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Decreased Metabolism in the Cerebral Cortex in Early-Stage Huntington's Disease: A Possible Biomarker of Disease Progression?

Hyeeun Shin,[a] Man Ho Kim,[b] Su Jin Lee,[c] Kyung-Han Lee,[d] Mi-Jung Kim,[e] Ji Sun Kim,[f] Jin Whan Cho[f]

[a]Department of Neurology, Eulji General Hospital, Eulji University School of Medicine, Deajeon, Korea
[b]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[c]Department of Nuclear Medicine, Ajou University School of Medicine, Suwon, Korea
[d]Departments of Nuclear Medicine and [f]Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[e]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background and Purpose Huntington's disease (HD) is an autosomal-dominant inherited neurodegenerative disorder. Genetic analysis of abnormal CAG expansion in the IT15 gene allows disease confirmation even in the preclinical stage. However, because there is no treatment to cure or delay the progression of this disease, monitoring of biological markers that predict progression is warranted.

Methods FDG-PET was applied to 13 patients with genetically confirmed HD in the early stage of the disease. We recorded the initial and follow-up statuses of patients using the Independence Scale (IS) of the Unified Huntington's Disease Rating Scale. The progression rate (PR) was calculated as the annual change in the IS. The patients were divided into two groups with faster and slower progression, using the median value of the PR as the cut-off. FDG-PET data were analyzed using regions of interest, and compared among the two patient groups and 11 age- and sex-matched controls.

Results The mean CAG repeat size in patients was 44.7. The CAG repeat length was inversely correlated with the age at onset as reported previously, but was not correlated with the clinical PR. Compared with normal controls, hypometabolism was observed even at very early stages of the disease in the bilateral frontal, temporal, and parietal cortices on FDG-PET. The decreases in metabolism in the bilateral frontal, parietal, and right temporal cortices were much greater in the faster-progression group than in the slower-progression group.

Conclusions A decrease in cortical glucose metabolism is suggested as a predictor for identifying a more rapid form of progression in patients with early-stage HD.

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Key Words Huntington's disease, biomarker, FDG-PET, progression, cortical metabolism.

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Correspondence
Jin Whan Cho, MD, PhD
Department of Neurology,
Samsung Medical Center,
Sungkyunkwan University,
School of Medicine,
50 Irwon dong, Gangnam-gu,
Seoul 135-170, Korea
Tel +82-2-3410-1279
Fax +82-2-3410-0052
E-mail jinwhan.cho@samsung.com

Introduction

Huntington's disease (HD) is an autosomal-dominant genetic neurodegenerative disorder with a high genetic penetrance. Affected individuals present with chorea and cognitive and psychiatric dysfunction, usually in middle age, which progress to dementia. The duration of the illness between onset and death varies, but usually ranges between 14 to 18 years.[1] The typical clinical features of hereditary chorea together with caudate atrophy on brain imaging allow the clinical diagnosis of HD. Molecular genetic analysis of the CAG expansion in the IT15 gene on chromosome 4p16.3 makes it possible to confirm the diagnosis of HD, even at the preclinical stage.[2] How-

ever, there are no treatments available to prevent, cure, or delay the disease progression, making it necessary to explore biological markers that could predict disease progression.

The main pathological features of HD include loss of the medium spiny neurons of the neostriatum, which leads to caudate atrophy that is visible in brain imaging.[3] The striatal loss of glucose metabolism has also been revealed in the preclinical stage of HD.[4-7] However, it is known that pathological changes also occur in the cortex.[8,9] Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging of the brains of HD patients reveals decreased metabolism in cortical areas, suggesting that the cognitive and psychiatric symptoms associated with HD are not mediated purely by subcortical damage.[5,7,10,11] In this study we tested the hypothesis that changes in cerebral cortical metabolism in early-stage HD detected by FDG-PET could be used to monitor the disease progression.

Methods

Subjects and review of medical records

We performed a retrospective review of medical records, and interviewed the family members cohabitating with 28 enrolled patients with genetically confirmed HD who were available for a follow-up interview. FDG-PET was applied to 13 of the patients who were in the early stage of the disease. To monitor disease progression, we obtained the age at onset, initial manifestations, disease duration, family history, main symptoms at first visit, CAG repetition length, and functional statuses at onset and during follow-up by means of medical record reviews and interviews. The protocol used for this study was reviewed and approved by the institutional review board of Samsung Medical Center.

