers and their proxies agreed on apathy severity. The AES score significantly increased from the early motormanifest to late motormanifest stage. Pre-motormanifest HD gene expansion carriers scored themselves significantly higher on the AES than their proxies, whereas no differences were found between all motormanifest HD gene expansion carriers and their proxies. Apathy severity increases in the motormanifest stages of HD. HD gene expansion carriers can adequately assess their level of apathy on a self-report questionnaire. Our results even suggest that slight changes in the degree of apathy in pre-motormanifest HD gene expansion carriers remain unnoticed by their proxies.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disorder caused by an expanded trinucleotide expansion which codes for mutant huntingtin on chromosome 4[1]. HD is clinically characterized by a triad of symptoms: motor abnormalities, behavioural symptoms, and cognitive deterioration[2]. The formal clinical diagnosis of HD is typically based on the appearance of unequivocal motor signs even though behavioural signs and cognitive decline often occur before motor sings are present[2, 3], but with the identification of the exact location of the huntingtin gene, individuals at risk can be tested for the expanded HD gene before any signs and symptoms become apparent. New guidelines have agreed that clinical diagnosis can be made solely on behavioural and/or cognitive signs[4].

The behavioural symptoms in HD are diverse[5, 6]; the most common behavioural symptoms are depressed mood, irritability, and apathy with a prevalence varying from 33% to 76% dependent on definition, measurement tools used, and disease stage[6]. Of all behavioural symptoms, apathy - defined as 'lack of motivation resulting in diminished goal directed behaviour, cognition, and emotion'[7] - is the only behavioural symptom which is closely related to disease progression in HD[5]. Therefore, it is suggested that apathy is caused by the neurodegenerative process in HD and could be seen as a marker of disease progression[8]. In HD, apathy is also associated with cognitive dysfunction and the use of psychotropic medication[9]. In their review of rating scales for behavioural symptoms in HD, Mestre et al.[10] discuss three scales for assessing apathy in HD. Several studies[11-13] have used the Apathy Scale (AS), which is based on the Apathy Evaluation Scale (AES)[14], however the AS was suggested for screening only. The AES was suggested for assessing severity of apathy in HD. The reviewers mention a possible lack of insight by HD patients and they therefore favour the clinician version of the AES.

Previous studies have shown that HD patients can be unaware of the signs and symptoms of the disease, including behavioural symptoms[15, 16]. The degree of impaired awareness of their own disability (anosognosia) varies dependent on symptom and its severity, cognitive function, and disease stage[16]. In clinical trials, a proxy is often asked to rate behavioural symptoms to avoid the risk of unawareness in HD gene expansion carriers (HDGECs). However, since it is not always possible to include HDGECs together with a reliable proxy only, it is of great relevance to evaluate whether HDGECs themselves are capable to adequately rate the severity of apathy using a self-report questionnaire.

So far, only two studies have been conducted to investigate the level of agreement between HDGECs and their proxies in rating severity of apathy using a self-report

questionnaire. However, the results of these studies are conflicting: one study found a difference in the severity of apathy between clinically diagnosed HDGECs and their proxies[11], but the second study did not find a difference in the total apathy score between pre-manifest and manifest HDGECs and their proxies[17]. These different results could be ascribed to different methodology of the studies: the former used the AS and included clinically diagnosed HDGECs only, whereas the latter used the AES and included both pre-manifest and manifest HDGECs. The AS is an abridged version of the AES[18], and on face value, the two questionnaires are comparable, although there is lack of psychometric data for the assessment of apathy with the AS in HD[10]. Because of the aforementioned conflicting results and the discussed unawareness of apathy in HDGECs, we have conducted an additional study to evaluate whether HDGECs are less aware of their apathy severity than their proxies.

