Reduced amplitude of the sural nerve sensory action potential in PARK2 patients

Abstract—The authors performed nerve conduction studies in nine PARK2 and eight idiopathic Parkinson disease patients and found a significant reduction of sural sensory nerve action potential (SNAP) amplitude in eight PARK2 patients who mostly remained asymptomatic. These data suggest that sensory axonal neuropathy may be a common clinical feature of PARK2 and a reduced amplitude of sural SNAP could be a diagnostic indicator of PARK2.

NEUROLOGY 2005;65:459–462

Y. Ohsawa, MD; K. Kurokawa, MD; M. Sonoo, MD; H. Yamada, MD; S. Hemmi, MD; K. Iwatsuki, MD; H. Hagiwara, MD; T. Murakami, MD; T. Shirabe, MD; T. Shimizu, MD; and Y. Sunada, MD

Numbness, tingling, burning, and pain are common sensory symptoms of Parkinson disease (PD).¹ Several lines of evidence (e.g., the lack of objective sensory loss, the normal nerve conduction study [NCS],¹ the high occurrence on levodopa-off period, and the drastic improvement of pallidal deep brain stimulation) suggest that these sensory symptoms are not of peripheral but of CNS origin. However, 11 of 29 patients with juvenile parkinsonism of unknown etiology showed abnormal NCS in peroneal motor or sural sensory nerves.² We investigated two autosomal recessive juvenile parkinsonism (PARK2) patients complaining of a tingling sensation with objective sensory loss in the foot (Patients 1, 2 in the table). Based on reduced sural sensory nerve action potential (SNAP) amplitude in these patients, we hypothesized that a mutation of the PARK2 causative gene, *Parkin*,³ results in sensory axonal neuropathy. We investigate this hypothesis by examining NCSs in a series of PARK2 and idiopathic PD patients, together with the expression analysis of the *Parkin* gene in the peripheral nervous system.

Methods. We performed this study in patients under the age of 60 years, because sural SNAP amplitude reduces with aging, and is sometimes absent even in normal subjects over the age of 70 years.^{4,5} Diagnosis of PARK2 was confirmed by DNA analysis using exonic PCR amplification of the *Parkin* gene as described previously.³ All PARK2 or idiopathic PD patients were interviewed to determine whether they were experiencing sensory

symptoms. Those patients with other causes of neuropathy (e.g., medications including amantadine, exposure to toxins, diabetes mellitus, uremia, hypothyroidism, pernicious anemia, vitamin B6 deficiency, alcohol abuse, syphilis, gammopathy, malignancy, collagen vascular disease) as determined by laboratory testing or medical consultation were excluded from this study. Patients with obesity or leg swelling were also excluded. Seventeen patients with PARK2 or idiopathic PD were enrolled in this study. Two patients, who were clinically diagnosed with idiopathic PD, turned out to have sporadic PARK2 by DNA analysis.

NCS was performed on the median motor and sensory, the ulnar motor and sensory, the tibial motor, the peroneal motor, and the sural sensory nerves using standard methods described previously.^{4,5} For sural NCS, signal averaging of 20 to 50 responses was used. Peak-to-peak amplitude was used for the amplitude measurement and nerve conduction velocity (NCV) was calculated using the onset latency.^{4,5} Age- and sex-matched normal control subjects (20 men, 50.2 ± 5.3 years old; 20 women, 42.0 ± 5.1 years old) were used to determine the standard value of the sural SNAP amplitude, and logarithmic values were used to obtain a normal distribution. The value corresponding to the mean minus 2.5 standard deviations was used as the lower limit of the normal value (7.2 μV for men, 5.1 μV for women).

