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Multidimensional Analysis Of Advanced Stage Huntington's Disease From Neurocognitive And Psychofunctional Perspectives With Morphometric Correlations: Case Series

Multidimensional Analysis Of Advanced Stage Huntington's Disease

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Abstract

Huntington's disease (HD) is a progressive neurodegenerative monogenic disorder that multifaceted clinical and radiological analysis correlations are not yet understood. We aim to evaluate advanced-stage HD patients for multidimensional clinical deterioration with objective scales and correlate with morphometric-based measurements. Ten advanced HD patients evaluated with the Unified Huntington's Disease Rating Scale (UHDRS) were subjected to psychofunctional assessment for behavioral and neurocognitive decline, and total functional capacity (TFC), functional assessment scale (FAS) for functional determination. In morphometric assessment, bicaudate ratio (BCR), bifrontal ratio (BFR), frontal horn area (FHA), frontal horn ratio to intercaudate distance (FH/CC), and caudate volume and caudate volume ratio (CVR) were analyzed and correlated with relevant parameters. The most frequent functional decline was in occupational and financial ability in UHDRS TFC (5.60±2.27), social/financial engagement, and self-care impairment in FAS (11.10±3.48). Cognitive decline was especially in quick thinking and responding to stimuli in sufficient quantity and on time. Caudate volume loss was more severe on the right(6.50±1.18) and inferior sections (21.65±7.30). A negative correlation was found between intercaudate distance and verbal fluency test (rho=-0.775). Parkinson's disease sleep scale and inter caudate distance were negatively correlated (rho=-0.559), and a positive correlation was found in bifrontal distance/caudate distance (rho=0.559). There was a negative correlation between the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, Hamilton Depression Rating Scale, and Hamilton Anxiety Rating Scale and FHD (rho=-0.671, rho=0.61 and rho=0.571, respectively). In light of current findings, caudate atrophy is an important indicator of cognito-functional disability, especially in verbal ability. The right hemisphere seems to be more vulnerable to the neurodegenerative processes, and mood disorders appear to be related explicitly to right frontal lobe degeneration. Psychofunctional deterioration may begin years before clinical diagnosis; HD should be considered in the differential diagnosis of aberrant psychofunctional deterioration in young patients.

Keywords: Caudate Atrophy, Hamilton Depression Rating Scale, Hamilton Anxiety Rating

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Introduction

Huntington's Disease (HD) is an autosomal dominant inherited progressive neurodegenerative disease caused by an expansion in CAG trinucleotide repetition encoding polyglutamine in the structure of Huntingtin IT15 (HTT) protein located on the short arm of chromosome 4 (1). The basic radio-pathological process is characterized by prominent cell loss and atrophy in the striatum (2). Neuropsychiatric disorders may present with symptoms such as apathy, irritability, impulsivity, and obsessiveness, which can be described as hypo-frontal or executive dysfunction syndrome long before the manifest stage, many of which are undiagnosed at this stage (3). In this case series, psycho-functional decline along with functional and cognitive impairment in specific domains that should be recognized beyond the motor findings of HD in clinical practice was investigated, and these findings were correlated with morphometric descriptions on a radiological basis.

2. Case Series

Ten preliminary clinically and genetically diagnosed advanced-stage Huntington's disease patients were evaluated with UHDRS' four main domains (4) and psychofunctional scales. Each of the motor, functional, cognitive, behavioral, and neuropsychiatric scales was evaluated in each patient at the first and second visits (3 months after the first visit) by the corresponding author (E.D.U) and two other clinical neuroradiologists blinded to the patient's information. The neuroradiological correlations of each scale with the morphometric measurement analysis results were evaluated. The case series study was conducted in accordance with the Helsinki Declaration. Written consent was obtained from each participant.

The study was conducted in accordance with the Helsinki Declaration. The study was planned as a 'Case Series.' Approval was granted by a written consent (Informed Volunteer Consent Form) form obtained from each participant by the corresponding author and declared to the center (Nevşehir State Hospital Administrative Unit). The consent form, patient demographic, and clinical and imaging information of each patient included in the study were recorded and stored in the patient forms by the corresponding author.

