Huntington's disease: cognition and apathy

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Chapter 4
Influence of medication use on cognitive performance in Huntington's disease

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Submitted

Abstract

Background: In Huntington's disease (HD), cognitive decline starts early and continues as the disease progresses. As cognition is recognized as a potential clinical trial endpoint, it is essential to identify factors which can influence cognitive performance in HD. Medication treating non-cognitive neuropsychiatric disturbances and tetrabenazine, which are generally known to have a negative influence on cognition, are often prescribed in HD patients.

Objective: This study evaluates whether cognitive performance differs between users and non-users of these drugs at HD clinics throughout Europe.

Methods: In total, 2,289 participants of the REGISTRY study fulfilled the criteria for cognitive assessment and recorded medication use at their baseline visit. Participants were grouped according to disease stage and medication use: i.e. benzodiazepines, selective serotonin reuptake inhibitor (SSRI) antidepressants, antipsychotics, atypical antipsychotics and tetrabenazine. Univariate general linear model analysis was conducted.

Results: Medication use was common in the REGISTRY cohort. In total 42% of the participants used any of the predefined drugs whereas percentage of medication used increased from 12% in the pre-motormanifest stage to 81% in the advanced motormanifest stages. A significant effect of antipsychotic use on the Stroop Word Test was found in the early HD stages.

Conclusions: No effect of benzodiazepines, SSRIs, atypical antipsychotics and tetrabenazine on cognitive performance was found. Only the use of antipsychotics had a negative effect on cognitive performance in the early stages and should be considered when designing clinical trials with cognition as clinical endpoint.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited, progressive neurodegenerative disease caused by a CAG repeat expansion in the huntingtin gene on chromosome 4[1]. HD is characterized by a triad of symptoms: motor abnormalities, behavioral signs and cognitive deterioration[2]. As the exact location of the expanded gene is known, individuals at risk can be tested for the expanded HD gene before any symptoms or signs appear.

Motor abnormalities are the most characteristic signs of HD, but gene-expansion carriers and caregivers perceive cognitive decline and behavioral signs to be the most burdensome[3, 4]. These can precede motor signs by several years[5-13]. As cognitive decline starts early and continues as the disease progresses, cognition is recognized as a potential endpoint in clinical trials. Nowadays, a broad range of cognitive domains is evaluated in almost all clinical trials[14], including psychomotor speed which starts to slow down early on and continues to worsen throughout the later HD stages[15, 16]. It is essential to know which factors could possibly influence cognitive performance in HD in order to evaluate whether potential interventions could stop or slow down cognitive decline in HD.

As there is no cure for HD, medication is prescribed to manage HD symptoms. Many HD gene expansion carriers take psychotropic medication for behavioral and depressive signs; i.e. medication targeting non-cognitive neuropsychiatric signs[2, 17]. For instance, one study showed that in a European HD population 84% of HD patients received symptomatic treatment[18]. Unfortunately, there is only low level of evidence on the effect and side effects of using certain medication in HD, most prescriptions are based on clinical experience[19, 20]. Depression is common in HD and is often treated with antidepressants with a first choice of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). There is some evidence that some SSRIs might have a positive effect on cognition in the prodromal phase of HD, i.e. before any definite HD symptoms are present[21]. Behavioral symptoms, e.g. anxiety, are often treated with benzodiazepines[20]. However, the effect of benzodiazepine on cognitive performance in HD is not well documented. We do know from other studies that the higher the intake of benzodiazepines the greater risk of cognitive impairment and in the elderly population it is related to a higher risk of dementia[22, 23]. In a French study it was shown that also the use of antipsychotics is common in HD and some have a negative effect on cognition[24]. In another study it was found that HD patients using antipsychotic medication (classical and atypical) or tetrabenazine had a faster disease progression[25]. By taking these reports together, there is some indication that the use of these types of medication have an impact on cognitive performance on HD.

Some of these studies only evaluated whether using one or few drugs has an effect on cognitive performance, but not the entire medication group was evaluated. But for many clinical trials individuals are not allowed to take any of these drugs because it might influence the outcome measures.

Therefore, the aim of this observational, explorative study is to investigate whether there is a difference in cognitive performance between HD gene-expansion carriers using medication targeting non-cognitive neuropsychiatric signs or tetrabenazine compared to non-users in a clinical HD population. We expect that the SSRI group has the same cognitive performance as non-users. For all other medication groups, we expect that users display a more impaired cognitive performance. This is evaluated in a large HD population seen at several specialized HD clinics throughout Europe, no medication use was adapted for this study.

