pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(1):87-89 / https://doi.org/10.3988/jcn.2022.18.1.87

Huntington's Disease Presenting as Adult-Onset Parkinsonism

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Dear Editor,

Huntington's disease (HD) is archetypally characterized as progressive cognitive decline, psychiatric disturbance, and involuntary movements.[1-7] Chorea is the most common movement feature, appearing in over 90% of HD patients.[3] These symptoms usually start between 30 and 40 years of age, with this variation in the onset age being influenced by the cytosine-adenine-guanine (CAG) repeat expansion length.[2-4] The Westphal variant of HD that presents as a distinct clinical entity characterized by parkinsonism is prevalent in juvenile-onset HD and has longer CAG expansions than the typical choreic form of adult-onset HD.[1-3,7] Therefore, a sole manifestation with parkinsonism in adult-onset HD is rare.[1,2,6,8] Previous studies have found that the Westphal variant accounts for 85% of cases of juvenile-onset HD, whereas only 6%−9% of patients with adult-onset HD have initial manifestations of parkinsonism.[3,5,6] Here we report the clinical assessment and course of an adult patient with HD who presented as young-onset parkinsonism with a diffuse presynaptic dopaminergic deficit and showed early responsiveness to levodopa.

A 34-year-old male developed progressive bradykinesia and gait disturbance over 4 months. He had no underlying medical problems or medication use, but there was a 10-year history of vivid dream and dream enactment behaviors. He was an only child and had no definite family history on his mother's side. The findings of a neurological examination of his mother were normal. His father died in his 40s after suffering from progressive motor deterioration with psychiatric problems following a traffic collision. No reliable family history was obtained from his father or other relatives because he had not had contact with them since he was a child.

A neurological examination of the patient revealed generalized symmetric parkinsonism including masked face, bradykinesia, rigidity, and postural instability (Supplementary Video 1 in the online-only Data Supplement). His speech was mildly dysarthric, and deep tendon reflexes were increased. He had a score of 36 on the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale, and was at stage 3 on the Hoehn and Yahr scale. Administering levodopa at 200 mg daily provided symptomatic improvement, and his UPDRS motor score reduced to 26.

Possible causes of young-onset parkinsonism were evaluated based on these findings. Brain magnetic resonance imaging (MRI) using various imaging sequences did not reveal any signal abnormality other than brain atrophy (Fig. 1A-H). ^{18}F-FP-CIT positron-emission tomography (PET) for presynaptic dopamine transporter imaging revealed symmetric decreased uptake in the bilateral striatum including caudate and putamen overall compared with a healthy control (Fig. 1I-L). Considering the unclear family history, gene tests were performed for spinocerebellar ataxia 2 and *PARK2*, and the findings for both were normal.

However, unlike for cognition, the scores on the Mini Mental State Examination and Montreal Cognitive Assessment were unexpectedly low at 23 and 22. MRI showed mild diffuse cortical atrophy and caudate atrophy (Fig. 1A-H). An examination of his eye movement revealed delayed saccadic initiation without any gaze limitation. Based on these findings, ge-

Received August 19, 2021
Revised November 2, 2021
Accepted November 2, 2021

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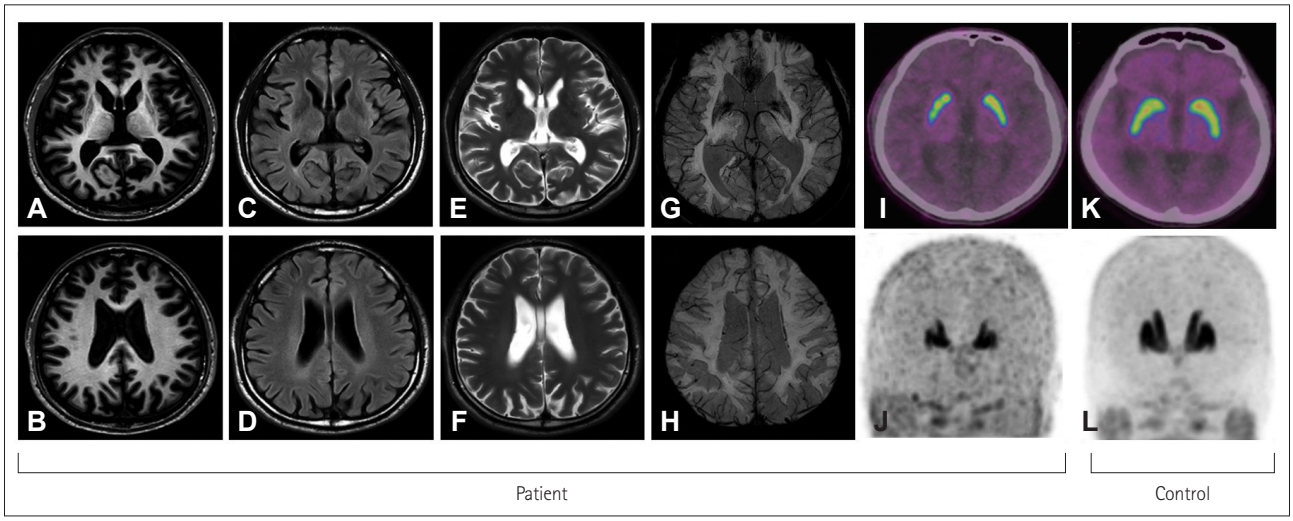

