

Familial and Sporadic Chronic Progressive Degenerative Parietal Ataxia

Ryuta Morihara, M.D.,¹ Toru Yamashita, M.D., Ph.D.,¹ Kentaro Deguchi, M.D., Ph.D.,¹

Tomoko Kurata, M.D., Ph.D.,¹ Emi Nomura, M.D.,¹ Kota Sato, M.D., Ph.D.,¹

Yumiko Nakano, M.D.,¹ Yasuyuki Ohta, M.D., Ph.D.,¹ Nozomi Hishikawa, M.D.,

Ph.D.,¹ Takeshi Ikeuchi, M.D., Ph.D.,² Masataka Kitaguchi, M.D., Ph.D.,³

and Koji Abe, M.D., Ph.D.¹

¹Departments of Neurology, Dentistry and Pharmaceutical Sciences, Graduate School of Medicine, Okayama University, 2-5-1 Shikata-cho Kita-ku, Okayama 700-8558, Japan

²Department of Molecular Genetics, Bioresource Science Branch, Center of Bioresource, Brain Research Institute Niigata University, 1-757 Asahimachidori, Chuo-ku, Niigata 951-8585, Japan

³Department of Neurology, Baba Memorial Hospital, 4-244 Hamaderahunao-cho Higashi nishi-ku, Sakai 592-8555, Japan

Correspondence to:

Koji Abe, M.D., Ph.D.,

Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho Kita-ku, Okayama 700-8558, Japan

Tel.: +81-86-235-7365, **Fax:** +81-86-235-7368

E-mail: p2k07ll9@cc.okayama-u.ac.jp

Abbreviations: ApoE, apolipoprotein E; CCD, crossed cerebellar diaschisis; ECD, Tc-ethyl cysteinate dimer; eZIS, easy Z-score imaging system; MAPT, microtubule-associated protein tau; MMSE, mini-mental state examination; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, positron emission tomography; SNPs, single nucleotide polymorphisms; SPECT, single photon emission computed tomography; VL, ventrolateral nucleus.

Abstract

Background & Objective: Parietal ataxia has been mainly reported as a consequence of acute ischemic stroke, while degenerative parietal ataxia has not been reported.

Methods: We investigated clinical characteristics, neuroimaging data, and genetic analysis of patients with cerebellar ataxia plus parietal atrophy.

Results: We identified seven patients, including five patients from two families, with chronic progressive cerebellar ataxia due to degenerative parietal atrophy but not stroke. Age at onset of ataxia was 57.6 ± 6.9 years. All patients showed chronic progressive cerebellar ataxia with severity of ataxic gait > limb ataxia > dysarthria. Patients showed no cognitive dysfunction, muscle weakness, or parkinsonism, and only two patients showed mild sensory disturbances. The seven patients showed lateralized limb ataxia with greater contralateral parietal lobe atrophy by magnetic resonance imaging, and hypoperfusion by single photon emission computed tomography, without any abnormal cerebellar pathology (i.e., crossed cerebellar diaschisis). Pathogenic mutations in the microtubule-associated protein tau gene were not found using two single nucleotide polymorphisms.

Conclusions: This is the first description showing unique clinical features of familial and sporadic chronic progressive degenerative parietal ataxia.

Keywords: parietal ataxia, parietal lobe atrophy, crossed cerebellar diaschisis, MAPT

Parietal ataxia is defined as secondary cerebellar ataxia attributable to primary cerebral parietal lesions. Appenzeller *et al.*, [1] and Ghika *et al.*, [2] reported that ischemic stroke patients with parietal lobe infarctions show cerebellar ataxia with no muscle weakness or sensory deficits. Likewise, Futamura *et al.*, [3] reported 13 cases of ataxia in acute parietal lobe infarction without any organic lesions in the cerebellum or brainstem. Ischemic parietal ataxia is characterized by cerebellar signs in limbs opposing the primary brain infarct area, which is interpreted as the phenomenon of crossed cerebellar diaschisis (CCD) [4], i.e., acute stroke damage in an unilateral parietal lobe reduces metabolic activity and blood flow of the contralateral cerebellar hemisphere via deactivation of the cortico-cerebellar pathway [5] [6]. Although parietal ataxia has mainly been reported as a consequence of acute brain infarction, Steilin *et al.*, [7] described two children with congenital cerebellar ataxia and parietal lobe atrophy by computed tomography (CT). Here, we report seven patients with degenerative parietal ataxia, including five patients from two families, who show chronic progressive cerebellar ataxia with brain atrophy limited to the parietal lobe.

