ORIGINAL ARTICLE

Relationship between the Characteristics of Parkinsonian Lumbago and Efficacy of Neurotropin

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ABSTRACT

Objective: **Parkinsonian lumbago is usually caused by lesions of the thalamus or spinothalamocortical pathways. Decreased lumbago directly improved quality of life.**

Materials and Methods: **We succeeded to treat Parkinsonian lumbago of elderly patients.**

Results: **One patient could walk independently during outpatient care and enjoy ground golf, even though near 24 years have passed since the onset of Parkinson's disease (PD).**

Conclusion: **Safe habits and hobbies for the elderly of whole-body exercise such as ground golf exercise habits, rehabilitation, medications and Neurotropin are suspected to be favorable for long-term prognosis of PD.**

KEY WORDS

Parkinsonian lumbago, Neurotropin, Parkinson's disease (PD), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), ground golf

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INTRODUCTION

An α-synuclein (aSyn) fragment, known as the non-amyloid β component of Alzheimer's disease amyloid, originally found in an amyloid-enriched fraction[1-18]. In the process of seeded nucleation, aSyn acquires a cross-sheet structure similar to other amyloids[1-18]. PD patients carrying glucocerebrosidase (GBA) mutations show intraneuronal accumulation of aSyn called Lewy bodies and Lewy neurites[1-18]. ASyn (PARK1), Parkin (PARK2), and GBA(PARK9) were found in PD[19-24]. PARK1 is created in the gut and may migrate via the vagus nerve to the brainstem and then to the substantia nigra. Furthermore, the bacteria Proteus mirabilis has been associated with higher levels of PARK1 and an increase of motor symptoms in PD patients[2,23,25-46]. Further elucidation of the causal role of PARK1, the role of inflammation, the gut-brain axis, as well as an understanding of the individual differences in immune stress responses is needed to better understand the pathological development of PD. PD patients have altered gut microbiota and colon problems years before motor issues arise. Inoculation of PARK1 preformed fibrils into the mouse gastrointestinal tract induces Lewy body-like aggregates in the brainstem via the vagus nerve[19-24]. As the PD progresses, Lewy bodies develop in the substantia nigra, areas of the midbrain and basal forebrain, and finally, the neocortex[2,23,25-46]. The aggregation of PARK1 in Lewy bodies appears to be a link between reduced DNA repair and brain-cell death in PD. individuals with PD have PARK1 deposits in the digestive tract as well as the brain. Lewy bodies first appear in the olfactory bulb (OB), medulla oblongata, and pontine tegmentum; individuals at this stage may be asymptomatic or may have early nonmotor symptoms[2,23,25-46]. Changes in perception may include an impaired sense of smell, disturbed vision, pain, and paresthesia (tingling and numbness). These symptoms can occur years before diagnosis of PD[5,7,10-21]. Gastrointestinal issues in PD include constipation, impaired stomach emptying (gastric dysmotility), and excessive production of saliva can be severe enough to cause discomfort or endanger health. Other upper gastrointestinal symptoms include swallowing impairment (Oropharyngeal dysphagia) and small intestinal bacterial overgrowth[19-24]. PD and autoimmune disorders share genetic variations and molecular pathways. The neuroimmune interaction is heavily implicated in PD pathology. Autoimmune diseases linked to protein expression profiles of monocytes and CD4+ T cells are linked to PD. Immune cell implicated in PD are peripheral monocytes and have been found in the substantia nigra. Monocytes isolated from PD patients express higher levels of the PD-associated protein, LRRK2. Peripheral inflammation can affect the gut-brain axis, an area of the body highly implicated in PD. PARK9 plays a protective role against the aggregation of PARK1 by maintaining the integrity of the lysosomal membrane and also promotes the ATPase-independent secretion of PARK1 through nanovesicles. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a drug known for causing irreversible parkinsonism. As for the change of dopamine receptors in MPTP-induced monkey parkinsonism, an increase of ^{3}H-spiperone binding sites in the striatum was observed as having been confirmed autoradiographically by us in brains of Parkinson's patients[2,24,36-46]. PARK1 null mice are resistant to MPTP toxicity. Age is an appropriate predictor of disease progression. The rate of motor decline is greater in those with less impairment at the time of diagnosis, while cognitive impairment is more frequent in those who are over 70 years of age at symptom onset. Disability is initially related to motor symptoms. As the disease advances, disability is more related to motor symptoms that are uncontrollable by medication, such as swallowing and speech difficulties, and gait and balance problems; and to levodopa-induced complications. A severity rating method known as the Unified PD rating scale (UPDRS) is the most commonly used metric for a clinical study. The Hoehn and Yahr (HY) scale defines five basic stages of progression[1-5,46-69]. Non-dopaminergic basal ganglia neurotransmitter systems, possibly implicate in the pathogenesis of motor complications, may also contribute to lumbago[1-5]. Parkinsonian lumbago is usually caused by lesions of the thalamus or spinothalamocortical pathways[6,7,11-13]. Involvement in Parkinsonian brain and nerves causes some Parkinsonian lumbago[8-12]. Lumbago may occur as a result of the monoamine deficiency that characterizes PD[4-7].

