



A Rare Patient with Hereditary Spastic Paraparesis with Parkinsonism

Halil Onder¹ Selcuk Comoglu¹

¹Neurology Clinic, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

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Address for correspondence Halil Onder, MD, Neurology Clinic, Diskapi Yildirim Beyazit Training and Research Hospital, Şehit Ömer Halisdemir Street. No: 20 Altındag 06110, Ankara (e-mail: halilOnder@yahoo.com).

Abstract

Keywords

- hereditary spastic paraplegia
- parkinsonism
- DatSCAN
- pyramidal syndromes
- diagnosis

Herein, we present a rare patient with hereditary spastic paraparesis (HSP) in whom significant parkinsonism was involved in the clinic. Besides, the dopamine transport single-photon emission computed tomography scan also showed decreased tracer uptake in the bilateral striatum. Via the presentation of this patient, we discuss the parkinsonian findings in patients with HSP. We think that the observations of dopaminergic neuron vulnerability in HSP patients raise the possibility that degeneration of central dopaminergic neurons may contribute to the phenotype of HSP. The documentation of these rare variants will aid to understand the unknown pathophysiology of the disease course.

Key Messages

Parkinsonian signs may be an accompanying feature in patients with hereditary spastic paraparesis (HSP). Dopaminergic neuron vulnerability in HSP patients raises the possibility that degeneration of central dopaminergic neurons may contribute to the phenotype of HSP.

Introduction

A 69-year-old male patient presented with progressive gait disturbance that had emerged over the last 6 years. The patient stated that he felt stiffness in his feet and suffered from slowness particularly in his lower extremities. One year after the onset of these symptoms, the patient had applied to another neurology clinic where the lower extremity spasticity was noted. However, 2 years later, levodopa was initiated for newly developing parkinsonian signs that had provided a marked improvement in his gait. At follow-up, his gait gradually deteriorated, and levodopa-induced dyskinesia had also emerged the last year. Further interrogation revealed that the

patient suffered from constipation for a long time and symptoms of rapid eye movement sleep behavior disorder for the last few years. He had no symptoms such as dizziness, erectile dysfunction, or gastroparesis, related to autonomic dysfunction. At admission to our clinic, the patient was on treatments of levodopa/benserazide (4×125 mg), amantadine 100 mg, ropinirole 0.375 mg, and levodopa/carbidopa 50/200 mg. He stated a benefit from levodopa lasting for 3 hours; however, he suffered from severe “off” periods before levodopa dosage. Besides, severe, disabling dyskinesias were observed during medication “on” period. His parents were nonconsanguineous and the family history was unremarkable. The patient was orientated and cooperative. During the interview, the patient’s communication and mental status were evaluated to be within normal limits. His speech was compatible with spastic dysarthria and palatal reflexes were bilaterally increased. The sensory, cerebellar tests and motor examinations were within normal limits. However, the deep tendon reflexes were increased, and severe lower extremity spasticity was observed. Confirming the pyramidal tract dysfunction, bilateral Babinski

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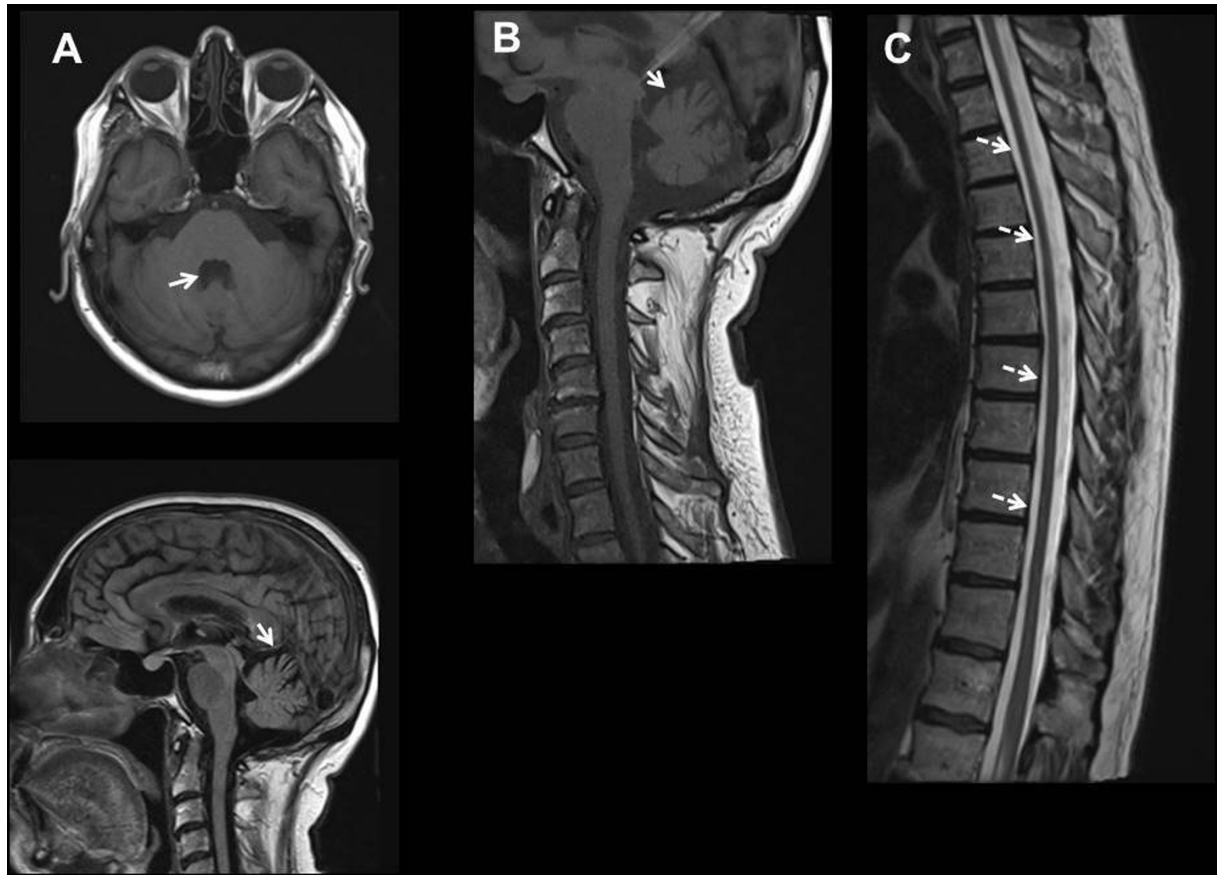