2. Materials and Methods

2.1. Case presentation

Patients with cerebellar ataxia plus parietal atrophy without any organic lesions (such as strokes and tumors) in the parietal lobe were retrospectively recruited. In total, seven patients were identified, including five patients from two families. All subjects provided a clinical history and underwent a clinical examination and evaluation. For cerebral cortical function, mini-mental state examination (MMSE) [8], aphasia, apraxia,

and agnosia were examined. Other neurological findings examined included ataxia, tendon reflexes, muscle tonus, muscle atrophy, muscle weakness, sensory disturbance, and parkinsonism. Ataxia was assessed by presence of a wide-based gait, the finger-nose test, heel-knee test, diadochokinesis, existence of dysarthria, and gaze-evoked nystagmus. For sensory functions, pain, touch, vibration, position sense, two-point discrimination, and graphesthesia were examined.

2.2. Neuroimaging

Brain magnetic resonance imaging (MRI) with a 1.5 Tesla or 3.0 Tesla scanner was performed on all seven individuals. High-resolution anatomical images were acquired by MR angiography (MRA) in sagittal (T1-weighted), coronal (T1-weighted), and axial (T1-weighted, T2-weighted, fluid attenuation inversion recovery, and diffusion weighted) planes.

Single photon emission computed tomography (SPECT) with ^{99m}Tc -ethyl cysteinate dimer (^{99m}Tc -ECD) was performed in five affected individuals. Statistical imaging analysis was performed using the easy Z-score imaging system (eZIS) [9].

2.3. Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes of five affected individuals with written informed consent. All 16 exons (0–4, 4A, and 5–14) and all splicing sites between each exon of the microtubule-associated protein tau gene (*MAPT*) were amplified by polymerase chain reaction (PCR). Amplification products were subjected to the Sanger method for direct sequencing, covering all coding regions and splicing sites with known mutations.

There are three relatively common allelic variants of apolipoprotein E (APOE), known as APOE-ε2, APOE-ε3, and APOE-ε4, which are defined by two single nucleotide polymorphisms (SNPs): rs429358 and rs7412. PCR amplification products including these two SNPs were subjected to direct sequencing.

3. Results

3.1. Clinical characteristics

Table 1 summarizes the clinical findings of the seven patients. Pedigrees A and B are shown in Fig. 1. Autosomal dominant inheritance is suspected in Pedigree A. Mean age at disease onset was 57.6 ± 6.9 years (mean $\pm$ SD; range 44–64 years), with an ataxic gait being the most frequent initial symptom. Mean illness duration was 9.1 years, and mean age at examination was 66.7 years. MMSE was conducted in five patients with MMSE scores of 28.0 ± 2.8 (range 23–30). No patient showed aphasia, apraxia, or agnosia. Symptoms of cerebellar ataxia were categorized as ataxic gait, limb ataxia (hypermetria, decomposition, and dysdiadochokinesis), dysarthria, and gaze-evoked nystagmus. All patients showed chronic progressive cerebellar ataxia, with severity in the following order in most cases: ataxic gait > limb ataxia > dysarthria. Although individual III-5 in Pedigree A did not show limb ataxia, the other six patients showed limb ataxia with laterality (Table 1). No patient showed gaze-evoked nystagmus. Four patients showed hyperreflexia in the upper and lower limbs with increased muscle tone. Muscle atrophy and weakness were not observed. Only two patients (individuals II-1 and II-2 in Pedigree B) showed disturbances of superficial, deep, and combined sensation. The other five patients did not show any sensory disturbances. Parkinsonism

was not found.

3.2. Neuroimaging findings

Brain MRI showed atrophy of the bilateral parietal lobe in six patients (Fig. 2, arrows and arrowheads), excluding individual III-5 in Pedigree A, who had the shortest illness duration (2 years). In contrast, the cerebellar hemispheres and vermis were well preserved in all cases. Further, ^{99m}Tc-ECD SPECT in one patient (individual II-6 in Pedigree A) and eZIS analysis in four patients (individuals II-1 and -2 in Pedigree B, and sporadic patients 1 and 2) revealed hypoperfusion in bilateral parietal lobes but not the cerebellum (Fig. 2, bottom, arrows and arrowheads).