Progression rate

The functional statuses of the patients were assessed using the Independence Scale (IS) of the Unified Huntington's Disease Rating Scale. We defined the progression rate (PR) as the annual change in the IS score; that is, the annual difference in IS between disease onset and follow-up evaluation [(IS at onset-IS at follow-up point)/(duration of disease)]. The median value of the PR for our 28 patients was used as a cut-off value to compare patients on whom FDG-PET (n=13) was performed, because an objective reference has not been reported; 7 and 6 patients were assigned to the slower- and faster-progression groups, respectively. Age and duration of disease did not differ between the slower- and faster-progression groups.

FDG-PET and imaging analysis

FDG-PET was applied to early-stage HD patients who had not reported any impairment of the activities of daily living (ADL) or cognitive defects, at a mean of 2.2 years after symptom onset. To determine if there were metabolic differences between normal and HD patients, 11 normal-control images were obtained from age- and sex-matched patients (mean age=48.6 years, 5 males and 6 females) with no history of neurological or psychiatric disorders and no evidence of neurological abnormalities upon examination.

Brain PET was performed 30 min after injecting 370 MBq FDG. Emission data were acquired for 10 min on a GE Advance PET scanner (GE Healthcare, Milwaukee, WI, USA). Tomographic images were reconstructed by filtered back-projection using a Hanning filter (4.5 mm cut-off frequency) and a uniform attenuation coefficient of 0.096 cm^{-1}. Images were stored on a 128×128 matrix with 1.95 mm pixel size and 4.25 mm slice thickness.

PET images were evaluated by segmental region of interest (ROI) analysis, which was performed on caudoputamen- and cerebellum-level transverse tomographic images constructed from three adjacent slices. On each image, 12 anatomically configured ROIs were drawn using a segmental analysis algorithm (Xeleris Software, GE Healthcare, Milwaukee, WI, USA), and average counts were obtained (total count/number of pixels) for each ROI. The ratios of the ROI values for the bilateral frontal, temporal, parietal, occipital cortices, thalami, and caudate nuclei to that of the cerebellar ROI value were used for comparisons.[11] In addition, the PR and metabolic differences between HD patients with slower and faster progression were compared based on the ROI ratios described above.

Statistical analysis

The relationship between CAG repeat length and age at onset was determined by correlation analysis. We used partial correlation analysis to determine the factors influencing PR such as age at onset, disease duration, and CAG repeat length. We used the Kruskal-Wallis test to compare the ratios of the cerebral ROIs to the cerebellum ROI on FDG-PET among patient groups and control subjects. The Mann-Whitney test was used to compare the mean differences in the ratios of ROIs between the slower- and faster-progression groups and the controls. All of the statistical analyses were performed using PASW (version 18.0, IBM).

Results

We evaluated the PRs in 28 patients, consisting of 9 men and 19 women from 26 different pedigrees. The median PR score was -4.3 IS per year and the mean duration of the disease was 7.6 years. The PR was not significantly correlated with the

number of CAG repeats or age at onset. Demographic features and clinical data of 13 patients who were investigated using FDG-PET are summarized in Table 1. The mean CAG repetition size was 44.7 (with a range of 36-55), and it was correlated with the age at disease onset; this association is already well known. The most common initial manifestation at the first visit was abnormal involuntary movement (i.e., chorea). FDG-PET was applied to all these patients within 3 years of the onset of HD. They were able to work and perform the normal ADL, and had similar IS scores (of above 80) at the time of the scan. The mean follow-up IS was 6.6 years (with a range of 3-11 years) after symptoms onset.

Progression rate and metabolism as assessed by FDG-PET

To determine the relationship between PR and metabolic activity in the brain, two categories of HD patients were defined by using the median value of the PR in our cohort as a cut-off value to compare between slower- and faster-progression groups. Dividing the 13 patients into a faster-progression group (above the median value, n=6) and a slower-progression group (below the median, n=7) revealed differences in FDG-PET metabolism. The metabolisms in the bilateral caudate nuclei, frontal, temporal, and parietal cortices of HD patients were decreased compared to those of controls. The decreases in metabolism in the bilateral frontal, parietal cortices, and right temporal cortex were greater in the faster-progression group. The faster progression group showed hypometabolism throughout the cortex except for the occipital region relative to controls. The metabolism detected in the temporal cortex did not differ significantly between the slower-progression and control groups. The metabolism in the occipital cortex and the thalamus ratios did not differ among the three groups (Table 2, Fig. 1).