Methods

Participants

The REGISTRY study[19] is a European, multicentre, longitudinal, observational study conducted in 17 countries. The Leiden University Medical Center (LUMC) is the largest REGISTRY site. All REGISTRY participants at the LUMC seen between January 2013 and August 2014 and their proxies were asked to fill out the AES. The LUMC acquired ethical approval for this study and all participants gave written informed consent. In total 109 (31 pre-motormanifest, 49 early motormanifest, and 29 late motormanifest) HDGECs and their proxies completed the Registry battery and additional questionnaire. All HDGECs were genetically confirmed with a CAG >39. HDGECs with a total motor score (TMS) of ≤5 on the Unified Huntington's Disease Rating Scale (UHDRS)[20], indicating no substantial motor signs, were defined as pre-motormanifest. The group with a TMS of >5 was considered to be motormanifest with obvious HD motor signs. This motormanifest group was further divided into early motormanifest and late motormanifest according to disease stage based on the Total Functional Capacity (TFC) score[21]. TFC stage 1 and 2 were considered early motormanifest and stage 3 and 4 were considered late motormanifest. No participants of stage 5 participated in this study.

Clinical measures

The Apathy Evaluation Scale (AES) was used to quantify the level of apathy. The AES has three versions available: one for the patient, one for the proxy, and one for the care professional/investigator; in this study the patient and proxy version were used. The AES was developed to provide a global measure of apathy on an 18-item questionnaire, rated on a 4-point Likert scale with a maximum score of 72[14]. The HDGECs and proxies were independently of each other asked to rate to which degree they agree with a specific statement, for instance '*S/he gets things done during the day'* [14].

Statistical analysis

To assess group differences in the demographic and clinical characteristics ANOVA or the non-parametric counterpart was used. As the use of certain medications can affect apathy[9], the following groups of medication were identified to have a possible effect on the level of apathy: SSRI, SNRI, antipsychotics (atypical and typical), tricyclic antidepressants, buproprion, benzodiazepines, and tetrabenazine. A binary variable was created to indicate whether the HDGEC used any of this medication. To evaluate whether there was a difference between the three groups (pre-motormanifest, early, and late motormanifest) on the severity of apathy, an analysis of covariance was carried out with medication use and age entered as a covariate. The Wilcoxon signed-rank test was used to assess whether gene carriers and their proxies rated apathy severity differently.

IBM SPSS version 23 was used for all analysis. A significance threshold was set to 0.05 and if multiple comparison was carried out Bonferroni correction was applied.

Results

The group characteristics are described in table 1. The three groups differed significantly in age ($F(2,106)=33$, $p<0.01$), TMS ($H(2)=79$, $p<0.01$) and medication use ($\chi^2(2)=12$, $p<0.01$); i.e. medication use increased from 23% in pre-motormanifest group to 65% in the late motormanifest group. The groups did not differ in CAG length and gender.

The analysis of covariance of the AES patient version revealed that the three groups differed significantly in apathy score ($F(2,102)=5$, $p<0.01$). Post-hoc analysis showed that the pre-motormanifest group scored on average 10 points lower on the AES ($p<0.01$) than the late manifest group. The early motormanifest group scored

significantly lower on the AES than the late motormanifest group (mean difference 6 points, p=0.03). No significant difference was found between the pre-motormanifest and the early motormanifest groups, see figure 1.

The Wilcoxon signed Rank test showed that there was no difference in apathy score when the total group of HDGECs was compared with the rating of their proxies (Z= -0.65, p=0.52). However, when the three HDGEC groups were analysed separately, the pre-motormanifest HDGECs rated themselves as being more apathetic than their proxies (Z= -2.6, p<0.01), figure 1. The pre-manifest HDGECs rated themselves one point higher (worse) on 8 of the 18 questions than their proxies, figure 2. In the early and late motormanifest groups no significant difference was found between total AES score of the HDGECs and their proxies. Notable, the proxies of the early motormanifest HDGECs group rated apathy on 3 items one point higher than the HDGECs themselves, but this did not result in a significant different total AES score.