Methods

Participants

REGISTRY is a European, multicenter, longitudinal, observation study, facilitated by the European Huntington's Disease Network (EHDN). A total of 2,289 confirmed HD gene expansion carriers with a CAG > 39 of the REGISTRY study were included; all completed the cognitive assessment at baseline. Participants without any motor signs, as defined by a total motor score (TMS) of ≤5 on the Unified Huntington's Disease Rating Scale (UHDRS)[14], were considered pre-motormanifest. These participants were further divided into 'far from estimated disease onset' (pre-A) and 'close to estimated disease onset' (pre-B), calculated by the Langbehn formula[26-29] and split at the median of 13.3 years. Participants with unequivocal motor symptoms, TMS >5, were further divided into disease stages based on total functional capacity scale[30]. The last two disease stages were merged into one due to the small number of participants in these two groups, stages 4 and 5. Ethical approval was obtained for all sites and all participants gave written informed consent. The study was conducted by trained professionals and all data were monitored. For a full description of the study, see Orth et al.[31].

Assessments

HD gene expansion carriers were assessed for day-to-day functioning, motor, behavior and cognition. The cognitive battery of the Unified Huntington Disease Rating Scale (UHDRS)[14] was used to evaluate cognitive performance: letter verbal

fluency test (total number correct in one minute for three letters; as the study was administered in different countries, the letters also differed by country), Stroop Color-Word-Interference Test: word-reading, color-naming and interference condition (total number correct for each condition in 45 seconds; here the colors are red, blue and green), and the Symbol Digit Modalities Test (total number correct in 90 seconds).

All medications used were recorded in the REGISTRY study. For analysis purposes, participants were grouped as follows: taking benzodiazepines, selective serotonin reuptake inhibitor (SSRI) antidepressants, antipsychotics, atypical antipsychotics or tetrabenazine. For more information on the exact medication taken, see supplementary appendix 1. Participants were allowed to take other medication prescribed for other conditions such as hypertension.

Statistical analysis

To assess whether there were group characteristic differences an ANOVA or, when appropriate, a chi-square test was used.

Univariate general linear model was applied to evaluate whether medication users performed differently on the cognitive tasks than non-medication users during the baseline visit. In this model, medication group and disease stage are added as fixed factors, gender, age, CAG length and years of education as covariates; interaction effect of disease stage and medication use was also added to the model. For the multiple comparison analysis, a conservative significant level was used: $p = 0.05$ divided by the number of tests performed (i.e. $p = 0.002$).

Table 1: Group characteristics

	PreA N=283	PreB N=239	Stage 1 N=712	Stage 2 N=619	Stage 3 N=378	Stage 4+5 N=58
Age[a]	34 (8)	42 (10)	47 (11)	51 (12)	53 (11)	54 (11)
CAG repeat length[a]	42 (2)	44 (3)	44 (3)	44 (3)	44 (3)	45 (4)
Years of education[a]	13 (3)	13 (7)	12 (5)	11 (4)	11 (6)	10 (3)
Sex (Male/Female)[b]	96/187	104/135	384/328	304/315	189/189	20/38

PreA: pre-motormanifest A; PreB: pre-motormanifest B
[a]Mean (standard deviation)
[b]Total number

Results

The six disease stage groups differed significantly from each other based on: age ($F(5,2283)=139.44$, $p<0.01$), years of education ($F(5,2152)=12.26$, $p<0.01$), CAG repeat length ($F(5,2283)=22.83$, $p<0.01$) and gender ($\chi^2(5) =39.59$; $p<0.01$), see table 1.

In total 58% of the participants did not use any medication. If disease stage was considered, the percentage of participants not taking medication gradually declined from pre-A (88%) to stages 4 and 5 (19%), see table 2. In addition, polypharmacy increased from pre-A (3%) to stages 4 and 5 (48%). About 85% of the medication users were already on medication for at least 2 months with stable doses.

The use of antipsychotics had a significant effect on the results of the Stroop Word Test ($F(1, 1993)=14.9$, $p=0.0001$), suggesting that participants using antipsychotics scored worse on the Stroop Word Test than non-users, see figure 1. Antipsychotics users in group stage 2 and stage 3 scored on average lower than then non-users (mean difference: 13 and 10, respectively). However, this effect disappeared with the interaction effect of all disease stages ($F(4, 1993)=0.47$, $p=0.76$). The use of benzodiazepines, SSRI antidepressants, atypical antipsychotics or tetrabenazine had no effect on cognitive performance on any of the administered tasks.