Decreased lumbago directly improved quality of life. Ground golf is good effect of elderly health lifespan[19-24]. Parkinsonian patients experience any combination of lumbago, anxiety, and depression[4-7]. Constipation is one of the symptoms associated with an increased risk of PD and may precede diagnosis of PD. Exercise in middle age may reduce the risk of PD later in life. Caffeine also appears protective with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee[1,25-36]. Coffee drinkers, tea drinkers, and tobacco smokers are at a reduced risk. The use of ibuprofen and a decreased risk of Parkinson's development[2,24,36-46]. We dramatically succeed to treat lumbago with additional Neurotropin treatment in the advanced stage of elderly PD woman[2,47-56]. The use of Neurotropin in lumbago of PD seemed a promising tool to improve lumbago[2,47,56-67].

MATERIALS AND METHODS

Study population: We experienced an 82-year-old male and an 87-year-old female with Parkinsonian lumbago patients. They were clinically followed. After treatment with Neurotropin, their lumbago dramatically improved. We analysed them.

The present study conformed to the provisions of the declaration of Helsinki in 1995 (as revised in Edinburgh in 2000)[1-5].

RESULTS

Case 1 was an 82-year-old male. Chief complaints were hand tremor(4-6 Hz) and gait disorder. He had the hobbies of ground golf (twice a week, 2 hours each time, walking 3,000 to 4,000 steps), walking 1 km on days without ground golf. He had no smoking or drinking habits. At 58 years old occasional tremors(4-6 Hz) in the right hand appeared at rest. It gradually appeared on the left hand as well. At age 60 resting tremors(4-6 Hz) also appeared in both lower extremities. He visited a nearby neurology clinic and was diagnosed with PD. Medication of levodopa tablet (10:1 levodopa mixture with carbidopa) was started, and symptoms improved to some extent. At age 61 bradykinesia worsened, and he leaned forward and walked in short steps. At 70 years old difficulty turning over and putting on and taking off clothes. In particular, the right hand holding chopsticks began to tremble while eating. Drinking water with a straw because the water in the cup spills. He came to our medical center from his house at 10 km for 1 hour. He was able to enter the examination room on his own. His height was 169 cm, weight 75 kg (BMI 26.3), blood pressure 100/70 mmHg, and pulse 72 bpm. Mildly decreased sense of smell. He had mask-like facial expression, dysarthria (low voice, monotonous), resting tremor(4-6 Hz) of extremities, dexterity movement disorder of both fingers, rigidity of extremities (right > left), bradykinesia, impaired postural reflexes, forward leaning posture, short gait, tendency to fall, difficulty in standing up from the floor, decreased peripheral skin temperature of both lower extremities, orthostatic hypotension (OH) (recumbent blood pressure 120/70 mmHg → standing blood pressure 90/50 mmHg), constipation, and frequent urination. Coefficient of variation of R-R interval decreased to 0.76%. The 30-second gravic body sway test (stabilometry) showed a slight increasing of the total locus length of 54.1 cm with both leg stand with eyes open and 56.7 cm with eyes closed. Brachial-ankle pulse wave velocity (right 2265 cm/s, left 2112 cm/s) was high. His pharmacotherapy was levodopa 300 mg, zonisamide 100 mg, pramipexole 1.5 mg, droxidopa 600 mg, sennoside 36 mg, furosemide 10 mg, potassium L-aspartate 300 mg, and ethyl tocopherol nicotinate 600 mg/day. He got speech therapy and physical therapy training twice a month, 1 hour each. Ethyl icosapentate 1200 mg/day was added because systemic arteriosclerosis was suspected as indicated by peripheral circulatory disorders such as edema in the lower extremities and decreased skin temperature, and high baPWV values. Regarding details of dysarthria, a moderate decrease in volume and mild breathy hoarseness were observed, but articulation accuracy at the monosyllable level was high, and speech articulation was 2 out of 5 (the level where there are sometimes unaccuracy words). Speech therapy training aims to improve speech accuracy by being conscious of the increase in voice volume when speaking, and through regular outpatient rehabilitation training and home training. It is possible to maintain an appropriate voice volume in daily conversations and practice to make it a habit. Physical therapy training consisted of maintenance of joint range of motion, prevention of contracture, walking while standing, balance maintenance, and postural change training. At 71 years old, he applied for a specific disease (Japan intractable disease) from the Japanese Ministry of Health, Labor and Welfare, and was approved as a PD with HY stage 3 and degree of disability stage 2. The UPDRS score was a total score of 69 points; part 1 (the functions of mentation, behavior and mood) was 1 point, part 2 (the activities of daily living) was 36 points, part 3 (the motor functions) was 27 points, and part 4 (evaluates the complications