Table 1: Group characteristics

Characteristics	Pre-motormanifest (N=31)		Early motormanifest (N=49)		Late motormanifest (N=29)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age in years[b]	38	9	54	11	57	11	p<0.01[a,b]
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	
CAG larger length	43	3	43	3	43	2	p=0.33
Total motor score	1	2	22	23	52	22	p<0.01[a,b,c]

SD: Standard deviation
[a]significant difference between pre-motormanifest and early motormanifest
[b]significant difference between pre-motormanifest and late motormanifest
[c]significant difference between early motormanifest and late motormanifest

Figure 1: Patient and proxy Apathy Evaluation Scale (AES) score

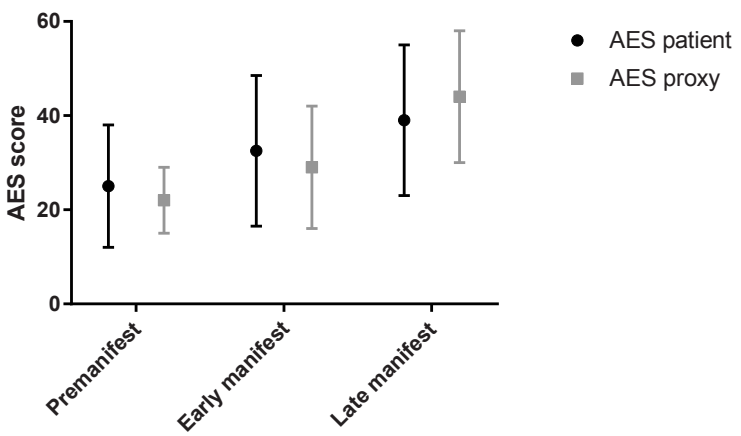
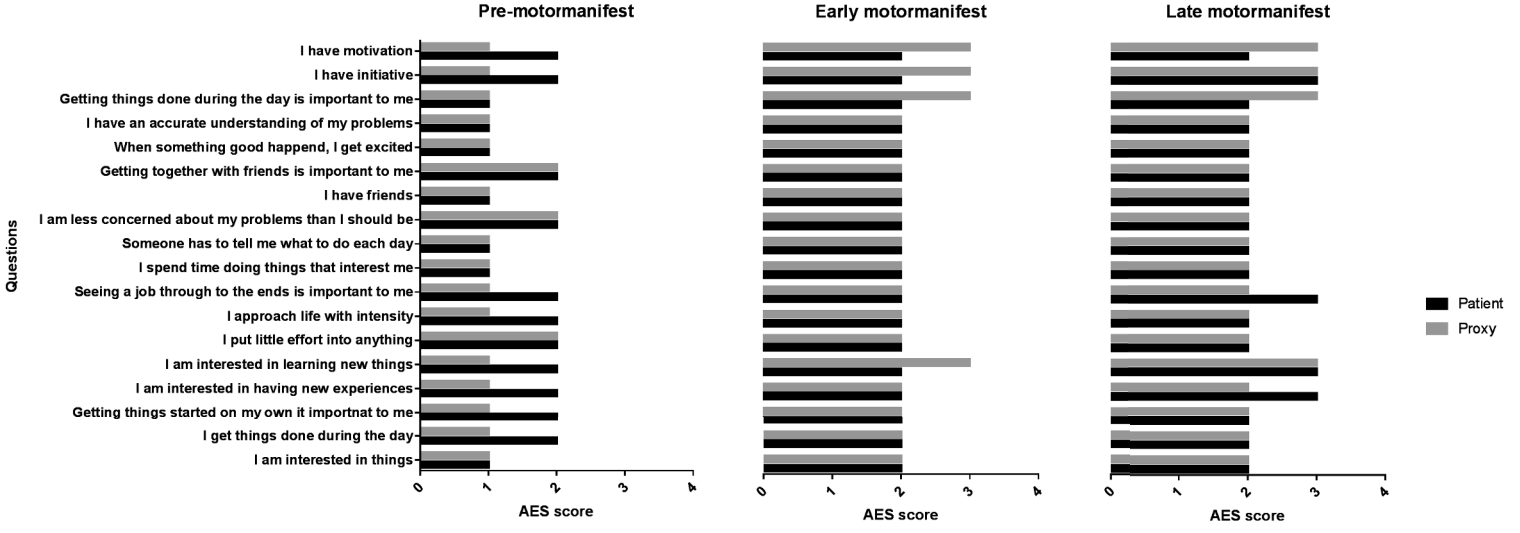


Figure 2: Average score on each question per participant group



Reference: Marin R.S., Biedrzycki RC, & Firinciogullari S. 1991. Reliability and validation of the Apathy Evaluation Scale. Psychiatry Res. 38 (2): 143-62.

