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Comparative Analysis of Cognitive Profiles of Huntington's and Parkinson's Diseases

Huntington ve Parkinson Hastalığının Bilişsel Profillerinin Karşılaştırmalı İncelenmesi

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Abstract

Objective: In this study, our aim is to define the cognitive profile specific to Huntington's disease (HD) in comparison to Parkinson's disease (PD) without any accompanying cognitive involvement and to search for its relationship with CAG repeat number.

Materials and Methods: Demographic data and detailed cognitive test results of HD and PD patients were reviewed, analyzed retrospectively and were compared to results of healthy controls (HC). Cognitive test battery included minimental state examination (MMSE), Beck's depression inventory, enhanced cued recall (ECR), semantic fluency, digit-span forwards and backwards, trail making part A (TMT A) and B, reciting months backwards, phonemic fluency, Stroop, clock drawing, Benton's line orientation, Benton's facial recognition and Hooper visual organization tests. Instrumental activities of daily living test (IADL) was given for evaluating independence of patients in daily life. The relationship between test results and CAG repeat number and CAP score (product of CAG repeat number and age) for HD were evaluated.

Results: Age, disease duration and number of years of education were similar between HD and PD. All cognitive test results of HD group were significantly worse than those of HC. HD group also scored significantly worse than PD group in MMSE, ECR, semantic fluency, TMT A, reciting months backwards, phonemic fluency, Stroop 1-5, clock drawing, Hooper visual organization and Benton's facial recognition tests. CAP score was significantly correlated with the results of Stroop part 3-4 and scores of IADL.

Conclusion: This study showed that HD has a cognitive profile with certain particular features, which differentiates it from PD. We can also conclude that cognitive decline takes place earlier in the course of HD compared to PD and it is more severe. CAP score was found corelated with executive functions and ADL in HD, confirming that the severity of pathological involvement is directly related to the cognitive profile of patients as well as their life quality.

Keywords: Neurodegenerative diseases, CAP score, neuropsychiatric tests, depression, executive functions

Öz

Amaç: Bu çalışmada amacımız, Huntington hastalığına (HH) özgü bilişsel profili, Parkinson hastalığının (PH) bilişsel yakınmaların belirgin olmadığı erken dönemi ile karşılaştırmalı olarak değerlendirmek ve bu bilişsel değişikliklerin CAG tekrar sayısıyla ilişkisini araştırmaktır.

Gereç ve Yöntem: HH ve PH hastalarının demografik verileri ve ayrıntılı bilişsel test sonuçları retrospektif olarak değerlendirildi ve sağlıklı kontrollerin sonuçları ile karşılaştırıldı. Bilişsel test bataryası, standardize minimental test (SMMT), Beck depresyon ölçeği, artırılmış ipuçlu hatırlama (AİH), semantik akıcılık, ileri ve geri sayı menzili, iz sürme testi (İST) A ve B, ayları geriye doğru sayma, fonemik akıcılık, Stroop, saat çizme, Benton çizgi yönünü belirleme, Benton yüz tanıma ve Hooper görsel organizasyon testlerini içermekteydi. Günlük yaşam aktiviteleri (GYA) ise enstrümental günlük yaşam aktiviteleri testi ile değerlendirilmişti. HH'nin test sonuçları ile CAG tekrar sayısı ve CAP skoru (CAG tekrar sayısı ile yaşın çarpımı) arasındaki ilişki de incelendi.

Bulgular: HH ile PH'nin ortalama yaşları, eğitim ve hastalık süreleri benzerdi. HH grubunun tüm bilişsel test skorları, sağlıklı kontrollere göre istatistiksel olarak anlamlı şekilde daha düşük bulundu. HH grubu ayrıca SMMT, AİH, semantik akıcılık, İST A, ayları geriye doğru sayma, fonemik akıcılık, Stroop 1-5, saat çizme, Hooper görsel organizasyon ve Benton yüz tanıma testlerinde PH grubundan anlamlı olarak daha düşük puanlar aldı. CAP skoru, Stroop bölüm 3-4'ün puanları ve GYA skorları ile istatistiksel olarak anlamlı şekilde korele bulundu.

Sonuç: Bu çalışma, HH'nin, belli yönleriyle PH'den ayrışan ve kendine has özellikleri olan bir bilişsel bir profili olduğunu göstermiştir. Ayrıca kognitif kaybın HH seyri içinde, PH'ye kıyasla daha erken gerçekleştiği ve daha şiddetli olduğu sonucuna varabiliriz. CAP skorunun, HH'de yürütücü işlevler ve GYA ile ilişkili olduğu ve patolojik tutulumun şiddetinin hastaların bilişsel profili ve yaşam kalitesi ile doğrudan ilişkili olduğu da bu çalışma ile doğrulanmıştır.