Discussion

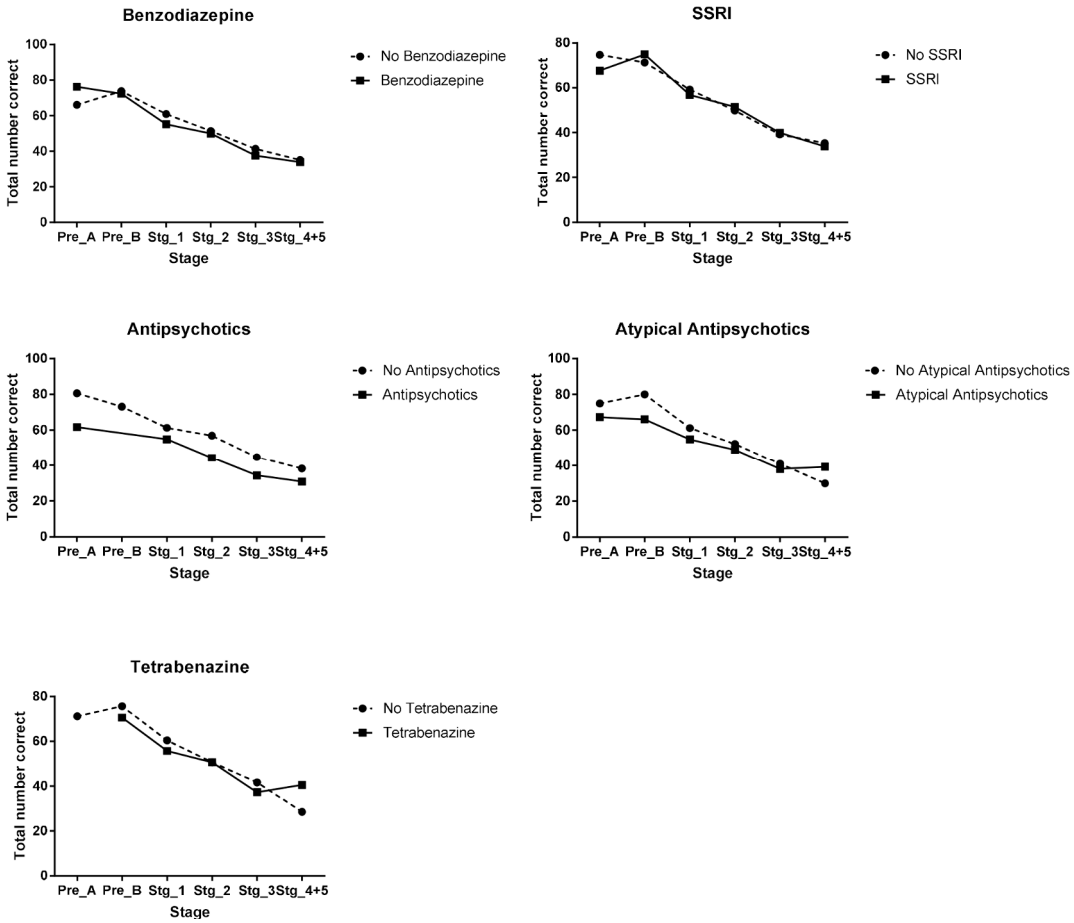
This study shows that about half of the HD-REGISTRY population used medication targeting non-cognitive neuropsychiatric disturbances and/or tetrabenazine. The percentage of HD gene carriers taking these medications increased from pre-motormanifest to the advanced HD. The most logical explanation for this increase throughout the disease stages is that advanced HD individuals have severe symptoms

Table 2: Total number of participants taking medications

	PreA N=283	PreB N=239	Stage 1 N=712	Stage 2 N=619	Stage 3 N=378	Stage 4+5 N=58
No medication[a]	251 (88%)	202 (85%)	463 (65%)	283 (46%)	113 (30%)	11 (19%)
Benzodiazepines[a]	6 (2%)	5 (2%)	23 (3%)	29 (4%)	9 (2%)	2 (3%)
SSRI[a]	16 (6%)	24 (10%)	84 (12%)	78 (13%)	43 (12%)	3 (5%)
Antipsychotics[a]	1 (<1%)	—	8 (1)	10 (2%)	14 (4%)	—
Atypical antipsychotics[a]	1 (<1%)	—	62 (9%)	86 (14%)	66 (17%)	13 (23%)
Tetrabenazine[a]	—	1 (1%)	6 (1%)	13 (2%)	9 (2%)	1 (2%)
Mix[a]	8 (3%)	7 (2%)	66 (9%)	120 (19%)	124 (33%)	28 (48%)