induced by anti-Parkinsonian drugs) was 5 points respectively[19-24]. Both the revised version of Hasegagwa's dementia scale (HDS-R) and the Mini-Mental State Examination (MMSE) scored 30 points respectively, no cognitive impairment was seen. Although he walked shuffling and had poor balance, he was able to take a bath by himself using a handrail. Regarding constipation, he had bowel movements once every 2 to 3 days. When walking, the forward bending posture is enhanced and the patient moves to the right. A rush phenomenon was also observed. Sitting blood pressure 92/62 mmHg, pulse 66 bpm. Droxidopa 600 mg/day was effective for OH. At 73 years old grip strength was 34 kg on the right and 12 kg on the left. When sitting, tilted to the right in addition to bending forward. The frequency of ground golf participation was increased (4-5 times/week). Since lumbago developed, neurotropin 624 mg(16 units)/day was added and his lumbago was relieved. Drowsiness developed after meals, especially after lunch. He often takes a nap. There were times when he suddenly fell asleep while eating and fell asleep at the dining table. At 74 years old he had nightmares during his sleep that caused him to move and fall under the bed twice (rapid eye movement sleep behavior disorder). Physical movement worsened and fatiguability appeared. His stooped posture, tilted posture to the right, difficulty in standing up, and difficulty in rolling over were aggravated. 4.5 mg/day of rotigotine patch was added. He participated in ground golf every day except Sunday. He was skilled enough to win several tournaments. Peak-dose dyskinesia of involuntary movements appeared. Defecation was 1 time/4 to 5 days, and constipation worsened. At 75 years old he became aware of freezing gait, whispering and wearing off, and decreased memory. Visual hallucinations (insects, etc.) Ground golf is fun and he can move around a lot, but after it ends, he feel tired all over his body. Sitting blood pressure 84/50 mmHg, pulse 78 bpm. There was an episode of orthostatic syncope. At 76 years old, visual hallucinations appeared. Movement worsened (immobility and gait disturbance worsened). A fall resulted in bruises and cuts on the right side of the face. Occasionally, eye-opening apraxia appeared. He fell while participating in a bus tour accompanied by his wife. At 77 years old falling indoors. Blood pressure 80/50 mmHg, pulse 64 bpm. Visual hallucinations (such as figures) appear in the evening or at night. Additional oral administration of butyric acid bacteria (Miya BM) 120 mg/day for defecation control. At 78 years old weight 63-65 kg, blood pressure 65/50 mmHg, pulse 67 bpm. No dizziness. 1 bowel movement/4-5 days. Oral sennoside 24 or 36 mg if no bowel movements for 5 days. He took a bus tour. At 79 years old ground golf participates 2-3 times a week. The oligarchy progresses. Occasional hallucinations (children and adults, sometimes holding sticks at the door). Dyskinesia appeared in the extremities and trunk. Due to exacerbation of dyskinesia, 100 mg/day of zonisamide was discontinued, and the dose of rotigotine patch was increased to 9 mg/day. Magnesium