



A Male Patient Showing Abnormal Gait and Dysarthria with Psychotic Symptoms

Anormal Yürüyüş ve Psikotik Semptomlarla Birlikte Dizartri ile Prezente Bir Erkek Hasta

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Abstract

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal-recessive and neurodegenerative disorder associated with progressive motor impairment and mental deterioration. The diagnosis of PKAN consists of clinical features and magnetic resonance imaging (MRI) evidence of iron accumulation in the brain, as well as evidence of mutations in the *pantothenate kinase 2 (PANK2)* gene. Typical clinical features of PKAN are motor symptoms including dystonia, involuntary movement, rigidity and dysarthria, as well as psychiatric symptoms such as anxiety, depression, and mental retardation. However, psychosis has not been reported often in cases of PKAN. This patient presented with anxiety, a tendency to startle easily, and rapidly deteriorating memory impairment. T2-weighted MRI of his brain indicated a specific pattern of hyperintensity within a hypointense medial globus pallidus with a mutation in the gene encoding *PANK2*. Components of the basal ganglia, including the globus pallidus, play a key role in motor symptoms, cognition, affect, and mood. The basal ganglia are also a central factor in the pathogenesis of psychiatric symptoms in schizophrenia. These lesions are able to aggravate various psychotic symptoms, cognitive function impairments, and mood disorders because PKAN is affected by abnormal iron deposition in the globus pallidus and substantia nigra pars reticulata.

Keywords: Pantothenate kinase-associated neurodegeneration, psychosis, neurodegenerative diseases

Öz

Pantotenat kinaz ile ilişkili nörodejenerasyon (PKAN), progresif motor bozukluk ve zihinsel bozulma ile ilişkili nadir bir otozomal resesif ve nörodejeneratif bozukluktur. PKAN tanısı, klinik bulgular ve beyindeki demir birikiminin manyetik rezonans görüntüleme (MRG) ile gösterilmesinin yanı sıra *pantotenat kinaz 2 (PANK2)* genindeki mutasyonların gösterilmesi ile konur. PKAN'nin tipik klinik özellikleri distoni, istemsiz hareketler, rijidite ve dizartri gibi motor semptomların yanı sıra anksiyete, depresyon ve zihinsel gerilik gibi psikiyatrik semptomlardır. Bununla birlikte, PKAN'li hastalarda psikoz sıklıkla bildirilmemiştir. Bildirdiğimiz hasta, anksiyete, kolayca irkilme eğilimi ve hızla ilerleyen hafıza bozukluğu ile başvurdu. Beyninin T2 ağırlıklı MRG'sinde spesifik bir bulgu olarak hipointens medial globus pallidus içinde hiperintens bir görünüm saptandı ve hastada *PANK2*yi kodlayan gende mutasyon tespit edildi. Globus pallidus da dahil olmak üzere bazal gangliyonların bileşenleri, motor semptomlar, biliş, duygulanım ve duygudurum üzerinde anahtar bir rol oynar. PKAN'de görülen globus pallidus ve substantia nigra pars retikulatadaki anormal demir birikimi çeşitli psikotik semptomları, bilişsel işlev bozukluklarını ve duygudurum bozukluklarını şiddetlendirebilir.

Anahtar Kelimeler: Pantotenat kinaza bağlı nörodejenerasyon, psikoz, nörodejeneratif hastalıklar

Introduction

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive condition involving neurodegeneration and iron accumulation in the brain. PKAN falls under the following categories: genetic disorder of iron and

other pigment metabolism, neuroaxonal dystrophy, vitamin E deficiency, and ceroid storage disease (1). PKAN is also the most prevalent form of neurodegeneration with brain iron accumulation. These are a wide range of disorders with markedly excessive regional brain iron deposition, particularly in the

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cerebellar dentate nuclei as well as regions of the basal ganglia including globus pallidus, substantia nigra pars reticulata, and striatum (2,3,4). PKAN is caused by mutations in the gene that encodes mitochondrial *pantothenate kinase 2* (*PANK2*), which is a rate-determining enzyme in coenzyme A (CoA) biosynthesis (5,6,7).

PKAN is characterized by the early onset of progressive movement alterations, including dystonia, rigidity, and choreoathetosis. Patients with PKAN may also present with a variety of psychiatric symptoms, primarily depression and mental deterioration (8). Additionally, magnetic resonance imaging (MRI) of patients with PKAN typically reveals the “eye of the tiger” sign (9). However, the diagnosis of PKAN is ultimately made through molecular genetic testing (8,10).