Anahtar Kelimeler: Nörodejeneratif hastalıklar, CAP skoru, nöropsikiyatrik testler, depresyon, yürütücü işlevler

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Introduction

Huntington's disease (HD) is an inherited neurodegenerative disease clinically characterized by cognitive, affective disturbances, chorea, and other extrapyramidal findings. Although chorea is the key feature of the disease that often leads to the diagnosis, cognitive and the behavioral abnormalities are more disabling for patients and present extra burden to caregivers (1). Cognitive impairment is progressive and can be a very early feature of HD. In typical cases, it is more prominent in executive functions initially and presents an example of frontal subcortical circuit dysfunction, but then the other cognitive domains, including memory, attention and visuospatial functions are also impaired (2). Neuroimaging studies showed that the magnitude of caudate atrophy was correlated with cognitive impairment in HD (3).

Cognitive impairment and behavioral alterations are also early and important features of Parkinson's disease (PD), a more frequently seen basal ganglia disorder. The profile of cognitive impairment, and also its anatomic, neurochemical, and pathologic correlates have been extensively studied in PD (4,5). Early-stage cognitive dysfunctions in PD are thought to be related to the disconnection between striatum and frontal cortex due to dopaminergic denervation, mainly in the dorsal and posterior putamen (6).

Interestingly, only a few reports in the literature aimed to disclose similarities or differences in cognitive profile in patients with HD and PD (7,8). In this study, we aimed to define the cognitive profile of patients with HD in comparison with age- and disease duration-matched patients with PD. We hypothesized that the features of cognitive profiles specific to each disease might differ due to differential striatal involvement, more rostrally by HD and caudally by PD. Defining specific cognitive features may also help design better targeted therapies. We also sought to determine whether cognitive impairment in HD had a relation with CAG repeat length and the CAG age product (CAP) score, which was developed to measure the impact of the mutant HD gene in a single case by taking into consideration both the severity of mutation and the length of exposure duration (9).

Materials and Methods

Subjects

Thirty-six patients with HD, 25 with PD, and 18 healthy controls (HC) were included in this study. All study subjects were evaluated in Hacettepe University Neurology Outpatient Clinic between 2012 and 2015. The patients with HD were clinically diagnosed and had CAG repeat expansion (≥36) in the huntingtin gene. The patients with PD were diagnosed according to the United Kingdom PD Society Brain Bank Research Center clinical diagnostic criteria (10). Patients with PD, who were age- and disease duration-matched with the patients with HD, were included in the study, so the mean age of patients with PD was younger than the general PD population and Hoehn Yahr stage was ≤2. All of the patients with PD were on dopaminergic drugs. HCs were age-matched individuals from the community who took the neuropsychological tests for screening purposes without having an overt cognitive problem. All participants gave informed consent.

The study was approved by Hacettepe University Non-interventional Clinical Researches Ethics Board (decision number: GO 20/426).

Cognitive Tests

Results of detailed cognitive tests were analyzed retrospectively. In the test battery, the Mini-Mental State Examination (MMSE) was performed for general cognitive evaluation and the Beck Depression Inventory (BDI) for depression. Memory was assessed using enhanced cued recall (ECR), semantic fluency; attention was assessed by digit span forwards and backwards, trail making test (TMT) A; executive functions were assessed by TMT B, months backwards, phonemic fluency, Stroop; and visuospatial functions by clock drawing, Hooper visual organization test, Benton's facial recognition test, and Benton's judgment of line orientation tests. Except for tests that measure time for the completion of the task (months backwards, TMT A and B tests), scores represented the total number of correct responses. Standardized measures and criteria were employed in the administration and scoring of the neuropsychological tests (11,12,13). BDI scores were used to determine the severity of depression; scores between 0-12 were classified as minimal symptoms, 13-18 mild, 19-28 moderate, and 29-63 as severe depression (14). Besides, subjects' dependence in activities in daily living was assessed using Lawton's instrumental activities of daily living (IADL) test, which is also assumed to determine the cognitive status of a subject (15). All subjects with PD took the cognitive tests during the "ON" state and their dopaminergic treatment doses were stable for the last 3 months.

