Bosphorus Medical Journal
Boğaziçi Tıp Dergisi

Original Article

DOI: 10.14744/bmj.2023.49389

Bosphorus Med J 2023;10(4):203–208

Evaluation of Cognitive Disorders in Huntington's Disease and Their Relationship with Motor Symptoms and Trinucleotide Repeat Expansion

Huntington Hastalığında Bilişsel Bozuklukların Değerlendirilmesi ve Motor Belirtiler ile Trinükleotid Tekrar Artışı Arasındaki İlişki

Esma Kobak Tur, Kadriye Güleda Keskin, Ceren Erkalaycı, Eren Gözke

Department of Neurology, University of Health Sciences, Fatih Sultan Mehmet Research and Training Hospital, Istanbul, Türkiye

Cite this article as: Kobak Tur E, Keskin KG, Erkalaycı C, Gözke E. Evaluation of Cognitive Disorders in Huntington's Disease and Their Relationship with Motor Symptoms and Trinucleotide Repeat Expansion. Bosphorus Med J 2023;10(3):203–208.

Received: 25.08.2023
Revision: 25.08.2023
Accepted: 12.09.2023

Correspondence:
Dr. Esma Kobak Tur. Sağlık Bilimleri Üniversitesi, Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, İstanbul, Türkiye

Phone:
+90 538 338 79 55

e-mail:
esmakbk@hotmail.com

ABSTRACT

Objectives: Huntington's disease (HD), characterized by choreiform movements, psychiatric problems, and dementia, is an inherited progressive neurodegenerative disorder. While HD is typically perceived as a motor disorder, cognitive decline could manifest before the clinical symptoms. Cognitive impairments might appear as emotional instability, decreased vocabulary, or impaired executive functions. Herein, we aimed to evaluate the cognitive findings of our patients diagnosed with HD and the relationship with disease parameters.

Methods: Our study included 15 patients and fifteen controls. To determine the clinical findings of the patients, the unified HD rating scale (UHDRS) was administered, and total motor score (TMS), independence scale scores, and functional capacity scores were calculated. To assess the cognitive status of individuals, the Montreal Cognitive Assessment Battery Turkish validated form (MOCA-TR), Stroop test Turkish validated form (Stroop test TBAG form), and Symbol Digit Modalities Test were conducted.

Results: The MoCA-TR scores were significantly reduced in HD patients compared to controls ($p<0.001$). Among all patients, there was a notable elongation in completion time for the Stroop test TBAG form than controls ($p<0.05$). The MoCA-TR showed a robust negative correlation with the TMS while exhibiting a marked positive correlation with the independence scale score and functional capacity. Conversely, the MoCA-TR demonstrated a moderate negative correlation with the disease burden score (DBS) and a pronounced negative relationship with the progression rate ($p<0.05$). A strong opposing correlation was observed between cytosine-adenine-guanine (CAG) repeats and the age of disease onset, whereas a highly significant positive relationship emerged between CAG repeats and the DBS ($p<0.05$).

Conclusion: We have demonstrated a strong correlation between patients' cognitive scores and disease clinical findings. Patients' cognitive scores have also been shown to impact disease burden and disease progression rate. The designation of cognitive impairment in the early stages could contribute to personalized disease-modifying treatment strategies.

Keywords: Cognition; cytosine-adenine-guanine; disease burden; huntington's disease; montreal cognitive assessment; stroop.

ÖZET

Amaç: Huntington hastalığı (HH), koreiform hareketler, psikiyatrik problemler ve bunama ile karakterize olan, kalıtsal ilerleyici bir nörodejeneratif hastalıktır. HH tipik olarak bir motor bozukluk gibi görülse de bilişsel gerileme hastalığın klinik belirtileri başlamadan önce bile ortaya çıkabilir. Kognitif bozulmalar; emosyonel labilite, kelime dağarcığı azalması, yürütücü işlevlerde bozulma gibi tablolarla prezente olabilmektedir. Bu çalışmada, genetik ve klinik olarak konfirme HH tanısı almış hastaların kognitif bulgularının ve hastalık parametreleri ile olan ilişkisinin değerlendirilmesi amaçlandı.