Fig. 1. Representative brain magnetic resonance imaging (MRI) and presynaptic dopamine transporter image. Axial T1-weighted (A, B), fluid-attenuated inversion recovery (C, D), T2-weighted (E, F) and susceptibility-weighted imaging (G, H) MRI did not reveal any abnormal signal intensities. However, diffuse brain atrophy, an enlarged ventricle, and marked atrophy of the caudate and putamen were observed. ^{18}F-FP-CIT axial and three-dimensional PET images showed diffuse decreased tracer uptake in the bilateral striatum (I, J) compared with a healthy control (K, L).

netic analysis for HD was done, which demonstrated heterozygous expansion of 50 CAG repeats on the Huntingtin gene. Finally, he was diagnosed with HD.

Over a 3-year follow-up, the levodopa dosage was increased from 200 mg to 600 mg daily. Even though he exhibited good drug compliance, his parkinsonism slowly progressed up to a recent follow-up. The last measured UPDRS motor score was 57, at which time he did not present wearing off or any choreic movement.

This case was an adult patient with HD in the fourth decade of life who presented with generalized parkinsonism and showed only a short-lasting and modest response to levodopa. Parkinsonism in HD is often observed even in adult HD patients, but the initial presentation of parkinsonism without chorea usually occurs at younger than 20 years, which is called the Westphal variant.[1-4,6,7] The present patient demonstrates that pure parkinsonism without any choreic movement can present even in a mature adult status. In addition, preexisting rapid eye movement sleep behavior disorder-like phenotype and levodopa responsiveness can masquerade as young-onset Parkinson's disease (PD). However, unlike PD, this patient showed symmetric akinetic rigidity with early postural instability. Moreover, the presynaptic dopaminergic neuronal density in the striatum was diffusely and symmetrically decreased in the caudate and putamen, which differs markedly from PD showing dorsal-to-ventral and posterior-to-anterior gradients of striatal denervation. In addition, delayed saccadic initiation and subclinical cognitive dysfunction gave diagnostic clues for HD.[9] Targeted panel sequencing and whole-exome sequencing are now popular, but because these tests might miss triplet repeats, suspicion of HD is important.

Neuropathologically, HD is primarily characterized by neuronal loss in the striatum and cortex.[1,2,4] Previous studies of classic HD have shown that chorea results from the early loss of indirect-pathway medium-sized spiny neurons (MSNs), and parkinsonism is a consequence of the additional dysfunction and the loss of direct-pathway MSNs.[4,6] However, in patients with akinetic-rigid HD, a near-total loss of both indirect and direct striatopallidal fibers have been reported rather than the selective depletion of the indirect pathway.[6] In addition, there is evidence from PET studies that the integrity of presynaptic and postsynaptic dopaminergic neurons is markedly reduced in HD.[10] The presynaptic dopaminergic denervation was found to be more pronounced in the subgroup of the akinetic-rigid phenotype compared with the choreiform phenotype, which may explain the partial levodopa responsiveness.[10] Progressive damage of presynaptic and postsynaptic nigrostriatal pathways may explain the lack of a response to levodopa in the present case.[1]

Supplementary Video Legend

Video 1. The patient showed action and postural tremor, and dystonic posturing in both hands. Generalized bradykinesia, stooped posture, and reduced arm swing, and delayed saccadic initiation are observed in this video.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.1.87.

Ethics Statement

We declare that the patient signed the consent form for publication both in print and online. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. This case study was approved by the Hallym University Sacred Heart Hospital Institutional Review Board/Ethnics Committee (IRB No 2021-04-016).

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (2020R1F1A1076697).

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