2.1. Rating Scales

2.1.1. Analysis of UHDR Domains

Motor and behavioral domains in HD were assessed by the UHDRS in order to see to what extent daily life activities are restricted and in which areas (4). Motor disability was evaluated in 5 main domains: Oculomotor (ocular pursuit, saccade initiation, saccade velocity), bradykinesia, rigidity (arms), dystonia (trunk, right upper extremity, left upper extremity, right lower extremity, left lower extremity), chorea (face, body, trunk, right upper extremity, left upper extremity, right lower extremity, left lower extremity). The behavioral section of the UHDRS consists of 11 items assessing the frequency and severity of complaints about mood/sadness, low self-esteem or guilt, anxiety, suicidal thoughts, disruptive or aggressive behavior, irritable behavior, obsessions, compulsions, delusions, and hallucinations. The functional capacity evaluation was assessed using the UHDRS scale with total functional capacity (TFC) and functional assessment scale (FAS). TFC is a sum of detailed measurements of functional capacity that consists of five global items that evaluate occupation, finances, domestic chores, activities of daily living, and care level, with scores on each item ranging from 0 to either 2 or 3 (e.g., "occupation — 0= unable, 1=marginal work only, 2= reduced capacity for the usual job, 3=normal") (5). The FAS is a more comprehensive measurement that evaluates tasks related to the occupation (e.g., accustomed/volunteer work), finances (financial management), activities of daily living (e.g., social engagement, self-care), domestic chores (e.g., home maintenance, laundry), level of care (e.g., home or supervised), and physical abilities (e.g., walking, getting out of bed, falls). The UHDRS (4) cognitive component consists of 3 tests that measure cognitive executive functions: The Stroop Color and Word Test (SCWT) (6), a verbal fluency test (VFT) (7), and the Symbol Digit Modalities Test (SDT) (8). The SCWT (6) is a neuropsychological test that assesses the ability to inhibit cognitive interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus. The VFT is a commonly used neuropsychological test and mainly examines the ability to spontaneously produce words orally within a fixed period. 2 types of verbal fluency ability, i.e., letter fluency and category fluency, are evaluated. The SDT is a matching test in which the participants are asked to match 9 abstract symbols with numerical digits using code. Only the written response format of the SDMT was administered.

2.1.2. Psychofunctional Evaluation

In the psychofunctional evaluation, the background information of each patient and the first neuropsychiatric finding before HD diagnosis, the date of the first application to the physician for this purpose, the time elapsed until the diagnosis of HD, the psychiatric diagnoses taken so far, and the neuropsychiatric drugs were evaluated. In the psychofunctional evaluation, Parkinson's Sleep Scale (PDSS) (sleep) (9), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) (impulsiveness) (10), Starkstein's Apathy Scale (SAS) (apathy) (11), Hamilton Depression Rating Scale (HDRS) (depression) (12), and Hamilton Anxiety Rating Scale (HAM-A) (anxiety) (13) were evaluated.

2.2. Morphometric Evaluation

Cranial images of the participants were obtained on the AW Volume Share 7 workstation using a 3-T Signa MR scanner (General Electric, Milwaukee, WI), and a T2 sequence of MRI was used. In morphometric assessment, bicaudate ratio (BCR), bifrontal ratio (BFR), frontal horn area (FHA), frontal

Table 1. UDRS motor, cognition, behavior domains and TFC domains were compared with MRI morphometric measurements.