Yöntem: Çalışmamıza 15 hasta ve 15 kontrol dahil edildi. Hastaların klinik skorlarını belirlemek için, Birleşik Huntington Hastalığı Değerlendirme Ölçeği (UHDRS) uygulandı, total motor skor (TMS), bağımsızlık ölçeği skorları ve fonksiyonel kapasite skorları hesaplandı. Hastaların kognitif durumunu belirlemek için Montreal kognitif değerlendirme bataryası Türkçe valide formu (MOCA-TR), Stroop test Türkçe valide formu (Stroop test TBAG formu) ve sembol sayı modaliteleri testi uygulandı.

Bulgular: Huntington hastalarında MOCA-TR skorları kontrollere göre anlamlı olarak azaldı (p<0,001). Hastaların Stroop testi TBAG formunun tamamlanma süresinde kontrollere göre belirgin bir uzama vardı (p<0,05). MoCA-TR skoru, hastaların bağımsızlık ölçeği puanı ve fonksiyonel kapasite skoru ile güçlü bir pozitif korelasyon sergilerken, toplam motor puanı ile güçlü bir negatif korelasyon gösterdi. Tersine, MoCA-TR skoru, hastalık yükü skoru ile orta derecede negatif bir korelasyon ve hastalık ilerleme hızı ile belirgin bir negatif ilişki gösterdi (p<0,05). CAG tekrarları ile hastalık başlangıç yaşı arasında güçlü bir negatif korelasyon gözlenirken, CAG tekrarları ile hastalık yükü skoru arasında oldukça anlamlı bir pozitif ilişki ortaya çıktı (p<0,05).

Sonuç: Çalışmada, hastaların kognitif skorları ile hastalığın klinik bulguları arasında güçlü bir ilişki olduğu gösterildi. Ayrıca hastaların bilişsel puanlarının hastalık yükünü ve hastalık ilerleme hızını da etkilediği belirtildi. Erken evrelerde bilişsel bozukluğun belirlenmesi, kişiselleştirilmiş hastalık değiştirici tedavi stratejilerine katkıda bulunabilir.

Anahtar sözcükler: Huntington hastalığı; sitozin adenin guanin; kognisyon; MoCA; Stroop testi; hastalık yükü.

Huntington's disease (HD) is an inherited, progressive neurodegenerative condition distinguished by choreiform movements, psychiatric issues, and cognitive decline. It arises from an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin (HTT) gene on chromosome 4p and is inherited following an autosomal dominant pattern.[1]

HTT is found in numerous tissues across the body. However, the primary pathology predominantly affects the central nervous system, prominently leading to atrophy of the caudate and putamen (collectively known as the neostriatum). HTT protein is believed to turn toxic due to CAG expansion.[2]

The typical count of repeats is 26 or fewer. Repeat numbering from 27 to 35 generally does not lead to symptoms, but exists a slight risk in the subsequent generation for expansion, potentially entering the range associated with disease causation. Repeats from 36 to 39 exhibit incomplete penetrance, with individuals possibly experiencing symptoms, albeit typically with a delayed onset in life. When the number of repeats reaches 40 or more, the disease fully manifests and results in symptoms.[3]

While no study has been conducted regarding the prevalence of HD in our country, the worldwide occurrence rate of HD stands at 4.88 cases per 100,000 individuals.[4]

Chorea, a central hallmark of HD, is the primary identifying symptom during the diagnosis phase. As the disease advances over time, the overall motor function gradually declines. The once prominent chorea might give way to a Parkinsonian state characterized by akinesia (lack of movement) and rigidity in the later stages of the disease's progression.[5]

Although HD is typically perceived as a motor dysfunction, cognitive decline can manifest even before the clinical symptoms of the disease. Cognitive impairments can present with symptoms such as emotional lability, decreased vocabulary, and impairment in executive functions.[6]

Due to HD presenting diverse symptoms, patients may be monitored under varying diagnoses. In this study, we aimed to evaluate the cognitive findings of patients with genetically and clinically confirmed HD who are being followed in our movement disorders clinic and assess their relationship with motor symptoms and trinucleotide repeat length.

