

LETTER TO THE EDITOR

A Rare Case of Late Adult-Onset Niemann-Pick Disease Type C

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Dear Editor,

Niemann-Pick disease type C (NPC) is an autosomal recessive neurodegenerative disorder caused by mutation of either NPC1 (> 95% of cases) or NPC2.^{1,2} Mutations in these genes lead to massive accumulation of cholesterol and glycosphingolipids within late endosomes and lysosomes.¹ NPC is characterized by heterogeneity in age at onset, which is related to variance in clinical presentation and progression.² Patients with NPC are classified into 5 subgroups on the basis of age at onset: pre/perinatal (< 2 months), early-infantile (2 months to 2 years), late-infantile (2 years to < 6 years), juvenile (6 years to 15 years), and adolescent/adult (> 15 years).^{1,2}

Adult-onset NPC shows a wide spectrum of neurological symptoms such as vertical supranuclear gaze palsy (VSGP), ataxia, dystonia, cognitive decline and psychosis, and less commonly visceral involvement.³ In clinical practice, adult-onset NPC is easily misdiagnosed or neglected due to rarity and clinical heterogeneity of this condition.⁴ In particular, late adult-onset NPC is very rare, and thus its clinical characteristics remain unclear.² Early diagnosis of NPC is important because treatment with miglustat has been shown to stabilize disease progression.² Herein, we present a patient with late adult-onset NPC who had onset of symptoms at 57 years of age.

A 63-year-old man visited Seoul National University Hospital due to his slowly progressive gait disturbance and difficulties with speech and swallowing that began 6 years ago. He also presented with a one-year history of cognitive decline. The patient had no history of previous neurological and psychiatric disor-

ders. There was no relevant family history. On neurologic examination, he showed vertical gaze limitations that were more pronounced in downgaze (Supplementary Video 1 in the online-only Data Supplement). There were no definite features suggestive of parkinsonism. The finger-to-nose test and heel-to-shin test showed dysmetria. He showed a mild wide-based gait with postural instability in turning (Supplementary Video 1 in the online-only Data Supplement). Tandem gait was impaired. The scores on the Mini-Mental State Examination, Montreal Cognitive Assessment, and Frontal Assessment Battery were 25, 24, and 13, respectively. Abdominal examination did not reveal any visceromegaly, which was confirmed by abdominal ultrasound. His clinical symptoms suggested the possibility of NPC or progressive supranuclear palsy with predominant cerebellar ataxia (PSP-C). The NPC suspicion index score⁴ was 100, indicating its high probability. Brain magnetic resonance imaging showed diffuse brain atrophy (Figure 1A-C). There were no abnormalities in ¹⁸F-FP-CIT positron emission tomography (Figure 1D). Ataxia gene panel testing showed that NPC was positive for 2 pathogenic variants (p.A518T and p.A1059G) of the NPC1 gene.⁵ The other genetic tests were all negative (Supplementary Table 1 in the online-only Data Supplement).

Our patient represents a unique case of NPC developing clinical symptoms at 57 years of age. Clinical features of this patient strongly suggest NPC. The genetic testing was also compatible with the recently proposed diagnostic criteria for NPC in which the diagnosis can be confirmed by the identification of two known or likely pathogenic alleles.¹ Although PSP-C should

