Neurology Asia 2015; 20(3) : 313 – 318

Ginseng may modify the progression of degenerative cerebellar ataxia: A report of two case

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Abstract

Cerebellar degeneration is a group of diseases that manifests as progressive ataxia, that finally led to death without specific treatment. We report here two patients with cerebellar degeneration, who had shown an improvement and less progressive course, which is associated with *panax ginseng* intake. Patient 1 was a 60-year-old woman with multisystem atrophy (MSA) type C with 5 year history of ginseng ingestion. Patient 2 was a 54-year-old woman with spinocerebellar ataxia (SCA) type 6, who had a history of ginseng intake for 30 months. Both the patients showed atrophic change in the cerebellum by brain magnetic resonance imaging. Cerebellar functions had been semi-quantified by International Cooperative Ataxia Rating Scale (ICARS) and monitored before and after the ginseng ingestion every 6 to 12 months. In Patient 1 with MSA type C, ICARS had improved from 21 to 17.5 ± 1.8 in the following 5 years. In Patient 2 with SCA, ICARS also showed an improvement from 22 to 6.0 ± 1.0 over 30 months. However, when she stopped taking ginseng, it progressed up to 13 points in two years. These observations provide a potential disease-modifying effect of ginseng on patients with cerebellar degeneration.

INTRODUCTION

Cerebellar ataxia is a complex signs of an inability to coordinate balance, gait, eye and extremity movements.[1] Progressive degeneration of the cerebellum is frequently seen in sporadic or hereditary ataxia with no effective treatment, although several pharmacological managements have been attempted.[2-4]

Ginseng, the root of *panax ginseng*, is one of the most famous traditional functional health foods that have been used in Asia, particularly the oriental countries. Pharmacologic effects of ginseng have been demonstrated in the central nervous system as well as in cardiovascular, endocrine or immune system.[5,6] There have been reports of ginseng enhancing cognitive performance in Alzheimer's disease (AD)[7-12], and improves movements deficit in Parkinson's disease (PD).[13,14] These reports suggest effects of ginseng on the cerebral cortex or subcortical structures in the brain. However, ginseng's efficacy in the cerebellum has been unknown since there has been no clinical trial or experimental study so far.[15]

Since 2005, registration of patients with cerebellar atrophy had begun in this institute (Department of Neurology, Seoul National University Hospital). Sporadic cerebellar degeneration (mostly MSA type C) and hereditary ataxia (SCA series) are main causes for cerebellar degeneration. Ataxia rating has been routinely performed every 6 to 12 month when the patients visited the hospital. In brief, International Cooperative Ataxia Rating Scale (ICARS) was proposed by 'The Ataxia Neuropharmacology Committee of the World Federation of Neurology'.[16] There are four categories. The first category is for 'posture and gait disturbances' that include gait speed, stand up, intervals of foots, body sway and sitting position. The second category is 'kinetic functions' with knee-tibia test, (+ tremor), finger to nose test (+ tremor), finger to finger, pronation-supination alternating movement and Archimedes' spiral. Speech function (pronunciation speed, dysarthria) is assessed in category 3. Final category is oculomotor dysfunctions that assess gaze-evoked nystagmus, ocular pursuit, and dysmetria of

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saccade. The scores range from 0 to 100, and the lower the score means better performance.

Therefore, the progression rate of individual patient can be monitored by analysis of ICARS score from medical record review. Most of the patients showed progressive declining course over time, and bed-ridden state eventually. However, unlike the others, two of the patients showed an improvement at certain point and maintained less progressive course. Medical records and history evaluation revealed that both of them had taken ginseng as an adjuvant functional food for a certain period.

Here, we report these two patients with cerebellar degeneration, with quantitative evaluation of cerebellar dysfunctions by ICARS during the disease course.