Methods

This study was conducted at the University of Health Sciences, Fatih Sultan Mehmet Research and Training Hospital movement disorders clinic. It is single-center and cross-sectional research. In our study, fifteen patients diagnosed clinically and genetically with HD and fifteen healthy controls of similar age and gender who had signed a voluntary consent form were enrolled.

The CAG repeat numbers, family history, body mass index (BMI), weight loss, clinical dominance of disease, disease onset age, and disease durations of patients were recorded. Furthermore, the disease burden score (DBS) (DBS=[CAG - 35.5]×age) and disease progression rate of all patients were calculated and recorded.[7] The progression rate was determined by dividing the duration of the disease (in years) by the patient's functional capacity score.[8]

We determined the clinical severity of HD using the unified HD rating scale (UHDRS). In addition, we calculated the total motor score (TMS), independence scale, and functional capacity scores.[9]

We administered the Turkish version of the Montreal Cognitive Assessment Scale (MOCA-TR), the Symbol digit modalities test (SDMT), and the Turkish version of the Stroop test (Stroop test TBAG form) to assess the cognitive status of patients and healthy controls.

The MOCA-TR utilized in the research comprises seven sections: visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation. A score of 26 or higher is categorized as having intact cognitive function.[10]

The SDMT is a measurement tool used to track cerebral dysfunction in children and adults. It consists of an arrangement of abstract geometric shapes alongside verbal and written numerical answers. The completion of the test takes approximately 5 min.[11]

Standardization studies for our country were supported by the Scientific and Technological Research Council of Türkiye through the Basic Sciences Research Group (TBAG). Therefore, the Turkish version of the test is entitled the Stroop Test TBAG Form.[12]

It consists of five parts: reading color names printed in black (Part 1), reading color names printed in different colors (Part 2), naming the colors of colored circles (Part 3), naming the colors of neutral words without color names (Part 4), and naming the colors of color names printed in different colors (Part 5).

Statistical analysis was conducted utilizing IBM SPSS Statistics 23 software provided by IBM SPSS, Türkiye. Descriptive methods, encompassing mean, standard deviation, median, frequency, ratio, minimum, and maximum, were employed to summarize the data. To compare the ordinarily distributed quantitative data in two-group comparisons, a Student's t-test was utilized. For the comparison of qualitative data between the two groups, the Mann–Whitney U test was employed. Pearson's chi-square was used to compare categorical data. To explore the relationships between variables, Spearman's correlation was applied. Statistical significance was determined at a significance level of $p<0.05$.

The study was done appropriately to the Helsinki Declaration and Ethical Committee approval date of April 13, 2023, and the number was 2023/66.

Results

The study was conducted with a total of thirty cases. The dominance of clinical findings were chorea in 10 (66.6%) patients, psychiatric symptoms in 4 (26.6%) patients, and bradykinesia in 1 (6.6%) patient. Although the average age of symptom onset for patients was 48.73±10.58, the average age of diagnosis for patients was 54.40±12.3. Four patients exhibited weight loss, with chorea being the predominant symptom across all of them. The mean CAG repeat numbers, family history, BMI, weight loss, clinical dominance of disease, disease onset age, disease durations, DBS, and progression rate of patients are shown in Table 1. In addition, the UHDRS TMS, independence scale, and functional capacity scores are presented in Table 1.

Table 1. Clinical characteristics of the patients

	Patient (n=15)
Sex (F/M)	8 (53%) /7
Age	54.40±12.3
Age of disease onset	48.73±10.58
Duration of disease	4.53±3.48
BMI	25.05±4.61
Weight loss (yes /no)	4 (26%) /11 (74%)
Dominans of disease(N/% bradykinesia, chorea, psychiatric)	1 (6.6), 10 (66.6), 4 (26.6)
Family history (N/% maternal paternal)	9 (60), 6 (40%)
CAG repeat length	42.53±2.59
Progression rate	2.25+2.72
Disease burden score	368.33±121.80
UHDRS- total motor scores	23.47±14.5
UHDRS- independence scale	69.33±22.1
UHDRS- functional capacity	5.80±4.87

N: Number; F: Female; M: Male; BMI: Body mass index; CAG: Cytosine-adenine-guanine; UHDRS:Unified Huntington's Disease rating scale.