Patients who exhibited atrophy by MRI and greater hypoperfusion in the right hemisphere by SPECT showed greater limb ataxia on the left side (arrowhead of individual II-6 in Pedigree A and sporadic patient 2). Similarly, patients who exhibited atrophy and greater hypoperfusion in the left hemisphere showed greater contralateral limb ataxia (arrowhead of individual II-7 in Pedigree A and sporadic patient 1). Individuals II-1 and II-2 in Pedigree B showed lateralized ataxia without strong lateralization by brain neuroimaging (Fig. 2, arrows).

3.3. Genetic analysis

The five individuals (individuals II-6 in Pedigree A, II-1 and -2 in Pedigree B, and sporadic patients 1 and 2) examined had no known mutations in coding regions and splicing sites of the *MAPT* gene. Sequence analysis identified two SNPs at c.1321c>T and c.*1145_*1146insT which are unlikely to affect protein function [10-14]. Sequence analysis of *APOE* identified four individuals with ε3/ε3 genotypes and one individual

with $\epsilon 2/\epsilon 3$ genotype (Table 1).

4. Discussion

Parietal ataxia is a rare condition of cerebellar ataxia caused by parietal lobe lesions, which is mainly due to brain infarction [1-3, 15]. In the present study, we identified seven patients, including five patients from two families, with chronic progressive cerebellar ataxia due to degenerative parietal atrophy but not stroke. The initial symptom in the patients was ataxic gait, followed by limb ataxia and dysarthria. Limb ataxia usually showed lateralization, which was associated with greater contralateral parietal atrophy (Table 1). The patients had no cognitive dysfunction, higher brain dysfunction, muscle weakness, or parkinsonism. Further, only two patients (29%) showed mild sensory disturbances (Table 1). Although the present patients have suspected tauopathy, which encompasses several different neurodegenerative disorders, pathogenic mutations in the *MAPT* gene were not found with only two known SNPs (Table 1).

Based on previous reports using positron emission tomography (PET) and SPECT, parietal ataxia is caused by CCD [4], in which acute stroke damage in one cerebral hemisphere reduces metabolic activity and blood flow of the contralateral cerebellar hemisphere via deactivation of the cortico-cerebellar pathway [5, 6]. Brodmann area 5 is the main parietal area projecting to and from the cerebellum via the pontine nucleus or thalamic ventrolateral nucleus [16, 17]. Thus, damages in the superior and inferior parietal lobes, where Brodmann area 5 is located, may cause cerebellar ataxia through interruption of the cortico-cerebellar pathway [3].

In the present seven patients, basically the same mechanism is suspected as CCD with parietal atrophy (Fig. 3). Nonetheless, we did not detect lateralized cerebellar hypoperfusion by SPECT in 5 of 7 present cases (Fig. 2). Meneghetti et al. reported that a persistent contralateral cerebellar blood flow depression was observed in patients with a large infarct, however, in patients with a small infarct, a transient crossed cerebellar low flow was observed, while the clinical symptoms persisted. They speculate that a large infarct suggests a permanent deactivation of cortico-cerebellar tracts, however, a small infarct suggests a reversible deactivation of the tract [18]. In the present patients, slowly progressive parietal degeneration may induce a reversible deactivation of the cortico-cerebellar tracts, therefore, decrease of contralateral cerebellar metabolic activity and blood flow may be a reversible event. Accumulation of more cases and long-term follow-up may clarify the detailed pathophysiological mechanism of cerebellar ataxia due to parietal atrophy.

Conflicts of interest

None.

Acknowledgements

We appreciate the cooperation of the patients. We thank Rachel James, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. This work was partly supported by a Grant-in-Aid for Scientific Research (B) 25293202, (C) 15K09316 and Challenging Research 15K15527 and Young Research 15K21181,

and by Grants-in-Aid from the Research Committees (Mizusawa H, Nakashima K, Nishizawa M, Sasaki H, and Aoki M) from the Ministry of Health, Labour and Welfare of Japan.