Typically, patients with PKAN present in the first decade of life with dystonia, dysarthria, rigidity, and pigmentary retinal degeneration (3,11). Atypical cases of PKAN do not present until the second or third decade of life and progress more slowly than typical cases (3).

Case Report

Clinical History, Neurologic Examination, and Laboratory Findings

A 35-year-old Korean male had abdominal pain and abnormal posture of the trunk and lower extremities. He additionally complained of difficulty in walking and had demonstrated an ataxic and spastic gait since November 2015. He had four half-brothers with whom he shared a father. His mother's pregnancy and delivery of him were normal. His medical history was significant for hepatitis A viral infection. Speech problems were noted when he was a high school student and he showed poor academic performance despite regular school attendance. He was otherwise healthy until the age of 32 when he began to demonstrate difficulty maintaining balance while walking and abnormal posturing of the trunk, where he arched backwards. However, all abnormal movements disappeared while he was sleeping. He additionally exhibited dysarthria, anxiety, symptoms of social withdrawal, and depression.

His physical examination revealed a young male of average build. There was no detectable rigidity in any of the four extremities and normal tendon reflexes were present. The extensor plantar reflex was present bilaterally. Furthermore, he exhibited dystonic posturing of the lower extremities, trunk, and neck. No tremor or choreoathetotic movements were seen. His fundus examination, as well as his neurologic and other systemic examinations, were unremarkable. Routine laboratory evaluations were normal: his serum ceruloplasmin level was 24 mg/dl (normal: 15-30 µg/dl), his 24-hour urinary copper excretion was 10 µg/day (normal: under 38-70 µg/day), his serum copper level was 105 µg/dl (normal: 64-134 µg/dl), and his peripheral blood films revealed no acanthocytes.

Neuroradiologic, Neuropsychological, and Genetic Test Findings

He was evaluated using (¹⁸F) (3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane positron emission tomography (FP-CIT PET), (¹⁸F) fludeoxyglucose (FDG) PET, brain 1.5 T MRI, as well as neuropsychological tests. MR imaging

revealed a prominent T2 dark signal intensity in the internal capsule bilaterally and definite hyperintense changes of the anterior medial portion of both globus pallidi. There were also focal encephalomalacic changes in each frontal lobe base (Figures 1, 2a, 2b, 2c, 3a, 3b, 3c).

(¹⁸F) FP-CIT PET showed symmetric and even striatal dopamine transporter binding. Visual inspection of the (¹⁸F) FDG-PET images indicated no significant hyper- or hypometabolic activity in the brain (Figures 4a, 4b, 5a, 5b, 5c). Statistical parametric mapping revealed definite hypometabolic areas in the putamen, caudate nucleus, and frontal gyrus ($p < 0.05$, FDR corrected, 100-voxel level, one sample t-test) (Figure 6a, 6b, 6c).

His mini-mental state exam score was 26 out of 30 and he was oriented to time, place and person with alertness; however, his immediate memory was below normal and word fluency, as well as inhibitory control ability, were abnormal in the addenbrookes cognitive examination. Also, confrontational naming problems and dyscalculia were shown but these did not significantly influence his ability to perform activities of daily living. His Korean-Beck Depression score was 23 out of 63, suggestive of significant depression.

Genetic testing identified two mutations (Glu 180 Gly and Asp378 Gly) involving exons 1 and 3 in his *PANK2* gene (Figure 7). These locations were the first mutations shown in this gene. Specifically, there were two alterations-c.539-561del and 1133A>G-in exon 1 and 3 of the cDNA sequence. These alterations resulted in a loss of the gene's functional properties by changing one amino acid.

Informed consent was obtained in writing from the patient's family for the publication of this case report.