		UHDRS motor score					UHDRS cognition score			Functional Assessment Scale	Total Functional Capacity
		Ocular Pursuit	Bradykinesia	Rigidity	Dystonia	Chorea	SDMT	SIT	VFT		
Magnetic Resonance Imaging Morphometric Evalution	Intercaudate Distance (mm)	rho=0,583 p=0,077	rho=-0,505 p=0,137	rho=0,415 p=0,233	rho=0,284 p=0,426	rho=0,284 p=0,426	rho=-0,226 p=0,531	rho=-0,537 p=0,110	rho=-0,775 p=0,008	rho=-0,505 p=0,137	rho=-0,836 p=0,003
	Bicaudate Ratio	rho=0,311 p=0,381	rho=-0,686 p=0,028	rho=0,681 p=0,030	rho=0,251 p=0,484	rho=0,251 p=0,484	rho=-0,511 p=0,131	rho=-0,775 p=0,008	rho=-0,497 p=0,144	rho=-0,686 p=0,028	rho=-0,671 p=0,034
	Frontal Horn Distance (mm)	rho=0,291 p=0,414	rho=-0,634 p=0,049	rho=0,791 p=0,006	rho=0,426 p=0,219	rho=0,426 p=0,219	rho=-0,598 p=0,068	rho=-0,354 p=0,316	rho=0,043 p=0,906	rho=-0,634 p=0,049	rho=-0,308 p=0,386
	Bifrontal Ratio	rho=0,206 p=0,567	rho=-0,606 p=0,034	rho=0,714 p=0,020	rho=0,394 p=0,259	rho=0,394 p=0,259	rho=-0,560 p=0,092	rho=-0,237 p=0,510	rho=0,161 p=0,656	rho=-0,606 p=0,034	rho=-0,280 p=0,433
	Bifrontal Distance/ Caudate Dsitance	rho=-0,361 p=0,306	rho=0,394 p=0,260	rho=-0,221 p=0,540	rho=-0,071 p=0,845	rho=-0,071 p=0,845	rho=0,091 p=0,802	rho=0,512 p=0,130	rho=0,763 p=0,010	rho=0,394 p=0,260	rho=0,631 p=0,039
	Frontal Horn Area (Right, mm)	rho=0,208 p=0,564	rho=-0,695 p=0,026	rho=0,778 p=0,008	rho=0,355 p=0,314	rho=0,355 p=0,314	rho=-0,573 p=0,083	rho=-0,598 p=0,068	rho=-0,148 p=0,684	rho=-0,695 p=0,026	rho=-0,459 p=0,182
	Frontal Horn Area Left, mm)	rho=0,208 p=0,564	rho=-0,548 p=0,101	rho=0,675 p=0,032	rho=0,213 p=0,554	rho=0,213 p=0,554	rho=-0,689 p=0,028	rho=-0,677 p=0,032	rho=-0,240 p=0,504	rho=-0,548 p=0,101	rho=-0,555 p=0,046
	Caudate Area (Superior, mm)	rho=-0,160 p=0,659	rho=0,679 p=0,031	rho=-0,729 p=0,017	rho=-0,321 p=0,366	rho=-0,321 p=0,366	rho=0,489 p=0,151	rho=0,697 p=0,025	rho=0,253 p=0,480	rho=0,679 p=0,031	rho=0,440 p=0,203
	Caudate Area (Middle, mm)	rho=-0,097 p=0,790	rho=0,554 p=0,047	rho=-0,558 p=0,044	rho=-0,569 p=0,036	rho=-0,569 p=0,036	rho=0,299 p=0,402	rho=0,317 p=0,372	rho=-0,043 p=0,906	rho=0,554 p=0,047	rho=0,370 p=0,292
	Caudate Area (İnferior, mm)	rho=-0,472 p=0,169	rho=0,382 p=0,277	rho=-0,311 p=0,381	rho=-0,355 p=0,314	rho=-0,355 p=0,314	rho=0,250 p=0,486	rho=0,177 p=0,625	rho=0,382 p=0,277	rho=0,382 p=0,277	rho=0,665 p=0,036
	Caudate Volume (Right)	rho=-0,243 p=0,498	rho=0,525 p=0,119	rho=-0,436 p=0,208	rho=-0,392 p=0,262	rho=-0,392 p=0,262	rho=0,232 p=0,518	rho=0,321 p=0,366	rho=0,222 p=0,537	rho=0,525 p=0,119	rho=0,605 p=0,044
	Caudate Volume (Left)	rho=-0,299 p=0,401	rho=0,562 p=0,041	rho=-0,482 p=0,159	rho=-0,499 p=0,142	rho=-0,499 p=0,142	rho=0,223 p=0,535	rho=0,388 p=0,267	rho=0,324 p=0,361	rho=0,562 p=0,041	rho=0,633 p=0,049
	Caudate Volume Ratio (Right)	rho=-0,354 p=0,350	rho=0,672 p=0,047	rho=-0,454 p=0,219	rho=-0,365 p=0,334	rho=-0,365 p=0,334	rho=0,276 p=0,472	rho=0,403 p=0,282	rho=0,395 p=0,293	rho=0,672 p=0,047	rho=0,670 p=0,048

Unified Huntington's Disease Rating Scale (UHDRS), Symbol Digit Modalities Test (SDMT), Stroop Interference Test (SIT), Verbal Fluency Test (VFT)

horn ratio to intercaudate distance (FH/CC), and caudate volume and caudate volume ratio (CVR) were analyzed and correlated with relevant parameters. BCR was calculated by dividing the frontal horns' caudate indentations by the brain's width on the same line (14). Bifrontal Ratio (BFR) measurements were obtained by dividing the distance between the most lateral ends of the frontal horns by the width of the brain on the same line using the same section (15). The caudate volume ratio (CVR) was calculated via the perimeters of the caudate, beginning at the level immediately superior to that in which the anterior commissure was observed. The borders of the caudate nucleus were determined laterally by the anterior limb of the internal capsule and medially by the frontal horn or lateral ventricle body. Three different sections were used for caudate volume measurements; the first section is the most superior slice, measured just inferior to the slice in which the caudate body was observed; the second was located superiorly through the level just below that in which the body of the caudate was observed; the third most inferior section was superior to the slice containing anterior commissure. Caudate volumes were calculated separately by summing the areas from all slices and multiplying this sum by slice thickness (7 mm). The caudate volume ratio was calculated by dividing the volume by the brain area in the section where BCR and BFR measurements were made and multiplying by 100. Frontal horn areas (FHA) were measured where BCR and BFR measurements were made. The frontal horn ratio was obtained by dividing the total area of the frontal horns by the brain area and multiplying by 100. The frontal horn area/inter caudate distance (FH/CC) ratio was obtained by dividing the frontal horn distance and the caudate distance (16).