MoCA-TR scores were considerably decreased in the HD patients compared to controls (p<0.001). When evaluating the domains of MoCA-TR in HD patients, visuospatial and executive functions, naming, attention, language, abstraction, and orientation were found to be statistically decreased than the control group (p<0.05). Nevertheless, there were no statistically noteworthy alterations among the HD and controls in delayed recall (p>0.05). Across all patients, there was a significant increase in Stroop test TBAG form completion time when compared to the controls (p<0.05) (Table 2).

Moca-TR exhibited a robust negative correlation with TMS and a strong positive correlation with the Independence Scale score and functional capacity. Conversely, Moca-TR showed a moderate negative correlation with DBS and a pronounced negative association with progression rate (p<0.05) (Table 3).

A strong inverse correlation exists between CAG repeats and disease onset age, while a highly significant positive association was observed between CAG repeats and DBS (p<0.05) (Table 4).

Discussion

Due to the diversity in clinical presentation of HD and its infrequent occurrence, patients are often followed and treated with different diagnoses, which results in delays in diagnosis. Young-onset patients generally exhibit more bradykinesia, dystonia, and rigidity when compared to cases where symptoms appear in adulthood, and they have less (sometimes none) chorea. They present psychiatric and cognitive difficulties. On the other hand, late-onset patients typically present with chorea-predominant HD.[13] In our study, one of our patients was being monitored with a diagnosis of Parkinson's disease, and four of our patients were being followed in psychiatric clinics. Although the age of disease onset of symptoms is young, the time of diagnosis is delayed by about 7 years in our patients.

Despite efforts to maintain adequate calorie intake, weight loss and cachexia are frequently observed in HD. Although the exact mechanisms behind weight loss are not yet fully understood, potential factors that might play a role include increased energy expenditure due to excessive movement and changes in cellular metabolism within muscle or adipose tissue.[14] In a study involving 517 early-stage HD patients, those with higher CAG repeat numbers exhibited a faster rate of weight loss. However, a relationship between patients' UHDRS scores increase and weight loss could not be found.[15] Although our patients' BMI was within normal limits, all patients with weight loss presented with chorea. We did not find a correlation between weight loss and disease parameters.

Table 2. Comparison of cognitive findings of the patients and controls

	Patients (n=15)	Controls (n=15)	p
Age	54.4±12.3	56.7±14.2	0.64
Sex (F/M)	8/7	8/7	1.0
BMI	25.1±4.61	26.6±5.1	0.39
MOCA-TR	15.0±6.1	24.9±3.1	[a]<0.001*
Visualspatial/Exec. functions	2.77±1.7	4.80±0.5	[a] <0.001*
Naming	2.54±0.6	3.0±0	[a] 0.01*
Attention	2.62±1.8	4.8±1.4	[a] 0.003*
Language	0.3±0.6	1.93±1.2	[a] 0.003*
Abstraction	0.8±0.8	1.87±0.5	[a] <0.001*
Delayed recall	1.15±1.4	2.33±1.7	0.06
Orientation	4.69±1.3	6.0±0	[a] <0.001*
Symbol digit modalities test	87.7±47.2	113.9 ±7.8	0.32
Stroop 1	27.1±12.2	10.3±2.5	[a] <0.001*
Stroop 2	35.0±15.9	13.4±8.1	[a] <0.001*
Stroop 3	39.6±24.1	14.0±2.9	[a] <0.001*
Stroop 4	58.1±25.9	19.0±5.18	[a] 0.002*
Stroop 5	62.1±23.5	26.1±8.2	[a] <0.001*

*p<0.05; [a]: Mann-Whitney U test; N: Number; F: Female; M: Male; BMI: Body mass index; MOCA-TR:Turkish version of montreal cognitive assessment scale.

Table 3. Correlation of the MOCA-TR score and disease parameters of Huntington's patients

Correlation Matrix of MOCA-TR

MOCA-TR	Age of disease onset	CAG repeat length	Duration of disease	Total motor scores	Independence scale	Functional capacity	Disease burden score	Progression rate
Spearman's rho	−0.221	−0.289	−0.341	−0.715**	0.720**	0.795**	−0.589*	−0.698**
p	0.467	0.338	0.255	0.006	0.005	0.001	0.034	0.008
n	13	13	13	13	13	13	13	13

*p<0.05, ** p<0.01, *** p<0.001, MOCA-TR: Turkish version of montreal cognitive assessment scale; CAG: Cytosine-adenine-guanine.