CASE REPORTS

Patient 1

A 60-year-old woman visited the neurology clinic complaining of dizziness and gait disturbance. These signs and symptoms had developed three years ago and progressed gradually over time. There was no exposure or intoxication histories that are known to cause cerebellar degeneration. She denied familial history of ataxia. On physical examination, blood pressure was 140/80 mmHg and she did not take anti-hypertensive medication. Other vital signs including pulse and respiration rate, body temperature were within normal ranges. There were no other abnormal findings. She appeared anxious and depressed. Cranial nerves examination showed mild impairment of saccadic eye movement with lingual type dysarthria. Sensory assessment was intact in all modalities. Bradykinesia was noted but muscle tone was spastic with increased deep tendon reflexes. There was ankle clonus with positive Babinski's sign. She was ataxic and unable to perform tandem gait. Adiadochokinesia was noted and dysmetria with intentional tremor were observed when she was asked to perform finger to nose test. Tremor on resting state was not observed. There were no sphincter dysfunctions or orthostatic hypotension. Brain magnetic resonance imaging (MRI) showed diffuse atrophy of the brainstem and the cerebellum, compatible with olivopontocerebellar atrophy, MSA type C (Figure 1). She had been taking L-Dopa (for the bradykinesia), nimodipine (calcium channel blocker), oxiracetam (cerebrotonic agent that enhance calcium reflux), calcium pantothenate (calcium supplement), bevantolol (beta-adrenergic inhibitor to control tremor), buspirone (serotonin type 1a agonist for anxiety and motor coordination), eperisone (muscle relaxant), and alprazolam (for anxiety). These medications had been taken for 18 months before ginseng intake, and maintained without alteration of dosage.

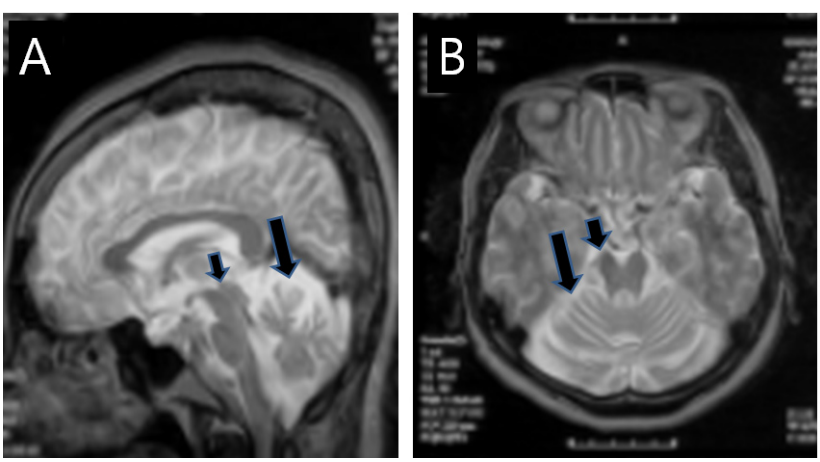

Figure 1: Brain magnetic resonance imaging of Patient 1

A. T2-weighted image, sagittal section shows atrophic changes of both cerebellum (large arrow) and brainstem (small arrow). The folia of the cerebellum are prominent. Size of the midbrain, the pons and the medullar oblongata are smaller than normal. The size of the cerebral hemisphere appears to be within normal range. These findings are compatible with olivopontocerellar atrophy (OPCA) or multisystem atrophy type C.

B. Axial section of T2-weighted image at the brainstem level shows prominent cerebellar folia from cerebellar degeneration. Size of the midbrain is reduced.

Table 1: ICARS scores of four categories in Patient 1

	Baseline	8 months	17 months	29 months	41 months	57 months	69 months
Posture & gait disturbances	8	7	9	9	10	7	7
Kinetic functions	10	7	5	9	5	7	11
Speech disorders	2	1	1	1	1	2	2
Oculomotor disorders	1	1	1	0	0	2	0

She began to take Korean Red Ginseng (KT & G, Republic of Korea) which is commercially available in South Korea. She reported that this ginseng appeared to reduce anxiety and depressive symptoms, thus she continued to take the ginseng as an adjunctive functional food. She claimed that the ginseng did help to change her mind to be more positive, and to help restore her mental energy. Medical records showed that approximately 4-5g of ginseng had been taken per day for 5 years. The ICARS score was 21 before she took the ginseng. During the period of ginseng intake, score had improved and maintained around 17.5 ± 1.8 (mean ± standard deviation; ranging from 13 to 21) over 5 years. Particularly, improved categories were 'kinetic function' (from 10 to 7.3 ± 2.3) and 'speech disorders' (from 2 to 1.3 ± 0.5). 'Knee tibia test' of 'kinetic function' category showed an improvement from 4 to 0. Dysarthria of 'speech disorders' category was improved from 1 to 0. Dysmetria of the saccade was also improved from 1 to 0 (Table 1). All the medications had not been changed before and after the intake of ginseng.