Discussion

HD is an inherited neurodegenerative disease. Clinical manifestations and a family history are suggestive for a diagnosis of HD, and this can be confirmed with genetic testing, enabling detection of patients in the presymptomatic stage. However, it is currently not possible to treat or cure this disorder, making it necessary to develop targeted drugs and strategies that can delay onset and modify progression. The development of effective treatment modalities requires the identification of biomarkers that can be used to monitor progression or predict onset. In this study we investigated whether changes in brain metabolism in early-stage HD can be used as a biological marker to predict HD progression.

It is well known that individuals with a large number of CAG repeats have earlier onsets of the disease. There have been some suggestions that a greater number of CAG repeats results in faster progression, but the relationship between CAG repeat length and progression is unclear.[12,13] Our statistical analyses found no significant correlations between CAG repeats and PR, although our small sample could have hindered the detection of statistically significant results.

Pathological changes that precede the onset of clinical symptoms have been found;[14,15] however, it is unknown when these changes begin. Many structural and functional neuroimaging methods are currently used in attempts to detect abnormalities in the brains of HD patients associated with clinical manifes-

Table 1. Clinical characteristics of 13 patients with Huntington's disease (HD) who were investigated using FDG-PET

Patient no.	Gender	Age at onset (years)	Age at PET	IS-PET	IS score at f/u	Duration	TNR	Initial main symptom	PR	Progression group
1	Female	32	35	90	60	7	49	Involuntary movement	-5.77	Faster
2	Female	41	44	90	70	10	41	Mild cognitive impairment	-3.00	Slower
3	Female	50	52	90	70	5	44	Involuntary movement	-6.00	Faster
4	Male	41	44	90	85	4	48	Involuntary movement	-3.75	Slower
5	Female	49	51	90	80	6	43	Involuntary movement	-3.33	Slower
6	Female	73	76	80	30	8	42	Involuntary movement	-7.89	Faster
7	Male	30	31	90	50	12	55	Involuntary movement	-3.92	Slower
8	Male	63	65	85	40	11	40	Involuntary movement	-5.44	Faster
9	Male	47	50	90	70	4	43	Involuntary movement	-7.50	Faster
10	Female	50	52	80	30	7	36	Involuntary movement	-7.15	Faster
11	Female	50	52	95	90	3	41	Involuntary movement	-3.33	Slower
12	Female	37	37	95	80	5	44	Involuntary movement	-4.00	Slower
13	Male	40	43	90	90	3	55	Involuntary movement	-3.33	Slower

Seven patients were assigned to the slower-progression group and six to the faster-progression group.
Duration: disease duration (years) at the time of follow-up, FDG-PET: fluorodeoxyglucose positron emission tomography, f/u: follow-up, IS: score of independence scale of the Unified Huntington's Disease Rating Scale, IS-PET: IS at the time of the FDG-PET scan, PR: progression rate (see main text), TNR: number of trinucleotide repeats.

Table 2. Comparison of regional metabolism among the faster-and slower-progression HD groups and the normal-controls group

	Patients		Controls	p^*	$p^\dagger$	$p^\ddagger$	$p^\S$
	Faster progression	Slower progression					
	n=6	*n*=7	*n*=11				
R frontal	0.98	1.13	1.28	0.001	0.022	0.002	0.016
L frontal	0.95	1.10	1.26	0.002	0.032	0.004	0.010
R temporal	0.92	1.02	1.28	0.014	0.032	0.012	0.135
L temporal	0.92	0.99	1.10	0.016	0.063	0.016	0.063
R parietal	1.00	1.11	1.28	0.003	0.032	0.005	0.021
L parietal	0.92	1.05	1.22	0.001	0.032	0.002	0.006
R occipital	1.11	1.25	1.21	0.190	0.086	0.191	0.441
L occipital	1.10	1.24	1.21	0.220	0.086	0.159	0.964
R thalamus	1.40	1.48	1.46	0.424	0.475	0.159	0.821
L thalamus	1.43	1.49	1.50	0.691	0.886	0.315	0.684
R caudate	0.33	0.52	1.42	<0.001	0.032	<0.001	<0.001
L caudate	0.32	0.50	0.14	<0.001	0.086	<0.001	<0.001

Numeric value for regions in each group is mean regional/cerebellar region-of-interest ratio.
*Kruskal-Wallis test among faster-progression patients, slower-progression patients, and controls, †,‡,§Mann-Whitney test for comparisons between faster- and slower-progression patients (†), faster-progression patients and controls (‡), and slower patients-progression and controls (§); *p* values <0.05 were considered statistically significant.
L: left, R: right.