References

- [1] Appenzeller O, Hanson JC. Parietal ataxia. *Archives of neurology*. 1966;15:264-9.
- [2] Ghika J, Bogousslavsky J, Uske A, Regli F. Parietal kinetic ataxia without proprioceptive deficit. *Journal of neurology, neurosurgery, and psychiatry*. 1995;59:531-3.
- [3] Futamura A, Kawamura M. Parietal Ataxia 13 Cases Plus a Review of Relevant Literature. *Showa Univ J Med Sci*. 2014;26:263-9.
- [4] Tanaka M, Kondo S, Hirai S, Ishiguro K, Ishihara T, Morimatsu M. Crossed cerebellar diaschisis accompanied by hemiataxia: a PET study. *Journal of neurology, neurosurgery, and psychiatry*. 1992;55:121-5.
- [5] Baron JC, Bousser MG, Comar D, Castaigne P. "Crossed cerebellar diaschisis" in human supratentorial brain infarction. *Transactions of the American Neurological Association*. 1981;105:459-61.
- [6] Sommer WH, Bollwein C, Thierfelder KM, Baumann A, Janssen H, Ertl-Wagner B, et al. Crossed cerebellar diaschisis in patients with acute middle cerebral artery infarction: Occurrence and perfusion characteristics. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2016;36:743-54.
- [7] Steinlin M, Schmitt B, Ferrini B. Congenital ataxia of parietal origin? Report of two cases. *Brain & development*. 1998;20:242-4.
- [8] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 1975;12:189-98.
- [9] Matsuda H, Mizumura S, Soma T, Takemura N. Conversion of brain SPECT images between different collimators and reconstruction processes for analysis using statistical parametric mapping. *Nuclear medicine communications*. 2004;25:67-74.
- [10] Crawford F, Freeman M, Town T, Fallin D, Gold M, Duara R, et al. No genetic association between polymorphisms in the Tau gene and Alzheimer's disease in clinic or population based samples. *Neuroscience letters*. 1999;266:193-6.
- [11] Ikeuchi T, Imamura T, Kawase Y, Kitade Y, Tsuchiya M, Tokutake T, et al. Evidence for a Common Founder and Clinical Characteristics of Japanese Families with the MAPT R406W Mutation. *Dementia and geriatric cognitive disorders extra*. 2011;1:267-75.
- [12] Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Annals of neurology*. 1998;43:815-25.
- [13] Santa-Maria I, Haggiagi A, Liu X, Wasserscheid J, Nelson PT, Dewar K, et al. The MAPT H1 haplotype is associated with tangle-predominant dementia. *Acta neuropathologica*. 2012;124:693-704.

- [14] Stanford PM, Brooks WS, Teber ET, Hallupp M, McLean C, Halliday GM, et al. Frequency of tau mutations in familial and sporadic frontotemporal dementia and other tauopathies. *Journal of neurology*. 2004;251:1098-104.
- [15] Ghika J, Ghika-Schmid F, Bogousslavsky J. Parietal motor syndrome: a clinical description in 32 patients in the acute phase of pure parietal strokes studied prospectively. *Clinical neurology and neurosurgery*. 1998;100:271-82.
- [16] Wiesendanger R, Wiesendanger M, Ruegg DG. An anatomical investigation of the corticopontine projection in the primate (*Macaca fascicularis* and *Saimiri sciureus*)--II. The projection from frontal and parietal association areas. *Neuroscience*. 1979;4:747-65.
- [17] Petras JM. Connections of the parietal lobe. *Journal of psychiatric research*. 1971;8:189-201.
- [18] Meneghetti G, Vorstrup S, Mickey B, Lindewald H, Lassen NA. Crossed cerebellar diaschisis in ischemic stroke: a study of regional cerebral blood flow by ^{133}Xe inhalation and single photon emission computerized tomography. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 1984;4:235-40.

Figure captions

Figure 1. Pedigrees A and B of individuals with cerebellar ataxia due to parietal atrophy

Affected individuals are shown with filled symbols, and deceased individuals with diagonal lines. Squares indicate males and circles females. Arrows indicate probands. The number at the lower left corner is the age at onset, while lower right corner is the current age or age at death.

Figure 2. Brain MRI (a–c) and SPECT (d, e) of the seven patients

Brain MRI showed bilateral parietal lobe atrophy in six patients, excluding individual III-5 of Pedigree A (a and b). In contrast, the cerebellar hemispheres and vermis were well preserved in all cases (c). With $^{99\text{m}}\text{Tc}$ -ECD SPECT, five patients showed hypoperfusion in bilateral parietal lobes but without cerebellar pathology (d and e). Arrows indicate atrophy or hypoperfusion. Arrowheads indicate greater atrophy or hypoperfusion compared with the contralateral hemisphere.

Figure 3. Theoretical model of parietal ataxia

Brodmann area 5 is the main parietal area, projecting to the contralateral cerebellum via the pontine nucleus (efferent pathway), and receiving cerebellar input via the thalamic ventrolateral nucleus (afferent pathway).