Total RNA was extracted from autopsied tissues, including human cerebrum, dorsal root ganglia (DRG), sural nerve, and thoracic sympathetic ganglia. *Parkin* gene expression was examined by semiquantitative RT-PCR and northern blotting according to the methods as described.³

Results. Clinical and electrophysiologic findings of nine PARK2 patients are summarized in the top section of the table. The mean age of the PARK2 patients was 49.6 ± 6.5 years (four men, 53.3 ± 4.6 years; five women, 46.6 ± 6.6 years). Seven patients (1, 2, 5 through 9) had PD family history and unique symptoms of PARK2, sleep benefit, levodopa-induced dyskinesia, wearing-off phenomenon, and foot dystonia.^{6–8} Among two patients (1, 2) complaining of foot dysesthesia, one (no. 2) had objective sensory loss of all modality in the foot and another (no. 1) had decreased vibration sense and absence of Achilles tendon reflex in the foot. Six patients had absence or decreased vibration sense in foot. Eight of nine PARK2 patients showed significant reduction of sural SNAP amplitude, but normal NCS findings in all other tested nerves. Of note, two patients (3, 4) with reduced sural SNAP amplitude having neither family history nor unique symptoms of PARK2 were clinically diagnosed with idiopathic PD. However, DNA analysis eventually revealed that they had sporadic PARK2.

Findings of eight idiopathic PD patients are summarized in the lower section of the table. The mean age of eight PD patients was 54.6 ± 3.3 years (four men, 55.3 ± 3.3 years; four women, 54.0 ± 3.7 years). Two patients (10, 11) had dysesthesia-like sensations in the foot without objective sensory loss during the levodopa-off period. In

From the Division of Neurology, Department of Internal Medicine (Drs. Ohsawa, Kurokawa, Yamada, Hemmi, Iwatsuki, Hagiwara, Murakami, and Sunada), and Department of Neuropathology (Dr. Shirabe), Kawasaki Medical School, Okayama; and Department of Neurology and Neuroscience (Drs. Sonoo and Shimizu), Teikyo University School of Medicine, Tokyo, Japan.

Supported by the Research Grant (14B-4) for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare; a Grant (15131301) for Research on Psychiatric and Neurologic Diseases and Mental Health from the Ministry of Health, Labor and Welfare; and JSPS KAKENHI 14370212 and Research Project Grants (No. 15-115B and 16-601) from Kawasaki Medical School.

Disclosure: The authors report no conflicts of interest.

Received November 8, 2004. Accepted in final form April 18, 2005.

Address correspondence and reprint requests to Dr. Yoshihide Sunada, Division of Neurology, Department of Internal Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki-City, Okayama 701-0192, Japan; e-mail: ysunada@med.kawasaki-m.ac.jp

Table Clinical and electrophysiologic findings of PARK2 (Patients 1 through 9) or Parkinson disease (PD) (Patients 10 through 17) patients

Case/sex/age, y	Age at onset, y	Mutation of Parkin	Family history	Sleep benefit	Dyskinesia	Wearing phenomenon-on/off	Foot dystonia	Foot dysesthesia
PARK2 (n = 9)								
1/M/48	41	Ex 3 del	+	+	+	+	+	+
2/M/56	43	Ex 3&4 del	+	+	+	+	+	+
3/M/58	52	Ex 3 del				+		
4/M/51	50	Ex 2 del						
5/F/44	20	Ex 3 del	+	+	+	+		
6/F/41	30	Ex 3&4 del	+	+	+	+	+	
7/F/46	30	Ex 3 del	+	+	+	+		
8/F/44	28	Ex 3 del	+	+		+		
9/F/58	40	Ex 3 del	+	+	+	+		
Mean $\pm$ SD								
PD (n = 8)								
10/M/56	52					+		+
11/M/55	54					+		+
12/M/51	50							
13/M/59	51							
14/F/54	48							
15/F/58	49					+		
16/F/55	50							
17/F/49	47							
Mean $\pm$ SD								

Mean $\pm$ SD values of levodopa dosage and SNAP parameters indicated at the bottom of each column.

* Data from the worse side recording.