oxide 660 mg/day was added for stubborn constipation. Good bowel control. The incidence of visual hallucinations was low. However, he was very drowsy and realized that he was forgetful and unable to remember new things. At 80 years old he canceled ground golf. Especially the right leg is hard to come out. Defecation was once/7 days, smooth with magnesium oxide 990 mg/day. Fall due to fainting due to OH. Dizziness on standing up sometimes appeared. Visual hallucinations (snakes, people outside) appeared in the middle of the night. Yokukansan was added at 2.5 g/day before going to bed at night. This helped him sleep better. Sometimes forgetful. Weight decreased to 62-63 kg. In mid-October, along with the development of drug eruption on the back skin, a mild malignant syndrome (immobility, general weakness, fever, blood CK 299 IU/L, CRP increased to 12.82 mg/dl) developed. Fluid replacement and yokukansan were discontinued, and the dose of magnesium oxide was reduced to 660 mg/day for improvement. Ground golf restart (once/week). He was transported by ambulance due to orthostatic syncope. Furosemide was discontinued because leg edema also improved. Since pruritus and redness (contact dermatitis) occurred at the application site after applying rotigotine 9 mg, the ropinirole hydrochloride patch was changed to 8 mg/day, and the dermatitis improved. At 81 years old ropinirole hydrochloride patch 8 mg/day was effective, and movement improved. From this time onwards, he walks alone, but uses a cane. Ground golf once a month. Visual hallucinations (snakes, people) appear at night. He also has urinary incontinence and wears diapers only at night. Midodrine hydrochloride 4 mg/day was added for hypotension. Blood pressure 100/61 mmHg, pulse 72 bpm. At 82 years old HY stage became stage 4 (severe disability was indicated, but walking was somehow possible without assistance). He required partial assistance for daily living and going to the hospital. The UPDRS was a total score of 86 points; part 1 was 6 points, part 2 was 37 points, part 3 was 35 points, and part 4 was 8 points respectively[19-24]. HDS-R was 17 points, and MMSE examination was 20 points. He was diagnosed with mild PD dementia[1,25-36]. Stabilometry showed increasing of the total locus length of 111.7 cm with both leg stand with eyes open, and 153.3 cm with eyes closed. During outpatient care, he was able to enter the room on his own without assistance, although his wife accompanied him. In order to avoid the risk of falling or orthostatic syncope, he took a shower, but he was able to do it by himself. Speech articulation is 2 out of 5, and in terms of eating and swallowing, there is no choking with food (ordinary food), but there is occasional light choking with water (about 2 to 3 times a month). His medications were levodopa 300 mg, selegiline hydrochloride 2.5 mg, pramipexole 1.5 mg, ropinirole hydrochloride patch 8 mg, droxidopa 600 mg, midodrine hydrochloride 4 mg, butyric acid bacterium (Miya BM) 120 mg, magnesium oxide 990 mg, sennosides 36 mg, tocopherol ethyl nicotinate 600 mg, omega-3 fatty acid ethyl 2 g, and Neurotropin 624 mg (16 units)/day.