Fig. 1 The cranial magnetic resonance imaging shows mild cerebellar atrophy and enlargement of the fourth ventricle (A–B). The spinal cord atrophy is also observed that is prominent in the thoracic spinal cord (C) (arrows).

sign and clonus reflexes were also positive. Extrapyramidal examinations showed bilateral bradykinesia, rigidity, and bradykinesia. Besides, postural instability was apparent (► **Supplementary Videos 1 and 2**). The results of the laboratory investigations including hemogram, routine serum biochemistry and serum levels of vitamins B12 and E, homocysteine, ceruloplasmin, venereal disease research laboratory, human immunodeficiency virus, and human T-lymphotropic virus were unremarkable. The cranial magnetic resonance imaging (MRI) showed mild atrophy of the cerebellum. Spinal MRI showed longitudinal spinal cord atrophy that was prominent in the cervical and thoracic spine (► **Fig. 1**). Nerve conduction study and needle electromyography (including various muscles innervated by distinct symptoms in both upper and lower extremities) revealed normal findings. Motor evoked potential responses, recorded bilaterally from the abductor digiti minimi, were found to be delayed. We have excluded the structural, inflammatory, and infectious causes, in addition to amyotrophic or primary lateral sclerosis, arteriovenous fistulas that might explain the clinical manifestations. Taken together, the clinical diagnosis of complicated HSP was established. Due to the atypical presentation of pyramidal signs, the dopamine transport single-photon emission computed tomography scan (DatSCAN) was also performed that showed decreased tracer uptake in the bilateral striatum, more significant in the putamen.

However, the next-generation sequencing-based HSP gene panels and whole-exome sequencing results were unremarkable. The amantadine dosage was increased to 300 mg daily that provided marked improvement in “on” period dyskinesia.

HSP is diagnosed after a thorough clinical examination and the identification of typical symptoms.¹ However, to confirm a molecular diagnosis of HSP, the identification of pathogenic mutations in a spastic paraplegia (SPG)-designated gene is required. On the other hand, despite the use of next-generation sequencing-based HSP gene panels or whole-exome sequencing, a genetic diagnosis cannot be made in 51 to 71% of all suspected cases of HSP.¹ In our patient, the genetic diagnosis was also lacking that was the main limitation of the report. However, the clinical presentation and delayed motor evoked potential responses and the laboratory data excluding the secondary causes led to the clinical diagnosis of HSP. Recent reports emphasized that patients with complicated HSP display widespread degenerative pathologies in the cerebellum, cerebral cortex, thalamus, and brainstem.² However, parkinsonism is uncommon in HSP, and the related literature data is limited.^{3–5} Therefore, the clinical manifestation of parkinsonism in our patient including severe on and off periods in the early course of the disease and the DatSCAN results showing decreased tracer uptake in the bilateral striatum is quite valuable. In a crucial study, Kim et al investigated nine HSP patient with (^{99m}Tc)

TRODAT-1 single-photon emission computed tomography and found reduced striatal ligand uptake in images of four of the patients.⁵ In a remarkable study using the *Drosophila* model of HSP,⁶ the DatSCAN with ¹²³I-ioflupane revealed that patients with the SPG11 mutation and parkinsonism exhibited abnormal DAT binding potential. A study on 35 patients with HSP demonstrated that 21% ($n=7$) of the patients had parkinsonian signs.³ DatSCAN was performed in three of these patients that showed bilateral presynaptic denervation in one patient, mild unilateral denervation in another subject, and normal findings in the third patient.³ In our patient, levodopa-induced dyskinesia had emerged in the early period of the disease. The occurrence of dyskinesia in the early period suggests severe striatal dopaminergic neuron damage and possible increased gamma-aminobutyric acid (GABA) (A) receptors content in the internal globus pallidus that was shown to exist in postmortem samples from levodopa-treated parkinsonian patients.⁷ A comorbid idiopathic Parkinson disease (PD) is a crucial possibility that needs to be excluded. However, the clinical manifestations of extrapyramidal signs were bilateral, tremor was not present, and the emergence of the levodopa-induced dyskinesia was at the very early period of the clinic, which was discordant for idiopathic PD. Besides, presynaptic dopaminergic denervation was also symmetrical in contrast with the findings in idiopathic PD.

The observations of dopaminergic neuron vulnerability in HSP patients raise the possibility that degeneration of central dopaminergic neurons may contribute to the phenotype of HSP. The documentation of these rare variants will aid to

understand the unknown pathophysiology of the disease course. The results of these reports may also suggest alternative classification methods, such as parkinsonian-pyramidal syndromes.⁴ These study results may also change the clinical evaluation processes of some subgroups of patients with pyramidal syndromes and atypical scenarios.

Conflict of Interest

None declared.

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