Discussion

In our cohort, apathy severity increased overall as the disease progressed throughout the clinically manifest stages. More precisely, the pre-motormanifest and early motormanifest group scored about the same on the AES, but there was a significant increase in AES score from the early motormanifest group to the late motormanifest group. This is in line with previous findings that apathy increases throughout disease progression and that apathy is a common behavioural symptom in the advanced disease stage[5]. We did not find a difference in apathy rating when the score of the entire HDGEC cohort was compared with the score of their proxies, indicating an agreement on the severity of apathy between HDGECs and their proxies. However, by evaluating the different disease stages separately, in our study pre-motormanifest HDGECs rated themselves higher on the AES than their proxies; indicating that pre-motormanifest HDGECs experienced a higher level of apathy than was noticed by their proxies. These findings are in line with Mason's et al.[17] study that the apathy score of the entire HDGEC group did not differ from their proxies' score, and that pre-motormanifest HDGECs tend to rate themselves as being more apathetic than their companions. However, differences with our study appear when evaluating the motormanifest groups: Mason et al. reported that early disease patients also tend to rate themselves as more apathetic, whereas in late stage disease the proxies scored higher than the HDGECs, which we did not find. This may be explained by the use of a different definition of the motormanifest groups in our study.

The other study that compared the self-reported with the caregiver assessment found that the proxies rated apathy as more severe than the HDGECs.[11] However, in this study only clinically diagnosed HDGECs were included and the AS was used. Their study population was divided according to their cognitive ability: the agreement between HDGECs with good cognitive abilities and their proxies was high and this agreement dropped as cognitive abilities declined. Since HDGEC with better cognitive function is related to early disease stage, this group is comparable to the early motormanifest HDGEC group in our study, in which we have also found that HDGECs and proxies agreed on the degree of apathy. However, we did not find that this agreement weakens in the late motormanifest group with assumed declined cognitive abilities.

By taking the results of these three studies together, it seems that HDGECs in the early stage of the disease and the proxies have equal awareness of apathy severity. However, the pre-motormanifest HDGEC experience more apathy than is noticed by their proxies. One explanation for this difference may be the hyper-alertness of pre-motormanifest HDGECs for the development of signs of the disease; the knowledge of being a HDGEC could lead to a higher report of possible symptoms. This effect may

disappear when HDGECs are clinically diagnosed – as in the early motormanifest stage. Another possible explanation for this difference is, these apathy symptoms are very subtle[3, 22] and it might be a more internal feeling of which the proxies are not aware. This is supported by that most discrepancies are on questions relating to internal drive, such as: 'I am interested in having new experiences'. The results of the three studies for the late motormanifest HDGECs diverted, although apathetic patients in advanced stages with cognitive impairments may be less aware of their symptoms.

One limitation of our study is that we might have a selection bias. We asked all REGISTRY participants during a specific time period to participate in this study. It is possible that more severe apathetic or cognitively impaired participants declined to participate in this study. In addition, we assumed that the proxy is the most reliable individual to indicate the severity of apathy of the HDGECs. However, the proxy is personally involved and might not be able to objectively judge the degree of apathy.

Concluding, this study replicates prior findings that apathy is more severe in the advanced disease stage, and it provides further evidence that the HDGECs were capable of assessing the level of apathy on a self-report questionnaire in the early stage of the disease. More precisely, in our study the pre-motormanifest individuals were aware of subtle changes which were unnoticed by their proxies. Taken together with the previous findings, this implies that the absence of a proxy is not a legitimate reason for exclusion in clinical trials for the assessment of apathy in the pre-motormanifest and early manifest disease stages.

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