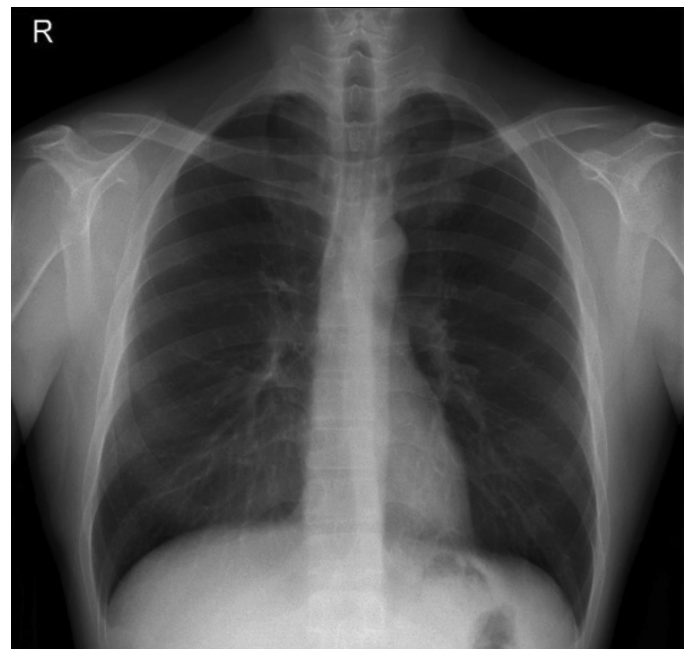


Figure 1. Non-specific findings in chest X-ray

Discussion

Pantothenate kinase is an essential regulatory enzyme in CoA biosynthesis from pantothenate (vitamin B5); as such, pantothenate kinase facilitates the effectiveness of CoA as a central factor in intermediary and fatty acid metabolism. In PKAN, a deficiency of *PANK2* is thought to result in mitochondrial accumulation of cysteine and cysteine-containing substrates, leading to rapid auto-oxidation in the presence of iron. This would result in free radical production and lipid peroxidation, and ultimately cell death. This male patient showed two mutations [c. (539-561del); (1133A>G)] [p. (Glu180Glyfs*42); (Asp378Gly)] from gene analysis for *PANK2* and his brain MRI demonstrated bilateral hyperintensity within a region of hypointensity in the medial globus pallidus

on T2-weighted and fluid attenuation inversion recovery images, named the “eye of the tiger” pattern. One of the mutations, c. (539-561del), might have been found for the first time in a Korean patient who was diagnosed as having *PANK2*. Homozygous, heterozygous, and compound heterozygous mutations in *PANK2* have been previously identified, including deletions, insertions, nonsense, and missense mutations. *PANK2* mutations in this patient generally resulted in premature protein termination. If we could perform genetic testing of his paternal relatives, it might allow us to understand the genetic origin of his disease.

Young-onset involuntary movements such as spinal myoclonus and multifocal dystonia, dysarthria and decreased intelligence, as well as psychotic symptoms, may lead us to investigate genetic movement disorders such as Wilson’s disease or PKAN.

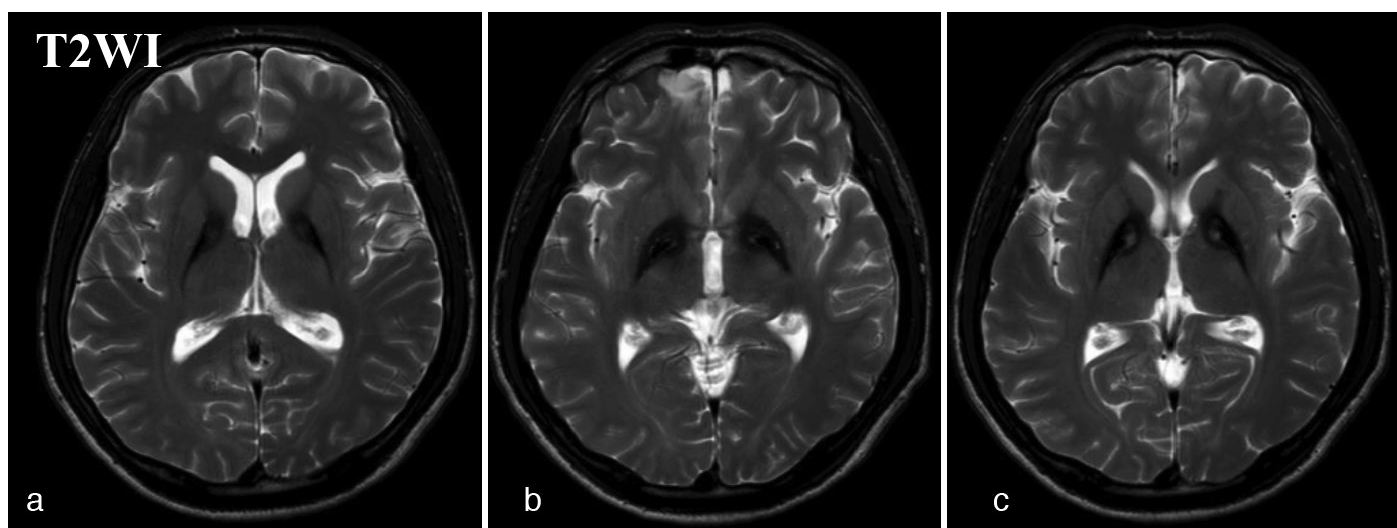


Figure 2. a, b, c) MR images depicted prominent T2 dark signal intensities in both internal capsules and definite hyperintensities in the anterior medial portion of both globus pallidi