In each patient with HD, the CAP score, which was developed to estimate the cumulative detrimental effect of mutant gene product in patients with HD, was calculated using the following formula: CAP=100x age at the time of neuropsychological testing x [(CAG repeat length-L)/S]; (L=30, scaling constant and S=627, normalizing constant) (9). It was shown to be an index that predicted the striatal pathologic burden, as confirmed in autopsy material (16).

Statistical Analysis

Quantitative data are presented by mean ± standard error of the means. Frequencies and percentages are given for nominal data. Quantitative data of the three groups were compared using One-Way ANOVA. Bonferroni's post-hoc comparisons were conducted to analyze differences between the two study groups. The chi-square test was used for the comparison of categorical data. Spearman's correlations for rank data was employed for correlation analysis of neuropsychological test scores and CAP scores. Statistical significance was set at $p<0.05$.

Results

Demographic features and neuropsychological test results are summarized in Table 1. Age was similar between groups. Years of education was significantly higher in the HC group compared with both the HD and PD groups ($p<0.001$), but similar between the HD and PD groups.

The HD group scored significantly worse than HCs in all tests in the cognitive battery, including MMSE ($p<0.001$), ECR ($p<0.001$), semantic fluency ($p<0.001$), digit span forwards ($p<0.001$), digit span backwards ($p<0.001$), TMT A ($p<0.001$), TMT B ($p<0.001$), reciting months backwards ($p=0.004$), semantic fluency ($p<0.001$), Stroop 1-5 ($p<0.001$), clock drawing

(p=0.014), Hooper visual organization (p<0.001), Benton's facial recognition (p<0.001), Benton's judgment of line orientation tests (p<0.001), and IADL (p=0.007).

When compared with the PD group, the HD group scored worse in MMSE (p=0.006), ECR (p<0.001), semantic fluency (p<0.001), TMT A (p=0.005), reciting months backwards (p=0.023), phonemic fluency (p=0.003), Stroop 1 (p<0.001), Stroop 2-3 (p<0.001); Stroop 4 (p=0.003), Stroop 5 (p=0.015), clock drawing (p=0.005), Hooper visual organization (p=0.002), and Benton's facial recognition tests (p<0.001).

On the other hand, the PD group also scored worse than the HC group in digit span backwards (p=0.003), TMT B (p=0.001), phonemic fluency (p=0.007), Hooper visual organization (p=0.003), Benton's facial recognition (p<0.001), and Benton's judgment of line orientation tests (p<0.001).

The mean BDI scores were similar between the groups; the severity of depression in each group is given in Table 2.

Correlation studies in subjects with HD showed that CAP scores were significantly and positively correlated with scores of Stroop 3 (r: 0.61; p=0.006), Stroop 4 (r: 0.51; p=0.028), and negatively correlated with activities of daily living scores (r: -0.46; p=0.026); CAG number was significantly and positively correlated with BDI scores (r: 0.519; p=0.019). Neither patient age nor disease duration was related to any of the cognitive measures studied.

Discussion

HD and PD are both progressive neurodegenerative diseases that affect the cortico-striato-thalamocortical networks and lead to various motor, cognitive, and behavioral symptoms. Their cognitive profiles may have similar features, considering the common neuropathologic involvement of basal ganglionic-cortical circuits (17). Detailed neuropsychiatric tests may sometimes give better information about the functional state of the affected networks and provide insights about the pathogenetic processes.