PreA: pre-motormanifest A; PreB: pre-motormanifest B
[a]Total number (%)

Figure 1: Performance on the Stroop Word Test per disease stage and medication group



which need to be managed with medication. In addition, the pre-motormanifest individuals might still benefit from non-pharmacological interventions which should first be explored in treating symptoms[20]. Throughout disease progression symptoms become more severe, global functioning decreases and medication treatment becomes useful, supported by adjunctive therapies, to manage all symptoms[32]. Polypharmacy is common in HD due to the complexity of the disease and several symptoms which need to be addressed[20] which is supported by our results that about 40% of all medication users used a mix of the pre-defined medication groups.

By evaluating the effect of medication use on cognitive performance, we only found a negative effect of antipsychotic medication on a task measuring psychomotor speed, that is the Stroop Word Test, in the early HD phase. This is an important finding for future clinical trials, especially because the effect was found in the early stages. Future clinical trials will most likely focus on pre-motormanifest and/or early HD gene carriers to evaluate whether treatment influences disease progression in an early

stage of the disease to ensure the highest quality of life for the HD gene carriers. With our findings we would recommend to be cautious to include HD gene carriers using antipsychotic medication if cognition is an important outcome measure of a clinical trial.

Secondly, our study showed that the use of benzodiazepine, SSRI antidepressant, atypical antipsychotic or tetrabenazine has no effect on performance of the UHDRS cognitive battery in the clinical setting. Our finding that tetrabenazine has no effect on cognition is in line with the 80 week open label study of tetrabenazine in HD in which cognitive decline resembled the natural deterioration in HD[33]. Regarding future clinical trials targeting cognition in HD, we advise that the use of benzodiazepine, SSRI antidepressant, atypical antipsychotic or tetrabenazine should be allowed if participants are on a stable dose and if there is no suggestion that these medications could have an adverse effect in combination with the investigational drug. This should make it easier to recruit participants for clinical trials as many HD gene carriers use these medications. It also allows to test an investigational drug in a cohort which more closely represents the population seen in clinics, rather than in a strictly pre-defined population and improves the chance to have a successful phase III study.

One of the limitations of this study is that we grouped together the most commonly used medications; i.e. treating slightly different acting agents in the same way. It is possible that one particular drug might have a relatively stronger effect on cognitive performance, but that this effect is masked by grouping several medications together. In addition, we chose to group the medication based on relatively broad categorization as used by the Dutch regulatory agency. These categorization is based on broad pharmacogenetics, we did not create more subgroups based on the mechanic profile of the acting agent. The reason for this is that most studies are based on animal or cell studies but we do not know how all the different acting agents work in the human brain or even in the diseased human brain. It might be of interest for future studies to explore this more extensively. Furthermore, we only looked at whether participants used medication, not at the exact doses taken, although we do know that the majority was on a stable dose. In addition, participants were allowed to take co-medications, such as antihypertensive drugs, combinations which could affect cognitive performance. On a positive note, the REGISTRY database provides an opportunity to look at real-life medication use and its effect on cognitive performance seen at the clinics.

To conclude, antipsychotics have a negative effect on cognitive performance in the early HD stages, whereas benzodiazepines, SSRIs, atypical antipsychotics and tetrabenazine seem to have no effect on cognitive performance in HD.

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Supplementary Appendix

Medications included in the different groups

Benzodiazepines: Alprazolam, Bromazepam, Brotizolam, Chlordiazepoxide, Clobazam, Clorazepate, Diazepam, Estazolam, Etizolam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Midazolam, Nitrazepam, Oxazepam, Prazepam, Temazepam, Zolpidem, Zopiclone

SSRI Antidepressants: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline

Antipsychotics: Amisulpride, Chlorprothixene, Fluphenazine, Flupentixol, Fluspirilene, Haloperidol, Perphenazine, Pimozide, Pipamperone, Sulpiride, Thioridazine, Tiapride, Zuclopenthixol

Atypical antipsychotics: Aripiprazole, Clozapine, Melperone, Olanzapine, Quetiapine, Risperidone

Tetrabenazine