An Apparently Sporadic Case With Parkin Gene Mutation in a Korean Woman

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Objective: To report the clinical features and results of iodine I 123-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (CIT) single photon emission computed tomography and molecular genetic analysis in a Korean woman with juvenile Parkinson disease with deletion in exon 4 of the parkin gene.

Design: Case report with molecular genetic analysis.

Patient and Results: The patient had bradykinesia, postural imbalance, and postural tremor since the age of 12 years. She developed wearing off early in the disease course. The [123I]-2β-carbomethoxy-3β-(4-iodophenyl)-tropane single photon emission computed tomography showed severe reduction of specific striatal CIT binding, comparable to that of Parkinson disease. The polymerase chain reaction products from the parkin gene showed homozygous exon 4 deletion.

Conclusion: In this sporadic juvenile Parkinson disease case, severe nigrostriatal dopaminergic damage and homozygous exon 4 deletion in the parkin gene were demonstrated.

Arch Neurol. 2001;58:988-989

K ITADA ET AL 1 reported a new gene defect causing autosomal recessive juvenile Parkinson disease in Japan. Since their report, evidence of other ethnic groups showing mutations in the same gene has been published,2-4 and the phenotype is not limited to juvenile onset,5 signifying the importance of this parkin gene. As a part of a systemic search for the genetic cause of parkinsonism in the Korean population, we are screening mutations in the parkin gene in patients with earlier onset of Parkinson disease. We identified a patient with juvenile Parkinson disease who had a homozygous exon 4 deletion.

RESULTS

The [123I]-β-CIT SPECT showed severe reduction of specific striatal CIT binding; specific striatal-to-occipital binding ratios were 2.35 on the right side and 2.57 on the left side (Figure 1B, and the case of juvenile Parkinson disease reported in Jeon et al5). The CIT SPECT done on her mother showed specific striatal-to-occipital binding ratios of 4.42 on the right side and 4.57 on the left side, which are normal for her age (Figure 1C).

Gene study showed homozygous deletion of exon 4 of parkin gene (Figure 2). This mutation was not seen in her mother or in her younger brother.

COMMENT

The classic phenotypes of patients with parkin gene mutation are juvenile onset, autosomal recessive inheritance, sleep benefit, early good levodopa response and rapid appearance of motor complication, and the absence of cognitive and autonomic dysfunction. However, gene testing has shown that the onset may be as late as age 58 years, it may appear sporadic, and sleep benefit may not be prominent. Even though our patient does not have a family history for the parkin gene, she has homozygous exon 4 deletion, suggesting that prevalence of heterozygous exon 4 deletion is high. Lewy body, which is considered a pathologic hallmark of Parkinson disease,7 is conspicuously absent in an autopsied case with parkin gene mutation.8 However, CIT SPECT study of our patient showed that the pattern of decrease in the dopamine transporter (ie, worse in the caudal part of the striatum) is quite similar to that of Parkinson disease. The degree of decrease in striatal CIT binding was very severe compared with other patients with Parkinson disease in our study. Severe nigrostriatal dopaminergic damage and absence of nonmotor symptoms in our patient suggest that the pathologic process is very selective in this disease. Striatal CIT binding in the mother was normal, supporting that this disease is a recessive disorder, and half of the gene is enough to maintain the dopaminergic cell viability.
PATIENT AND METHODS

The patient was briefly described as having juvenile Parkinson disease by Jeon et al. This 20-year-old woman had bradykinesia and tremor at the age of 12 years. She noted micrographia, leg dragging, and a tendency to fall. When seen at the age of 15 years, she had an impassive face, bradykinesia, mild rigidity that was worse on the left side, postural imbalance, and postural tremor. She did not have autonomic and cognitive changes. She had mild sleep benefit. Her father died of injuries sustained in a motor vehicle accident at the age of 40 years. At the time of the accident, he was reportedly healthy. Her mother and younger brother are healthy. Combined treatment with levodopa (100 mg) and benserazide (30 mg) (Madopar), 100 mg/d, and lisuride, 0.2 mg thrice a day, was started with complete resolution of neurological deficits. In 6 months, she developed wearing off. A combination of slow-releasing levodopa (200 mg) and benserazide (25 mg) (Madopar HBS), 100 mg twice a day, and lisuride, 0.4 mg 3 times a day, were prescribed with a good response for 4 years. She is taking a combination of selegiline hydrochloride, 5 mg twice a day, and levodopa, 200 mg, and carbidopa, 50 mg 3 times a day (Sinemet CR 1T) with motor fluctuation and dyskinesia.

The iodine I 123-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (CIT) single photon emission computed tomography (SPECT) was performed at the age of 17 years. An [123I]-β-CIT SPECT was performed and analyzed by the procedures described by Jeon et al. To investigate mutations in the parkin gene, we used the methods described in Kitada et al. Informed consent was obtained from all the participants after explaining about the experimental nature of the analysis of parkin gene and CIT SPECT study. The institutional review board of the hospital approved the genetic study and [123I]-β-CIT SPECT study.

Figure 1. The iodine I 123-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (CIT) single photon emission computed tomography in a normal subject (A), our patient (B) (Reprinted with permission from Annals of Neurology5), and our patient’s mother (C). The CIT binding is high in the striatum in the normal subject. Striatal CIT binding is decreased in our patient, but is normal in our patient’s mother. See “Methods” section in Jeon et al. Parkin indicates Parkinson disease.

Accepted for publication April 18, 2000.

The [123I]-β-CIT SPECT study was supported in part by grant 95-0403-96-3 from the Korea Science Foundation, Seoul, South Korea (Dr Jeon).

REFERENCES