SNAP = sensory nerve action potential; Ex = exon; del = deletion; + = positive.

sharp contrast to PARK2 patients, all eight patients with PD showed normal sural SNAP amplitude. There was no patient who showed slow NCV in PARK2 and PD.

The values of sural SNAP amplitude of each subject were plotted in figure 1. The frequency of reduced sural SNAP amplitude below normal lower limit in PARK2 patients was significantly ($p < 0.01$, Fisher's exact Test) higher than that in patients with PD. The mean value of sural SNAP amplitude was significantly ($p < 0.01$, Mann-Whitney U test) reduced in PARK2 patients, compared with patients with PD.

Semi-quantitative RT-PCR and northern blot analysis demonstrated that *Parkin* gene expression was markedly higher in the DRG and cerebrum than in the sural nerve, and expression was far less abundant in the thoracic sympathetic ganglia (figure 2).

Discussion. The present study showed that nearly all PARK2 patients have reduced amplitude of sural SNAP, suggesting that sensory axonal neuropathy may be a common clinical feature of PARK2. Only five PARK2 patients associated with neuropathy have been reported so far.⁷⁻¹⁰ Therefore peripheral

neuropathy has been believed to be an atypical presentation of PARK2.⁷⁻¹⁰ In our series of PARK2, only two patients showed subjective sensory symptoms.

Figure 1. Plots of sural SNAP amplitude value of men (left panel) and women (right panel) including normal control subjects, PARK2 patients, and patients with Parkinson disease. Dotted lines indicate normal lower limit (mean minus 2.5 SD) of sural SNAP amplitude. Circles indicate patients with (closed) and without (open) subjective sensory symptoms. All PARK2 patients except for one woman showed a reduction of sural SNAP amplitude. Of patients with subjective sensory symptoms (closed circle), the lower limit of sural SNAP amplitude clearly distinguishes PARK2 from PD patients.

Table Continued

Sensory examinations			Levodopa, mg/d	Median nerve SNAP*		Sural nerve SNAP*	
Pinprick	Touch	Vibration		Velocity, m/s	Amplitude, μV	Velocity, m/s	Amplitude, μV
N	N	D	200	51.1	9.8	51.1	0.4
D	D	D	200	52.1	16.2	49.3	1.0
N	N	N	300	54.5	9.4	47.8	5.4
N	N	N	100	52.2	21.3	53.2	4.9
N	N	N	300	57.2	26.3	42.2	12.3
N	N	N	200	60.0	12.9	49.6	3.7
N	N	D	200	62.7	7.2	44.5	0.1
N	N	N	300	54.4	20.7	43.1	1.1
N	N	N	200	49.3	7.2	49.3	1.1
			211.4 ± 60.1	54.8 ± 4.4	14.5 ± 6.9	47.8 ± 3.7	3.4 ± 3.8
N	N	N	600	60.4	19.3	49.1	10.3
N	N	N	500	59.1	14.3	50.1	12.1
N	N	N	300	60.4	12.1	54.1	8.5
N	N	N	400	51.1	14.6	48.7	8.1
N	N	N	300	51.3	11.4	48.7	8.1
N	N	N	600	58.3	11.3	47.2	9.8
N	N	N	300	52.2	26.9	53.2	19.3
N	N	N	400	47.1	12.2	50.7	13.3
			425.0 ± 128.1	55.0 ± 5.1	15.3 ± 5.4	50.2 ± 2.6	11.2 ± 3.8

However, eight of nine patients exhibited marked reductions in the sural SNAP amplitude, even in the absence of sensory symptoms. In sharp contrast, patients with idiopathic PD showed normal results even in the presence of sensory symptoms, which is consistent with previous NCS data.¹ Of note, two patients with a presumptive diagnosis of idiopathic

PD (nos. 3, 4) who showed a reduced SNAP amplitude were subsequently diagnosed with PARK2 as a result of DNA analysis. These cases should be classified as sporadic PARK2. Thus, our NCS data strongly suggest that reduced sural SNAP amplitude could distinguish PARK2 from idiopathic PD and that asymptomatic sensory axonal neuropathy is not