Case 2: An 87-year old female. From the age of 81 years, resting tremor of left hand and lumbago appeared. From the age of 82 years onward, the symptom had gradually extended to the lower left extremity and jaw. The patient had hypokinesia, a stooped posture and walking with short steps. From the age of 83 years, drooling appeared. She visited a neurologist in other hospital in February at age of 84 years. She was diagnosed with PD. 100 mg/day of levodopa was taken. The symptoms of muscle rigidity, hypokinesia and tremor improved. Levodopa was increased to 150 mg/day from September. However, drooling and lumbago became worse. And at the time of non effective of levodopa (off time), slow movement, gait disturbance and lumbago became worse. Some of pain drugs and massage were non effective. From the age of 86 years, abnormal sensation of feet, numb sensation of bilateral finger tops and OH appeared. Gait disturbance and hypokinesia became worse. Then levodopa was increased to 200 mg/day. Lumbago became worse and she consulted our hospital in January at the age of 87.

Physical examination combined with a routine general and vascular examination revealed a height of 142 cm, a body weight of 50 kg, a blood pressure of 133/70 mm Hg, and a regular heart rate of 66 beats/min. She had mask-like facial expression, speech disturbance (whisper, slurred), deglutition trouble, and drooling. She showed bilateral hand and jaw resting tremor (left side > right side), limbs muscle rigidity (left side>right side), and hypokinesia. She had disturbance of posture reflex, stooped posture, and right side sliding posture (pisa phenomenon). Her pathological reflex was negative. Sense torpor and numb sensation of finger tip, foot fingers and plantar feet existed. She had walking with short steps and without hand movements. She had frozen gait. She turned with gait assist machine with short steps. She had slight OH (supine position 142/80 mmHg, heart rate 64/ min; standing position 120/80 mmHg, heart rate 72/ min), strong constipation, and low peripheral skin temperature of bilateral fingers, foot fingers and plantar feet.

She was diagnosed with PD at modified HY stage 4. The UPDRS; part 1 became 2, part 2, 20 (on time); 28 (off time), part 3, 46 (on time), part 4, 3 and total, 71 (on time), respectively. The HDS-R became 25. Severity of pain measured on a VAS. Her VAS score for lumbago was 52 mm on a 0-100 mm scale.

Her parkinsonism had been controlled with 200 mg/day of levodopa and 1 mg/day of trihexyphenidyl. 624 mg (16 units)/day of Neurotropin pills was added from January. As a result of the Neurotropin treatment for 2 weeks, the lumbago slightly improved. The lumbago disappeared completely for 4 weeks. Her VAS score for lumbago became 0 mm on a 0-100 mm scale at March (after 8 weeks). After that, Parkinson's symptoms (hypokinesia, gait disturbance, adiadochokinesis disturbance, and movement diturbance) became worse, then levodopa was increased 300 mg/day. At September her VAS became 0 mm. Her modified HY and UPDRS were no change. No side effects of Neurotropin were observed.

DISCUSSION

There is a noticeable correlation between the severity of lumbago and motor complications[5,7,10-21]. Lumbago possibly is the consequence of the frequent or prolonged muscle hyperactivity associated with dyskinesia and motor fluctuations. The progression of PD can lead to degeneration of the lumbar spine, and this can lead to low back pain for 88% of this population. The knowledge about musculoskeletal conditions in PD is important for an interdisciplinary conservative or operative treatment decision. For conservative treatment Neurotropin decreases the prevalence of lumbago and improves quality of life. Some lesion of the nerves in the Parkinsonian brain causes depression, anxiety disorders, lumbago and movement disorders of PD. Abnormalities in nociception has been described in PD[1,3,6,7,11-13]. They have been considered to be due

to anomalies of central nociceptive processing and sensorimotor integration through the affection of basal ganglia and dopaminergic pathways. Abnormalities in sensory processing, through a basal ganglia involvement, are thought to be responsible for the sensory dysfunction. Parkinsonian lumbago could be in part due to central modification of nociception. Clinical and electrophysiological evaluation have shown the involvement of basal ganglia and thalamocortical-basal ganglia circuits are considered the basis for this sensory defect. Lumbago may be due to a dysfunction of pain pathways or the processing of pain inputs in the brain. Abnormalities of mechanical sensitivity and of nociception have been taken into account to explain the impaired balance control in PD or the primary Parkinsonian lumbago. The dysfunction may occur in dopamine-dependent centers regulating both autonomic function and inhibitory modulation of pain inputs. Hyperexcitability of locus ceruleus or dorsal horn neurons results in a decreased efficiency of descending pain inhibitory systems[4-8]. The central nervous system, with its dopaminagic deficiency, is suggested to be involved in lumbago due to "off" pain during Parkinsonism treatment[8]. Once this relationship is recognized, the lumbago can be managed by achieving better control of the disease. In case 2, levodopa decreased her lumbago in "on" conditions, however her lumbago did not disappear. We dramatically succeed to treat her lumbago with additional Neurotropin treatment.