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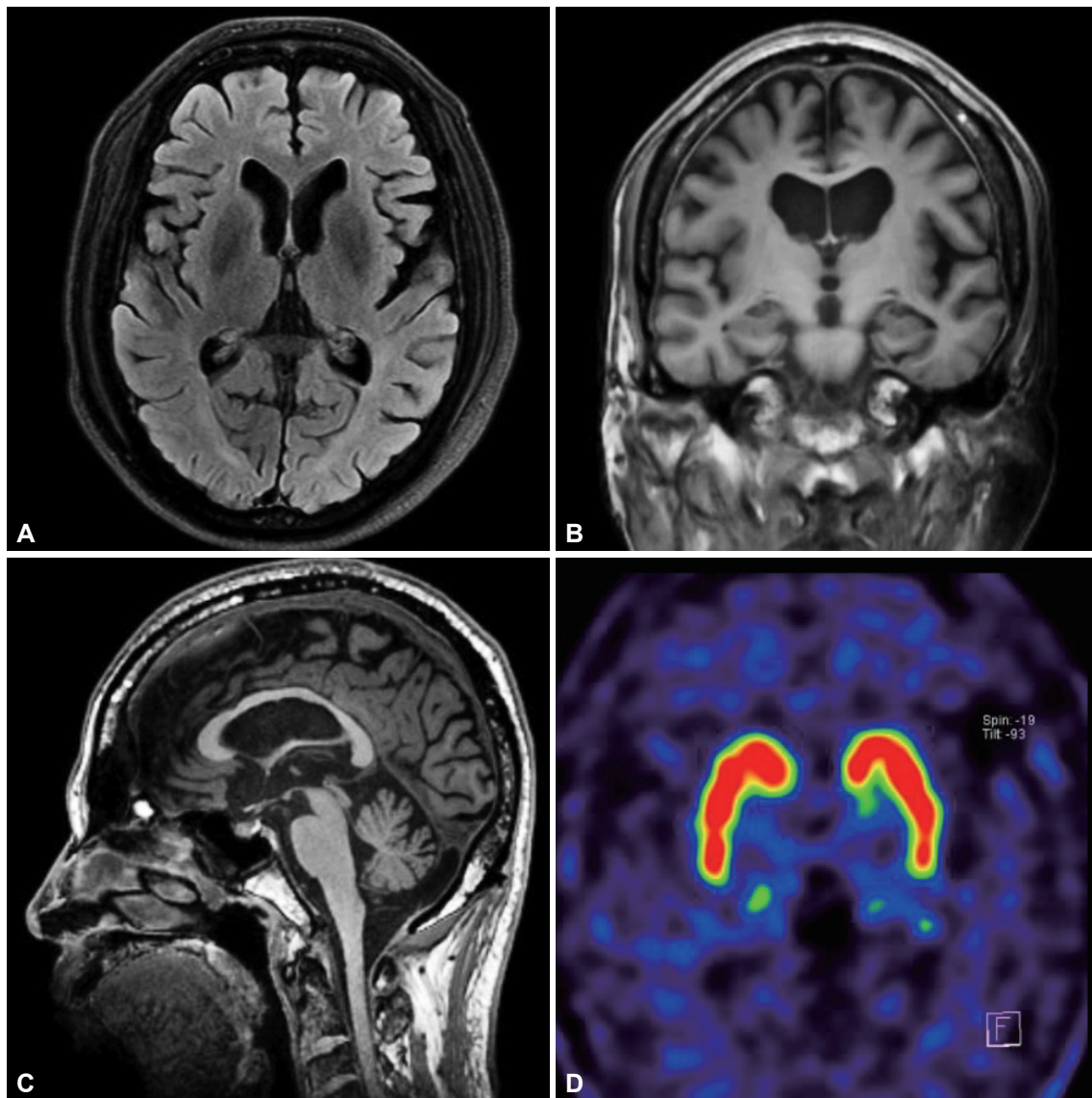


Figure 1. Neuroimaging findings. Brain magnetic resonance imaging reveals diffuse cortical atrophy on an axial fluid-attenuated inversion recovery image (A) and a coronal T1-weighted image (B) and midbrain and cerebellar atrophy on a sagittal T1-weighted image (C). ^{18}F -FP-CIT positron emission tomography shows normal presynaptic uptake (D).

have been considered in this case, the patient showed preserved dopamine transporter uptake. Furthermore, despite 6 years of disease duration, his symptoms were relatively mild. These findings suggest that the patient is less likely to have PSP-C. In Korea, Lee et al.⁶ first described two siblings diagnosed with adolescent/adult-onset NPC in their mid-20s. We believe that this is the second case report of adolescent/adult-onset NPC and the first case report of late adult-onset NPC in Korea.

A large international prospective registry including 163 NPC patients showed that adolescent/adult-onset accounted for 27% of the patients.⁷ In that study, the mean age (standard deviation) of symptom onset in adolescent/adult-onset group was 29.7 (10.0) years, implying that individuals with adolescent/adult-onset

NPC mainly develop initial symptoms during the third or fourth decade. However, NPC can present in the sixth decade, although it is extremely rare.² To the best of our knowledge, the onset of symptoms in our patient is only the second case reported with symptom onset at 59 years of age.³

In adult-onset NPC, diagnostic delay is common and often 5 years or more, as seen in our case. This delay may be minimized when VSGP is identified. Although VSGP can be observed in other neurological disorders, it is one of the earliest signs in NPC. VSGP is present in approximately 70–80% of the patients across all age at onset categories,² which suggests that clinicians should consider NPC in the differential diagnosis of VSGP, regardless of age at onset. However, despite the diagnostic utility

of VSGP, it may not be present when the patients are examined early in the disease course.¹ Thus, the absence of VSGP cannot rule out the diagnosis of NPC, and eye movements need to be checked regularly in patients with suspected NPC, but without VSGP.

Supplementary Video Legend

Video 1. The first part (1–23 seconds) shows reduced vertical gaze that was more pronounced in downgaze. The second part (24–36 seconds) shows a mild wide-based gait with postural instability in turning, but his arm swing and walking speed were preserved. The last part (37 onwards) shows impaired tandem gait.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.14802/jmd.19077>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Ryul Kim and Beomseok Jeon. Data curation: Ryul Kim and Dallah Yoo. Supervision: Beomseok Jeon. Visualization: Ryul Kim. Writing—original draft: Ryul Kim. Writing—review & editing: Dallah Yoo, Sangmin Park, Jung Hwan Shin, Ji-Hyun Choi, Han-Joon Kim, and Beomseok Jeon.

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