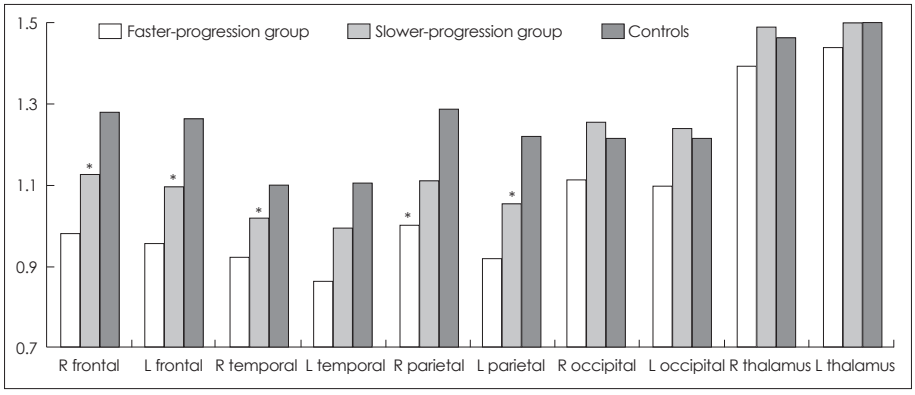

Fig. 1. Comparison of the FDG-PET regional cerebral/cerebellar region-of-interest ratio among faster- and slower-progression Huntington's disease (HD) groups and age- and sex-matched controls. The decreases in metabolism in the bilateral frontal, parietal cortices, and right temporal cortex were significantly greater in the faster-progression group than in the slower-progression group. The metabolism in the occipital cortices and thalami did not differ between the two HD groups. Data are not shown for the bilateral caudate nuclei because of severe decreases in both patient groups. *A statistically significant difference among the groups (p<0.05).

tations. Alterations in the striatal volume and a decrease in D2 receptor or glucose metabolism in the preclinical stage of HD have been reported, indicating the usefulness of brain imaging techniques for monitoring;[5,7,14,16-18] however, these methods do not provide information about progression after disease onset. Our data showed that glucose metabolism in the caudate nuclei was decreased in 13 HD patients who underwent FDG-PET regardless of PR. In other words, changes in striatal metabolism are not useful for monitoring the progression pattern after disease onset.

While striatal degeneration is the main pathology of HD, widespread cortical changes also occur in the early stages of this disease.[19,20] Previous FDG-PET studies have found decreases in both cortical and neostriatum metabolism, suggesting that cognitive dysfunction in HD does not have an exclusively subcortical origin, and making it possible to explain the various phenotypes of HD.[10,11] It was previously reported that altered cortical metabolism in the frontotemporal lobe was present at the preclinical stage, suggesting that cortical dysfunction begins before symptom onset.[21] However, the relationship between cortical metabolism and HD progression has not previously been investigated.

The present study applied FDG-PET to early-stage HD patients who had an IS score of more than 80 (indicating no problems performing the normal ADL). Widespread cortical hypometabolism (except in the occipital cortex) was observed in these patients. Additionally, the cortical metabolism in the frontotemporal and parietal cortices was significantly lower

in the faster-progression group than in the slower-progression group. Considering that functional deficits and disease duration did not differ significantly between these two groups, we postulate that decreased cortical metabolism in the early stage of HD is indicative of rapid progression. Our findings suggest that altered brain metabolism as assessed by FDG-PET can be used to predict disease progression. To confirm this hypothesis, additional prospective studies involving large numbers of subjects are required.

Our study was subject to several limitations. First, the small number of subjects reduced the statistical power. Second, the retrospective design of the study limited the available clinical information (e.g., neuropsychological function test). Third, since there is no unified scale for the clinical progression of HD, we arbitrarily used the decline in the IS score of the Unified Huntington's Disease Rating Scale as a marker of PR because this score most likely reflects the ability to perform the ADL in HD. A unified progression scale of HD will need to be evaluated in future studies. Lastly, the partial volume effect of PET analysis was problematic. Diffuse cortical atrophy accompanied by HD progression and hypometabolism in the faster-progression group might have originated from the greater severity of cortical atrophy. This problem could be resolved by structural imaging using magnetic resonance imaging in a future study. Furthermore, we used segmental ROI analysis because of easy accessibility, but more elaborate results may be expected using other image analytic methods such as statistical parametric mapping.

In conclusion, the results of this study suggest that the decrease in cortical metabolism in HD can be used to predict the PR. More HD patients should be tested to replicate our observation that the cortical metabolism can be used as a biological marker for HD progression.

Conflicts of Interest

The authors have no financial conflicts of interest.

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