Figure 2. (A) Semiquantitative RT-PCR analysis and (B) northern blot analysis of the Parkin mRNA in the cerebrum, dorsal root ganglia (DRG), sural nerve, and thoracic sympathetic ganglia. Expression of the Parkin gene was markedly higher in the DRG and cerebrum than in the sural nerve, and expression was far less abundant in the thoracic sympathetic ganglia.

an atypical but common clinical feature of PARK2 patients. Reduced sural SNAP amplitude in patients with PD under 60 years may be a diagnostic indicator of *Parkin* mutations. It is important to investigate the sural SNAP amplitude in asymptomatic family members in PARK2 pedigrees to confirm the segregation of sensory neuropathy with *Parkin* mutations in future study.

Interestingly, *Parkin* gene expression was abundant in DRG, which suggests that parkin may play an important role in maintaining normal integrity of the sensory nervous system. In contrast, *Parkin* mRNA is relatively sparse in sympathetic ganglia. This differential distribution of *Parkin* mRNA in the peripheral nervous system well correlates with clinical manifestations of PARK2; sensory neuropathy is common, whereas autonomic dysfunction is quite rare.^{6,7} Further studies to define the molecular mechanism underlying sensory neuropathy in PARK2 patients would be of benefit.

References

1. Koller WC. Sensory symptoms in Parkinson's disease. *Neurology* 1984; 34:957-959.
2. Taly AB, Muthane UB. Involvement of peripheral nervous system in juvenile Parkinson's disease. *Acta Neurol Scand* 1992;85:272-275.
3. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998;392: 605-608.
4. Rivner MH, Swift TR, Malik K. Influence of age and height on nerve conduction. *Muscle Nerve* 2001;24:1134-1141.
5. Dyck PJ, Karnes JL, Daube J, O'Brien P, Service FJ. Clinical and neuropathological criteria for the diagnosis and staging of diabetic polyneuropathy. *Brain* 1985;108(Pt 4):861-880.
6. Ishikawa A, Tsuji S. Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. *Neurology* 1996;47:160-166.
7. Khan NL, Graham E, Critchley P, et al. Parkin disease: a phenotypic study of a large case series. *Brain* 2003;126(Pt 6):1279-1292.
8. Lohmann E, Periquet M, Bonifati V, et al. How much phenotypic variation can be attributed to parkin genotype? *Ann Neurol* 2003;54:176-185.
9. Okuma Y, Hattori N, Mizuno Y. Sensory neuropathy in autosomal recessive juvenile parkinsonism (PARK2). *Parkinsonism Relat Disord* 2003;9:313-314.
10. Abbruzzese G, Pigullo S, Schenone A, et al. Does parkin play a role in the peripheral nervous system? A family report. *Mov Disord* 2004;19: 978-981.

Correction

Neurology 64 March 2005 (Suppl 1), Abstract P04.142. Memantine May Prevent Further Cognitive Decline in Subjects with the AIDS Dementia Complex with Detectable CSF HIV RNA

One of the authors of this study (SAL) is the named inventor on patents filed by Children's Hospital/Boston and Harvard Medical School concerning the neuroprotective effects of memantine. The inventor will derive no direct benefit and has no stock ownership in any company involved with the use of memantine for HIV-associated dementia, in accordance with university conflict-of-interest policies. He could participate in a royalty-sharing plan with the hospital, as per university guidelines, if memantine were approved and sold for treatment of HIV-associated dementia in the future. The inventor served as a consultant to this study and did not participate in direct patient care, collection of data, or data analysis.

Neurology®

Correction

Neurology 2005;65;462
DOI 10.1212/WNL.65.3.462

This information is current as of August 8, 2005

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/65/3/462.full
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Parkinson's disease/Parkinsonism http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism Peripheral neuropathy http://n.neurology.org/cgi/collection/peripheral_neuropathy
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.