Patient 2

A 54-year-old woman visited our outpatient clinic complaining of dizziness, progressive ataxia and speech disturbance. Brain MRI showed severe atrophic change in the cerebellum without atrophy of pons or basal ganglia (Figure 2). She was diagnosed with SCA type 6 (CAG repeat; 23/18) and has been followed-up for 2 years taking acetyl L carnitine, nimodipine, oxiracetam, clonazepam (for ataxia and tremor), ginkgo biloba and vitamin E. There had been no significant clinical improvement with the ICARS score ranging from 17 to 23.

When the patient took the Korean Red ginseng,

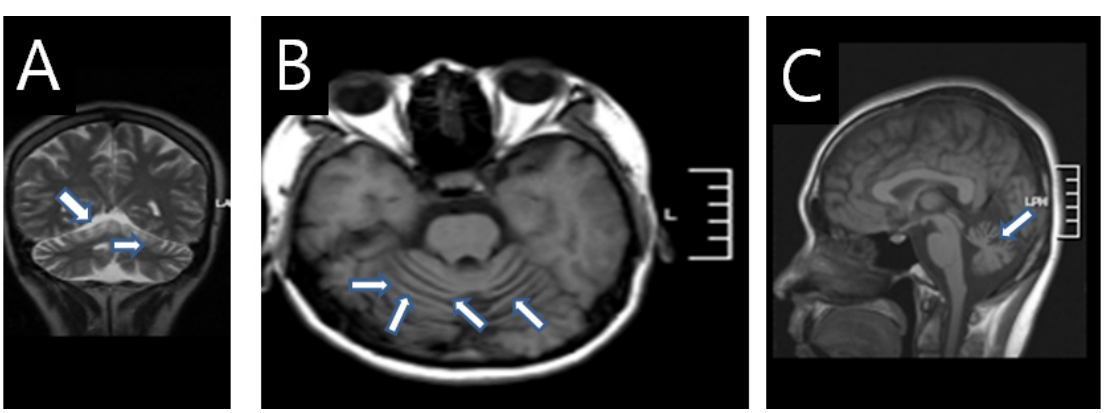

Figure 2: Brain magnetic resonance imaging of Patient 2

A. T2-weighted coronal section shows prominent cerebellar folia (arrow) with space in the infratentorial area, which is consistent with cerebellar atrophy.
B. T1-weighted sagittal image shows the prominent folia marking (arrows) in the cerebellum without atrophy of the brainstem or the cerebrum.
C. T1-weighted axial section shows the cerebellar atrophy (arrow) without atrophic changes of other structures.

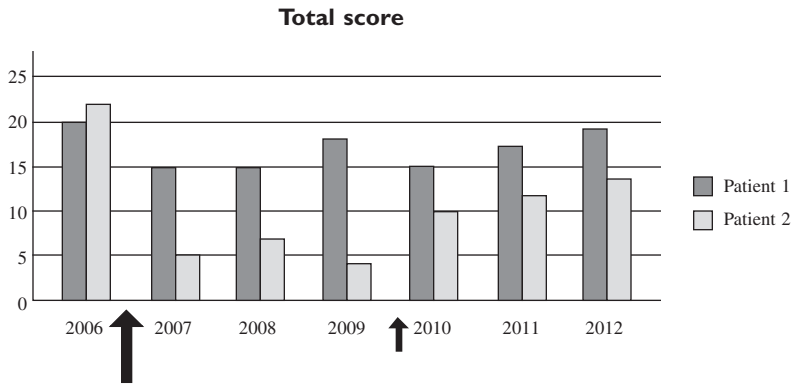

Figure 3: Serial changes of total scores of ICARS. As indicated by thick and long arrow (the time point of ginseng intake), the score improved and appeared to be maintained thereafter. Those findings were similar in both patients. However, the Patient 2 stopped ginseng between 2009 and 2010 (short arrow). X-axis: year, Y-axis: Total sum of all categories in ICARS

she claimed to be less dizzy with improvement of her gait. She said that it became easier for her to speak. These improvements had made her keep taking the ginseng. The daily quantity of ginseng was estimated at 4.5 g for the next 30 months. The ICARS score was 22 when she started taking ginseng. Two months following that, her ICARS score was 8. For the next 28 months, the averaged ICARS score was 6.0 ± 1.0 (ranged from 5 to 8). In 30 months, she stopped the ginseng. The reason for discontinuing was not recorded. After that, the cerebellar dysfunction worsened with the ICARS score of 11 at 10 months following discontinuation of ginseng. However, even in the recent 3 years, ICARS score ranged from 11 to 13 (mean ± SD; 12.3 ± 1.2), which was better than that when she began the ginseng intake. In particular, this patient showed markedly improvement in the category of kinetic function (from 10 to 0). Speech function had changed from 2 to averaged score of 1.7 ± 0.6, and the category of oculomotor deficit was from 2 to 1. Posture and gait disturbances also showed an improvement from 3 to 1 (Table 2).