2.3. Results

The average age of the patients included in the study was 52.3±2, and the most common neurologic/psychiatric comorbidities were neuropathic pain (40%) and psychosis (60%). Years since the psychiatric diagnosis was 8.5±2, the year was longer than the clinical diagnosis in all patients (±2 y). UHDRS TFC score average was 5.60±2.27 (ranges between 1-9), and the most frequent functional decline was observed in occupational and financial ability. The FAS score average was 11.10±3.48 (range between 8-18), and impairments in social/financial engagement and self-care were the most common findings. Cognitive decline was present in each domain, and dominant disturbance was observed in quick thinking, adequate and timely response to reactions (VFT was 17.7±2, SDMT 23.4±2, and SIT 34.4±2 for color, 24.7±2 for word and 20.2±2 for color-word, respectively).

The PDSS score was low in correlation with a disease duration of 39.40±16.33 (22-71). The mean ICD-related behavior score was lower than the average population (8.9±2), and the most common deficit was performing tasks or hobbies (8.90±3.73). A relatively high frequency was observed in apathy (24.50±4.03), and it showed augmentation in proportion to the duration of the disease. HDRS and HAM-A mean scores were 31.00±7.53 and 30.00±6.48, ranging from 18 to 39 and 18-37, respectively.

In a morphometric evaluation in line with the duration of the disease, an increase in frontal horn distance (29.99±4.00 (mean±SD)), bifrontal ratio (0.25±0.04 (mean±SD)), and a frontal horn area (88.30±14.70 for right and 85.68±15.93 for left) were determined. The increase in the right frontal area was relatively higher than the left side. There was a decrease in caudate volume in all measured sections, and a significant volume loss was observed, especially in the inferior section (73.94±7.75 (superior), 88.67±12.45 (middle), and 21.65±7.30 (inferior), respectively). Caudate volume loss was more severe on the right (6.50±1.18 (right) and 6.65±1.05 (left). Similarly, the caudate volume ratio was found to be lower on the right (5.53±1.09 (right) and 5.66±0.79 (left). The inter caudate distance (20.98±3.69 (mean±SD)) and bifrontal distance/ caudate distance (1.40±0.21 (mean±SD)) increase were determined.

2.3.1. Correlation Analyses

A Spearman correlation coefficient for the relationships between MRI morphometric measurements and UHDRS domains is demonstrated in Table 1. UHDRS motor domains showed a positive correlation between bradykinesia and BCR (rho=0.782), FHD (rho=0.617), FHAs (rho=0.775 for right and rho=0.884 for left, respectively). The caudate area (superior) (rho=-0.763) was found to be negatively correlated with it. Similar to bradykinesia, a positive correlation was found between rigidity and BCR (rho=0.681), FHD (rho=0.791), and FHA (rho=0.778 for the right and rho=0.675 for left). A negative correlation was found between the caudate area (superior and middle) (rho=-0.729 for superior and rho=-0.558 for middle) and rigidity. A negative statistically significant relationship was found between dystonia, chorea, and the caudate area (middle) (rho=-0.569 for dystonia and rho=-0.569 for chorea, respectively). In the UHDRS cognitive domains, a negative correlation was found between SDMT and FHA (left) (rho=-0.689) and between SIT and BCR (rho=-0.775), FHA (left) (rho=-0.677). A statistically significant positive correlation was found between FHA (left) and caudate area (superior) (rho=0.697). Also, a significant negative correlation was found between VFT and intercaudate distance, bifrontal distance/ caudate distance (rho=-0.775 and rho=0.763). In UHDRS functional domains, a positive correlation was found between TFC and caudate volume (right and left) (rho=0.665 and rho=0.633), CVR (rho=0.670), and BFD (rho=0.631), while there was a negative correlation between BCR (rho=-0.671) and TFC.

There was a negative correlation between PDSS and inter caudate distance (rho=-0.559) and a positive correlation between bifrontal distance/ caudate distance (rho=0.559). A negative correlation was found between QUIP-RS and FHD (rho=-0.671) and FHA (right) (rho=-0.56). A positive relationship was found between HDRS, HAM-A, and FHD (rho=0.61 and rho=0.571, respectively) (Table 2).