MR: Magnetic resonance

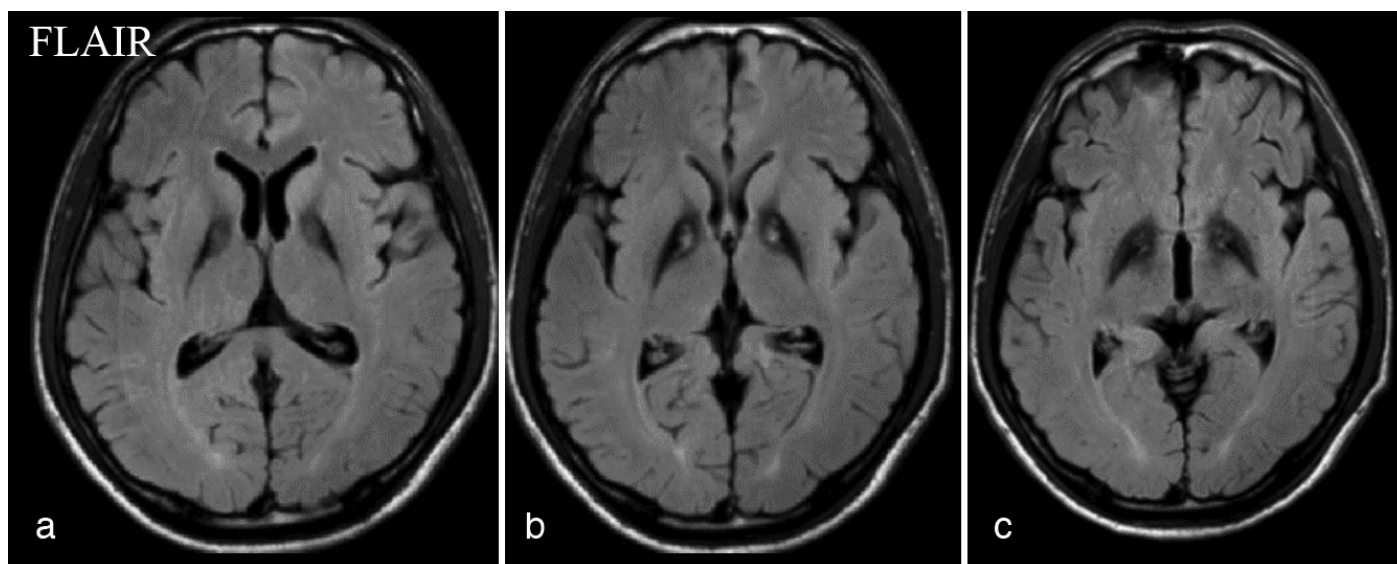


Figure 3. a, b, c) FLAIR MR images revealed dark signal intensities in both internal capsules and definite hyperintensities of the anterior medial portions of both globus pallidi

FLAIR: Fluid attenuation inversion recovery, MR: Magnetic resonance

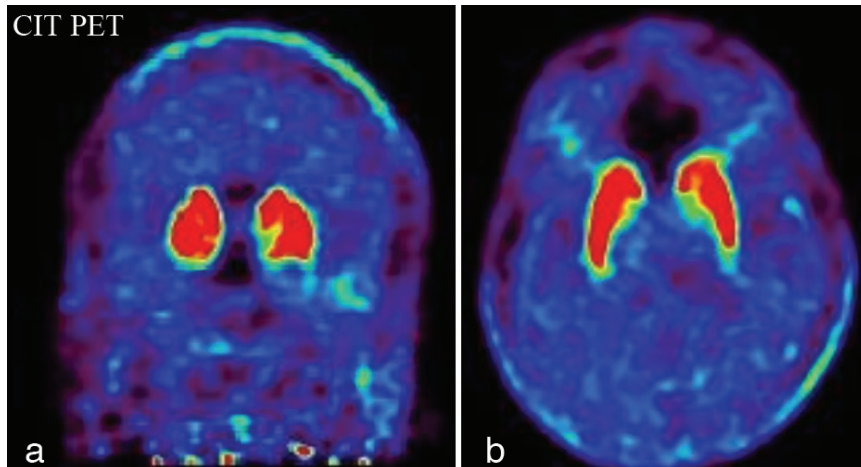


Figure 4. a, b) (^{18}F) FP-CIT PET showed symmetric and even DAT binding of both striata despite his involuntary movements. In contrast, a patient with parkinsonism showed a marked loss of (^{18}F) FP-CIT binding in putamen and caudate nucleus
 FP-CIT PET: (*3-fluoropropyl*)-2 β -carbomethoxy-3 β -(4-iodophenyl)nortropane positron emission tomography, DAT: Dopamine transporter