DISCUSSION

Ataxia is the main manifestation caused by the damage in the cerebellum. Cerebellar degenerations is one of the most common neurodegenerative disorders, next to Alzheimer's disease and Parkinson's disease. Although there is increasing knowledge on the genetics of cerebellar ataxia, till to-date, there is no effective treatment to reverse or arrest the degenerative process. Unlike Alzheimer disease and Parkinson disease, there is also no effective symptomatic treatment for ataxia from cerebellar degeneration.

Our ataxia registry was started on 21th Dec, 2004. Two hundred and eighteen patients with hereditary or sporadic cerebellar degeneration have been registered. Cerebellar functions were evaluated by ICARS scores every 6 to 12 month. Thus we can monitor the progression of disease semi-quantitatively. Unexpectedly, we found two

Table 2: ICARS scores of four categories in Patient 2

	Baseline	12 months	32 months	43 months	55 months	71 months	82 months
Posture & gait disturbances	8	4	4	2	4	6	7
Kinetic functions	10	0	0	0	5	4	3
Speech disorders	2	1	2	2	2	3	3
Oculomotor disorders	2	1	1	1	0	0	0

Table 2: She maintained ginseng up to 43 month. However, between 43 and 55 months, she had stopped ginseng and thereafter. ICARS score increased at 55 months but remained lower than the basal level.

patients who had been different from the others' progressive declining course. Further review of the paramedical environmental changes or other therapeutic modalities (for example, herb medication, exercise, acupuncture and functional food) were made in all the subjects, which may have disease-modifying effect. These enabled us to suspect that both of the patients may have been taking ginseng in common. In the rest of patients with ataxia, there was no record of other patient who took ginseng consistently over prolonged period. Intake of this functional food was not part of the physician's recommendation. Thus, physicians and examiners had been unaware of ginseng intake when they started and stopped ginseng.

The most popular ginseng product commercially available in Korea is 'Korea Red Ginseng' which is made by a special heating process from 6 year-old *panax ginseng* root. There is 500mg capsule form, and the usual recommended dose is 3 capsules per meal, 3 times a day. Further detailed information, such as number of missing days or changing into another ginseng product, were sometimes unavailable because of limitation with recall.

It is unknown how the consumption of ginseng can lead to improvement of cerebellar dysfunction. Human and experimental studies suggested that neurotoxicity in the cerebellum might be one of possible causes that results in the Purkinje cell damage, which is followed by degeneration of distal axons, the major efferent pathway.[17-20] For example, low-level of occupational exposure of acrylamide to humans produces neurotoxicity characterized by ataxia, skeletal muscle weakness and numbness of the hand and feet.[21,22] In acrylamide-induced neurotoxicity in rats, protective effect of *panax ginseng* extract has been reported, suggesting the possible neuroprotective role of ginseng on the cerebellar system.[15] In our patients, ginseng consumption has resulted in an improvement. It can be postulated that ginseng might play a protective role resulting in regeneration or recovery on the cerebellar pathway. When the Patient 2 stopped ginseng, the ICARS score declined again, which support the beneficial effect of ginseng. For the next three years without ginseng, ICARS score still remained better than that of basal level. This suggest that the effect of ginseng on the cerebellum may not be a transient phenomenon but due to structural change such as regeneration.

According to animal study, ginseng improved motor function in the experimental model of PD.[23] In our patients, improved categories in ICARS were 'knee to tibia', tremor, 'gait and body sway', 'finger to nose', 'finger to finger' and 'Archimedes' spiral,' These test items are different from those of subcortical nigrostriatal system in PD. These findings suggest that ginseng may lead to improvement not only on the motor circuit of subcortical striatal system but also the cerebellar system.

In summary, we observed the possible efficacy of ginseng on cerebellar dysfunctions in two patients, one has sporadic and the other hereditary cerebellar degeneration. However, these observations were based on only two patients, in a disease with the background of individual variation of disease progression. The other limitation was that this registry did not include video-recording. Instead, the monitoring was based on quantification by ICARS. To validate these observations, further studies with larger number of cerebellar ataxia patient as well as long-term observation with video-monitoring is warranted.

DISCLOSURE

This work was supported by the grants from the Korean Society of Ginseng, funded by Korea Ginseng Corporation.

Conflicts of interest: None

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