Table 4. Correlation of CAG repeat length and disease parameters of Huntington patients

Correlation Matrix of CAG repeat length

	Age	Age of disease onset	Duration of disease	Total motor scores	Independence scale	Functional capacity	Disease burden score	Progression rate
CAG								
Spearman's rho	−0.431	−0.679	0.098 **	0.201	−0.157	−0.128	0.833***	0.134
p	0.109	0.005	0.729	0.472	0.576	0.650	<0.001	0.634
n	15	15	15	15	15	15	15	15

*p<0.05; **p<0.01; *** p<0.001; CAG: Cytosine-adenine-guanine.

In previous studies, a correlation has been observed between the CAG repeat length age of disease onset and the decline in motor, cognitive, and functional capacity.[16] Günal et al.[8] demonstrated that more CAG repeats not only impact the age of disease onset but also accelerate its progression rate. Consistent with the existing literature, we found that the CAG repeat length influenced the age of disease onset. Additionally, we observed a strong relationship between the CAG repeat length and the DBS.

Research has shown a 50% reduction in striatal volume during the clinical diagnosis of HD.[17] Growing evidence indicates the presence of cognitive and psychiatric symptoms of the disease, emerging up to 15 years before its motor manifestations. Recent studies focused on comprehending the most incapacitating facets of HD have indicated that cognitive and behavioral changes exert the maximum burden on families. This circumstance has been closely linked to functional decline.[18] We have demonstrated a strong correlation between patients' cognitive scores, TMSs, independence scale scores, and functional capacity. Patients' cognitive scores have also been shown to impact disease burden and disease progression rate.

Cognitive changes in the prodromal period typically consist of executive function impairment, which involves difficulties in recalling and sequencing multiple tasks.[19] Along the course of the disease, cognitive impairments manifest with executive function deficits reflecting frontosubcortical circuit dysfunction, such as impulsive behaviors and apathy.[20] Failures in performing tasks requiring attention functions tend to increase with the clinical progression of HD.[18]

In our patients, visuospatial and executive functions, naming, attention, language, abstraction, and orientation were statistically decreased than the control group. Notably, there was no statistically significant difference in delayed recall between groups. In line with the literature, this suggests that the challenges in HD stem from an ineffective memory search process. Although cognitive irregularities manifest early in HD, memory loss becomes evident in the later stages of the disease.[21]

Individuals with early cognitive and behavioral changes might have a higher likelihood of anosognosia and thus might not arrive promptly for a motor examination. Even among individuals from the same family and possessing a similar CAG repeat, HD could exhibit a unique beginning and advancement in symptoms.[22]

Conclusion

Currently, there is no effective treatment to halt the progression of HD. Especially in the early stages, the designation of cognitive impairment could contribute to the evolution of comprehensive neuropsychological rehabilitation programs and the implementation of personalized disease-modifying treatment strategies.

Disclosures

Ethics Committee Approval: University of Health Sciences, Fatih Sultan Mehmet Research and Training Hospital, FSMEAH-KAEK 2023/66, April 13, 2023.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.K.T; Design – E.K.T, K.G.K; Supervision – E.K.T; Materials – E.K.T, K.G.K, C.E; Data collection &/or processing – E.K.T., K.G.K, C.E.; Analysis and/or interpretation – E.K.T, E.G.; Literature search – E.K.T, E.G.; Writing – E.K.T; Critical review – E.G.