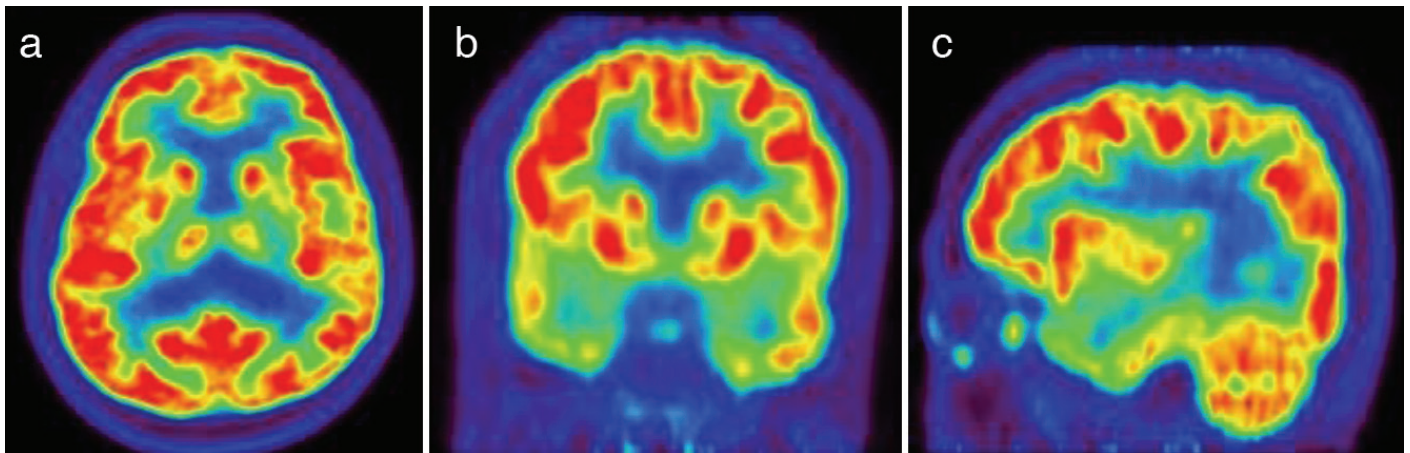


Figure 5. a, b, c) (^{18}F) FDG PET showed no significant findings compared with controls. Left: axial view, middle: coronal view, right: sagittal view
 FDG: Fludeoxyglucose, PET: Positron emission tomography