Table 1. Demographic features and neuropsychiatric test scores of study groups

	HD (n=36) Mean ± SEM	PD (n=25) Mean ± SEM	HC (n=18) Mean ± SEM	ANOVA F	p (HD vs PD)	p (HD vs control)	p (PD vs control)
Age	48.9±2.5	53.4±1.8	46.3±3.3	2.26	0.21	0.91	0.18
Sex (F/M)	18/18	10/15	13/5				
Education (years)	9.3±0.9	9.0±0.9	15.0±0.3	13.8	0.99	**<0.001***	**<0.001***
Disease duration (months)	53.5±7.3	66.2±12.4	N/A	1.26	0.27	-	-
IADL	7.0±0.2	7.6±0.2	7.9±0.1	5.4	0.96	0.41	0.56
BDI	13.1±2.1	11.6±1.7	6.8±1.4	0.85	0.13	**0.001***	0.28
MMSE	23.0±0.8	26.1±0.7	28.3±0.4	16.52	**0.002***	**<0.001***	**0.04***
ECR	37.2±2.1	46.5±0.5	47.4±0.3	20.26	**<0.001***	**<0.001***	0.35
Semantic fluency	10.3±0.9	18.6±1.1	19.4±1.0	35.47	**<0.0001***	**<0.001***	0.93
Digit span forward	4.3±0.2	4.8±0.2	5.4±0.2	9.51	0.09	**<0.001***	0.13
Digit span backwards	2.6±0.6	3.0±0.2	4.0±0.2	14.24	0.24	**<0.001***	**0.003***
Trail making A (sec)	107.4±13.7	63.4±7.5	28.7±2.3	18.13	**0.003***	**<0.001***	**<0.001***
Trail making B (sec)	279.2±30.4	211.3±26.8	68.3±4.9	14.14	0.39	**<0.001***	**<0.001***
Months backwards (sec)	100.1±22.6	38.3±12.3	16.8±3.3	5.18	0.09	**0.002***	0.28
Phonemic fluency	5.7±0.8	10.4±1.0	15.2±1.2	24.48	**0.001***	**<0.001***	**0.02***
Stroop (sec)							
I	15.7±1.1	10.6±0.8	8.6±0.6	19.38	**<0.001***	**<0.001***	0.13
II	16.2±1.5	11.5±0.6	9.1±0.6	11.64	**0.008***	**<0.001***	**0.01***
III	30.2±3.6	18.8±2.0	13.2±0.6	12.09	**0.01***	**<0.001***	**0.04***
IV	35.8±3.3	24.7±1.9	16.8±0.9	16.27	**0.01***	**<0.001***	**0.002***
V	53.4±5.1	38.6±3.0	26.8±1.9	13.37	**0.04***	**<0.001***	**0.007***
Clock drawing	2.8±0.2	3.7±0.2	3.7±0.2	8.36	**0.002***	**0.006***	1
Hooper visual organization test	12.2±1.3	17.9±1.1	23.9±0.7	28.05	**0.001***	**<0.001***	**<0.001***
Benton's judgment of line orientation test	11.4±1.7	13.6±1.2	22.1±1.0	16.16	0.41	**<0.001***	**<0.001***
Benton's facial recognition test	32.0±0.9	36.9±0.9	42.7±0.6	35	**0.001***	**<0.001***	**<0.001***

BDI: Beck depression inventory, ECR: Enhanced cued recall, F: Female, HC: Healthy control, HD: Huntington's disease, IADL: Instrumental activities of daily living, M: Male, MMSE: Mini-mental status examination, N/A: Not available, PD: Parkinson's disease, sec: Second, SEM: Standard error of mean, vs: Versus, *significant

Table 2. Severity of depressive symptoms in the study groups according to Beck depression inventory

BDI	HD (n=36)	PD (n=25)	HC (n=18)
Minimal symptoms	18 (50%)	11 (44%)	13 (72%)
Mild depression	4 (11%)	8 (32%)	3 (17%)
Moderate depression	11 (31%)	5 (20%)	2 (11%)
Severe depression	3 (8%)	1 (4%)	0 (0%)

BDI: Beck depression inventory, HC: Healthy control, HD: Huntington's disease, PD: Parkinson's disease

In this study, our aim was to compare the cognitive profiles of these two well-known neurodegenerative disorders to be able to differentiate between the cognitive impairment features of rostral versus caudal striatal involvement and also to understand if the differences were attributable to differing pathogenesis. As the specific differences may disappear in advanced stages of the disease, neuropsychiatric test results of patients with early-stage HD and PD without cognitive symptoms were evaluated retrospectively. Mean age and disease duration were similar between the two groups. Comparative analysis revealed that the cognitive status of the HD group was worse than that of PD group in general. The PD group had mild-to-moderate impairment in attention, executive, and visuospatial functions, but the HD group performed worse, especially in memory tests, as well as attention, executive, and visuospatial function tests compared with the PD group. Although in both diseases early cognitive dysfunction is the result of frontal lobe dysfunction due to striatal disconnection, the underlying neuropathologic processes affecting the striatum are completely different. Loss of GABAergic spiny projection neurons, more prominently in the caudate nucleus (rostral striatum) is characteristic of HD, whereas dopaminergic denervation of the caudal striatum is the main pathology in PD (18,19). Thus, the findings of our study can be explained by this discrepancy.

In the literature, studies about cognition in HD and PD mostly emphasized the memory function and these are rather old studies. In one such study, patients with PD (n=150) and HD (n=65) were compared for memory retrieval because both were expected to show frontostriatal dysfunction leading to memory retrieval deficit. They found that memory retrieval deficit was more common in patients with HD than in PD, but this was only valid for patients with HD with at least mild global cognitive impairment (20).