3. Discussion

Our study evaluated the functional, cognitive, behavioral, and motor domains of UHDRS and brain morphometric

Table 2. MRI morphometric measurement values and neuropsychiatric scales were compared.

		Neuropsychiatric Scales				
		PDSS	QUIP-RS	SAS	HDRS	HAM-A
Magnetic Resonance Imaging Morphometric Evalution	Intercaudate Distance (mm)	rho=-0,559 p=0,043	rho=-0,345 p=0,329	rho=0,477 p=0,164	rho=0,274 p=0,443	rho=0,286 p=0,424
	Frontal Horn Distance (mm)	rho=-0,073 p=0,841	rho=-0,671 p=0,034	rho=0,483 p=0,157	rho=0,610 rho=0,571 p=0,021	rho=0,571 p=0,034
	Bifrontal Distance/ Caudate Dsitance	rho=0,559 p=0,043	rho=0,098 p=0,787	rho=-0,194 p=0,590	rho=-0,256 p=0,475	rho=-0,255 p=0,476
	Frontal Horn Area (Right, mm)	rho=-0,152 p=0,675	rho=-0,56 rho=-0,622 p=0,042	rho=0,401 p=0,250	rho=0,482 p=0,159	rho=0,486 p=0,154
	Frontal Horn Area Left , mm)	rho=-0,152 p=0,675	rho=-0,622 p=0,035	rho=0,552 p=0,048	rho=0,268 p=0,454	rho=0,316 p=0,374

Parkinson's Sleep Scale (PDSS), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS), Starkstein's Apathy Scale (SAS), Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HAM-A)

measurements and determined correlation analyses. In correlation analyses, a striking decline in almost all domains was observed, which is in correlation with other current studies (17). Current data emphasize that the decrease in intercaudate distance, which is an essential indicator of caudate atrophy, and the decrease in the bifrontal distance, which is an indicator of widespread cortical atrophy, are important indicators of the progression of neurodegenerative disorders (18). Additionally, in a study conducted with premorbid HD patients, the SCL-90 Global Severity Index and Frontal Systems Behavior Scale (FrSBe) were compared with control individuals, and a statistically significant difference was found between the two groups (19). Similarly, in multiple sclerosis, one of the neurodegenerative diseases, Batista et al. reported that neocortex and basal ganglia volumes can be used to evaluate executive functions and that they decrease in correlation with the decline of these functions, especially in the advanced neurodegeneration process (20). Studies have shown that individuals with frontotemporal lobar degeneration (FTLD) initially present as a non-amnestic degenerative syndrome and tend to present primarily with behavioral and language-predominant symptoms, in which behavioral disinhibition is observed primarily with deficits in executive functions (21). As the degree of cerebral degeneration increases, deterioration is observed in both neurocognitive and functional domains and psychofunctional domains that the existing studies point to caudate volume reduction, ventricular enlargement, and widespread cortical atrophy in HD (22). In light of the current findings in this case series, it was found that there was a strong association between bradykinesia and rigidity and caudate atrophy and its indicators, and frontal lobe atrophy and its indicators were primarily associated with cognitive domains that a severe decline was observed mainly in episodic memory, processing speed, executive functioning, and visuospatial perception based on current data in similar studies. Functional disability is closely related to caudate and frontal lobe atrophy and its indicators. Although there are no objective, comprehensive studies to compare our current correlation data in HD, our case study has shown that frontal lobe atrophy and its indicators may be important indicators of personality/behavioral deterioration in HD.

4. Conclusion

In this case series study, HD was evaluated multifacetedly from neurocognitive and psychofunctional perspectives. The most frequent and severe decline in the relevant domains was determined, and its relationship with cerebral neurodegenerative processes was examined by morphometric evaluation of the relevant domains. Defining the neurocognitive and psychofunctional reflections of cerebral neurodegenerative effects, which begin long before clinical findings in HD, with cranial images and making a morphometric naming are essential for pre-mortal stage diagnosis and prognosis. This pioneering study is a guide for management, especially for making a correlation in advanced-stage HD in neurocognitive, psychofunctional, and neuroradiological axes. Further studies with more comprehensive scales are needed.

Acknowledgments

This study was performed in line with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. The study was planned as a 'Case Series' and approval was granted by written consent (Informed Volunteer Consent Form) form that was obtained from each participant by the corresponding author, and has been declarated to the center (Nevşehir State Hospital Administrative Unit).

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Disclosures

The study was designed, analyzed, written, and approved by the corresponding author (EDU).

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