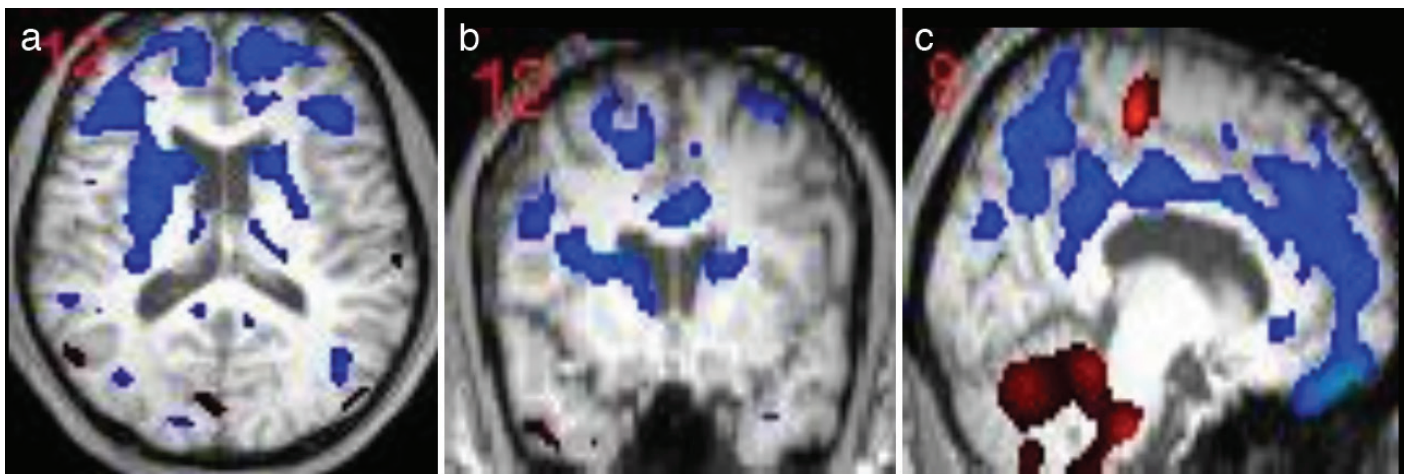


Figure 6. a, b, c) SPM analysis of (^{18}F) FDG PET images revealed that the blue regions indicated significant hypo-metabolism compared with other brain regions ($p < 0.05$, FDR corrected, 100-voxel level, one sample t-test), including bilateral putamen, caudate, inferior frontal gyrus (BA 47), middle frontal gyrus (BA 9), superior frontal medial gyrus (BA 8), cingulate gyrus and precuneus
 SPM: Statistical parametric mapping, FDG: Fludeoxyglucose, PET: Positron emission tomography, FDR: False discovery rate

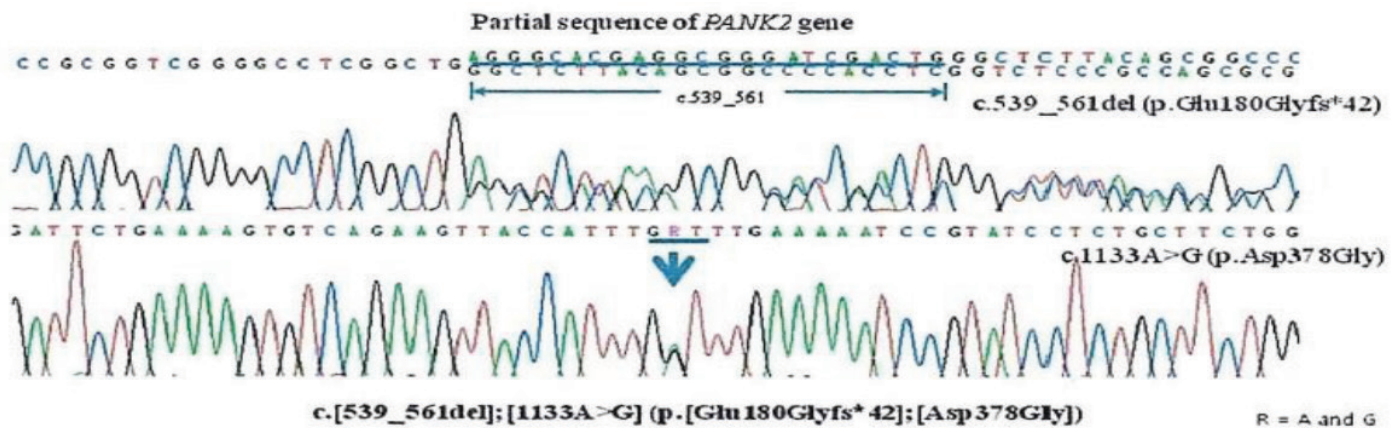


Figure 7. Gene analysis through PCR sequencing. Polymerase chain reaction (PCR) analysis of mutations using amplified DNA. Two mutations (Glu180 Gly and Asp378 Gly) involving exons 1 and 3 in the *PANK2* gene of the patient were identified. Specifically, two alterations, c.539-561del and 1133A>G, were found in exon 1 and 3 of the cDNA sequence, respectively. This resulted in the loss of functional properties by replacing one amino acid with another

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The authors performed the various roles for making this article. Mr. Dong Goo Lee performed the literature review, contributed to the introduction and revised the manuscript. Dr. Changxu Cui performed genetic analyses and contributed to the discussion. Prof. Eu Jene Choi collected the patient's history, performed the neurological examination, interpreted laboratory results and wrote the manuscript.

Ethics

Informed Consent: Informed consent was obtained in writing from the patient's family for the publication of this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.J.C., Concept: E.J.C., Design: E.J.C., Data Collection or Processing: E.J.C., D.G.L., C.C., Analysis or Interpretation: C.C., E.J.C., Literature Search: D.G.L., C.C., E.J.G., Writing: D.G.L., C.C., E.J.G.

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