In an older study, the subcortical dementia concept was evaluated by testing patients with HD and PD regarding verbal learning and memory, and a higher number of similarities than discrepancies were found (8). Patients with HD and PD were similarly impaired in immediate memory spans, learning in semantic clusters, and recalling consistently across trials. On the other hand, they both had normal retention of information over delay periods and normal vulnerability to interference. Different from patients with PD, those with HD had more difficulties in free recall and improving across learning trials, and they had increased perseveration rates (8).

In another study that compared the severity and specificity of cognitive impairment in Alzheimer's disease (AD), PD, HD and progressive supranuclear palsy, after applying a correction for global cognitive efficiency, the HD group was found to have difficulties in attention and learning, showing similar performances with AD group in memory tests in particular (7). In the same study, patients with HD who had moderate cognitive impairment scored worse than patients with PD with the same cognitive level in attention tests.

Attention is an important component of cognition, which is expected to be involved in both diseases. In our study, patients with HD showed worse performance compared with PD only in TMT A, but other tests evaluating attention, digit span forwards and backwards, were similar between the groups. In a study comparing HD, AD, and PD regarding visual attention and perception, the authors found that the attention shifting ability was preserved in HD, whereas patients with PD were especially impaired in maintaining attention to the same location, but better when the location of the target changed and perceptual errors were found to be related to this attention maintenance deficit (21). The same group also studied focused attention in HD and PD patient groups and showed that the reaction time for inconsistent stimuli was longer in HD compared with HC, whereas it was comparable to HC in PD, differentiating these two subcortical cognitive impairment syndromes (22).

In a recent study comparing the non-motor symptom profile of HD with PD, it was found that patients with HD more frequently had non-motor symptoms, and among these, attentional deficits and memory problems were at the top of the list (23). Depression and anxiety were found to be common in the HD group, but they did not detect a statistical significance in the frequency of depressive symptoms between the HD and PD groups (23). Similarly, we found that BDI scores and the frequency of depressive symptoms showed no significant difference between the groups.

In our study, we also showed that CAG repeat number was inversely related to the age of onset in HD. Although 56% of the variation in disease onset is determined by the expansion size of the CAG repeat (24), the relation of the CAG repeat number with the HD phenotype has not yet been established. Thus, the relation between the differential features of cognitive profile of HD and CAG repeat number may help to define its effect on phenotype. In addition, CAP score, which determines the duration and severity of exposure to the mutant gene product, was significantly correlated with the scores of Stroop part 3, 5 and activities of daily living. In the literature, CAP score is more frequently used in prodromal patients with HD as a proxy of genetic burden and as a predicting factor for the time of disease onset (25,26). In other studies, it was used as a normalization coefficient in the comparison of different clinical subtypes of HD (27,28). In our study, we used the CAP score as a disease severity marker beside CAG repeat length and searched for a relation between this score and results of cognitive tests.

The cognitive dysfunction profile of both PD and HD, as well-known striatal disorders, are traditionally classified under subcortical dementias; working memory, attentional control, and other executive functions are predominantly affected. Although striatum is the main site of pathology in both diseases, different neurotransmitter systems and different subcortical regions are involved in each. Thus, comparing the detailed cognitive profiles of PD and HD may help in defining the specific functions of

different components of the frontostriatal network. Our study provides information about the different aspects of cognitive involvement in HD compared with PD, which may help to design a comparative functional neuroimaging and morphometric study in the future.

Study Limitations

Our study has some limitations; a higher number of patients could have given better information about the differences in cognitive features of these two neurodegenerative disorders. The HC group may have shown better performance than the other disease groups due to more years of education in some of the domains of cognitive tests.

Conclusion

This study showed that HD had a cognitive profile with certain particular features, which differentiated it from PD. We can also conclude that cognitive decline takes place earlier in the course of HD compared with PD and it is more severe. The CAP score, which is thought to predict the striatal pathology in HD brains, was found to be correlated with executive functions and activities of daily living. This result confirms that the severity of pathologic involvement is directly related to the cognitive profile of patients, as well as their life quality.

Ethics

Ethics Committee Approval: The study was approved by Hacettepe University Non-interventional Clinical Researches Ethics Board (decision number: GO 20/426).

Informed Consent: All participants gave informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Y.Ç., Concept: E.S., B.E., Design: E.S., B.E., Data Collection or Processing: G.Y.Ç., G.E.G.A., Ö.Ç., Analysis or Interpretation: G.Y.Ç., G.E.G.A., Ö.Ç., Literature Search: G.Y.Ç., E.S., Writing: G.Y.Ç., E.S., B.E.

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