References

1. Dayalu P, Albin RL. Huntington disease: Pathogenesis and treatment. Neurol Clin 2015;33:101–14.
2. Snowden JS. The neuropsychology of Huntington's disease. Arch Clin Neuropsychol 2017;32:876–87.
3. Ha AD, Jankovic J. Exploring the correlates of intermediate CAG repeats in Huntington disease. Postgrad Med 2011;123:116–21.
4. Medina A, Mahjoub Y, Shaver L, Pringsheim T. Prevalence and incidence of Huntington's disease: An updated systematic review and meta-analysis. Mov Disord 2022;37:2327–35.
5. Wheelock V. The motor disorder. In: Nance M, Paulsen JS, Rosenblatt A, Wheelock V, editors. A physician's guide to the management of huntington's disease. 3rd ed. New York: Huntington's Disease Society of America; 2011. p.39.
6. Snowden J, Craufurd D, Griffiths H, Thompson J, Neary D. Longitudinal evaluation of cognitive disorder in Huntington's disease. J Int Neuropsychol Soc 2001;7:33–44.
7. Mason SL, Daws RE, Soreq E, Johnson EB, Scahill RI, Tabrizi SJ, et al. Predicting clinical diagnosis in Huntington's disease: An imaging polymarker. Ann Neurol 2018;83:532–43.
8. Günal İ, Güleryüz M, Aktan S. Trinucleotide repeat length and clinical progression in Huntington's disease. Marmara Med J 2000;13:19–21.
9. Huntington Study Group. Unified Huntington's disease rating scale: Reliability and consistency. Mov Disord 1996;11:136–42.
10. Ozdilek B, Kenangil G. Validation of the Turkish version of the Montreal cognitive assessment scale (MoCA-TR) in patients with Parkinson's disease. Clin Neuropsychol 2014;28:333–43.
11. Sheridan LK, Fitzgerald HE, Adams KM, Nigg JT, Martel MM, Puttler LI, et al. Normative symbol digit modalities test performance in a community-based sample. Arch Clin Neuropsychol 2006;21:23–8.
12. Karakaş S, Erdoğan E, Sak L, Soysal AŞ, Ulusoy T, Yüceyurt İ, et al. Stroop test TBAG form: Standardisation for Turkish culture, reliability and validity. J Clin Psy 1999;2:75–88.
13. Ribaï P, Nguyen K, Hahn-Barma V, Gourfinkel-An I, Vidailhet M, Legout A, et al. Psychiatric and cognitive difficulties as indicators of juvenile huntington disease onset in 29 patients. Arch Neurol 2007;64:813–9.
14. Lodi R, Schapira AH, Manners D, Styles P, Wood NW, Taylor DJ, et al. Abnormal in vivo skeletal muscle energy metabolism in Huntington's disease and dentatorubropallidoluysian atrophy. Ann Neurol 2000;48:72–6.
15. Aziz NA, van der Burg JM, Landwehrmeyer GB, Brundin P, Stijnen T, Roos RA; EHDI Study Group. Weight loss in Huntington disease increases with higher CAG repeat number. Neurology 2008;71:1506–13.
16. Capiluppi E, Romano L, Rebora P, Nanetti L, Castaldo A, Gellera C, et al. Late-onset Huntington's disease with 40-42 CAG expansion. Neurol Sci 2020;41:869–76.
17. Aylward EH, Sparks BF, Field KM, Yallapragada V, Shpritz BD, Rosenblatt A, et al. Onset and rate of striatal atrophy in preclinical Huntington disease. Neurology 2004;63:66–72.
18. Paulsen JS. Cognitive impairment in Huntington disease: Diagnosis and treatment. Curr Neurol Neurosci Rep 2011;11:474–83.
19. Paulsen JS, Langbehn DR, Stout JC, Aylward E, Ross CA, Nance M, et al; Predict-HD Investigators and Coordinators of the Huntington Study Group. Detection of Huntington's disease decades before diagnosis: The predict-HD study. J Neurol Neurosurg Psychiatry 2008;79:874–80.
20. Stout JC, Paulsen JS, Queller S, Solomon AC, Whitlock KB, Campbell JC, et al. Neurocognitive signs in prodromal Huntington disease. Neuropsychology 2011;25:1–14.
21. Duff K, Paulsen J, Mills J, Beglinger LJ, Moser DJ, Smith MM, et al; Predict-HD Investigators and Coordinators of the Huntington Study Group. Mild cognitive impairment in prediagnosed Huntington disease. Neurology 2010;75:500–7.
22. Ross CA, Reilmann R, Cardoso F, McCusker EA, Testa CM, Stout JC, et al. Movement disorder society task force viewpoint: Huntington's disease diagnostic categories. Mov Disord Clin Pract 2019;6:541–6.