Neurotropin is a biological material obtained from inflamed rabbit skin inoculated with vaccinia virus and has been widely used clinically as an effective agent for lumbago in Japan for many years[4-11]. The effect of Neurotropin in lumbago may be related to inhibit activation of the kallikrein-kinin cascade and consequently the formation of bradykinin[1,3,6,7]. Neurotropin inhibits the release of bradykinin. Neurotropin may act at a supraspinal site. Its effect is dose-dependent and probably involves the supraspinal site of action and the sequential activation of spinal noradrenalin neurons. The analgesic effects of Neurotropin are thought to be the activation of a descending pain inhibitory system. Neurotropin produces analgesia by activation of a descending pain inhibitory system. The analgesic action of Neurotropin is due to the enhancement of noradrenergic and serotonergic descending pain inhibitory pathways. It has been reported that chronic pain is pervasive in cases of PD, and that approximately 40% of patients with PD suffer from lumbargo[1,3,6,7,11-13]. The results of this study may have implications for understanding lumbago mechanisms in PD, with the ultimate aim of designing strategies to prevent or cure lumbago in patients with PD. Issues related to pain have a deep impact on quality of life. Lumbago sometimes aggravates quality of life of PD patients on addition with the severity of motor disturbance. Lumbago may subsequently contribute to the decrease of quality of life of PD. Neurotropin is more efficacious and has fewer adverse effects. Neurotropin is administered as a first-line drug. We present PD lumbago patients who responded to Neurotropin. Decreased lumbago directly improved thier quality of life[1-5].

For the 12 years from 70 years old to 82 years old, case 1's HY stage worsened only one stage. For the 11 years from 71 years old to 82 years old, his UPDRS total score also worsened only 17 points. For a long period of 11 to 12 years, his degree of progression of PD was considered to be slow in both stage and score. As shown by the results of the postural sway test, the postural reflex disorder was progressing, nevertheless he was able to stand up on the examination table by himself even with his eyes closed. Occasionally, visual hallucinations also appeared, which may have contributed to the worsening of the UPDRS part 1 scores. From the results of the postural sway test, it seemed that the worsening of The UPDRS score in part 3 was consistent. However, the fact that the UPDRS score part 2 remained almost unchanged is noteworthy. At 24 years(from 58 years old to 82 years old) after the onset of PD, this is rare case to be able to walk into the examination room on his own during outpatient visits. Oral administration was started at the age of 60, and the dose of 300 mg/day of levodopa remained unchanged until the age of 82. This is also rare. His stage has not reached HY stage 5; the final stage of PD (living in a bed or wheelchair without assistance) or level 3 of life dysfunction (requires full assistance in daily life, unable to stand up on his own)[2,24,36-46]. Therefore, it can be said that the long-term prognosis is extremely good. It is thought that he started ground golf tournament around the age of 59 when his PD symptoms had just started, and continued to enjoy his ground golf tournament championship almost every day. Ground golf was invented in 1982 in Tomari Village, Tottori Prefecture (currently Tomari, Yurihama Town) in Japan. It is a sport that everyone from children to the elderly can enjoy playing because it does not require advanced skills and the rules and preparation are simple. In addition, there are no restrictions on the time or number of players, and you can freely set the course anywhere as long as it is safe. Hit the ball with a club like in golf and count the number of strokes until it hits the hole post. The ball is safe because it rolls on the ground instead of flying through the air. There is also a hole-in-one system, in which case there is a privilege of subtracting 3 strokes from the player's total number of strokes on each hole, which is designed to encourage and motivate players. In addition, there is a proper mix of scenes where you exert your full strength and scenes where you exercise your concentration and coordination. This example had become proficient enough to win the regional ground golf championship many times. Together with his wife, he has been habitually continuing light whole body exercise while enthusiastically enjoying it as if it were a game. On a daily basis, he feels a sense of accomplishment and satisfaction, and he has continued good communication with his wife and colleagues. Such mental, physical activity and Neurotropin activates and maintains the activities of dopaminergic neurons and various neurotransmitter neurons, and has put the brakes on degenerative degeneration of dopaminergic neurons and other neurons over the long term as for 24 years[2,47-56].

The factors those contributed to the favorable long-term prognosis were the exercise habits of ground golf that were continued during the disease period, rehabilitaion, medication and Neurotropin. It was presumed that habits and hobbies of whole-body exercise such as ground golf, which can be safely continued in the sense of a game even for the elderly, have a positive effect on the long-term prognosis. Accelerated ground golf in not only healthy people, but also those with PD has focused new-found attention on this area. Our case is very suggestive in the areas of ground golf and PD[5-10].

This is the report of successful treatment of moderate lumbago in advanced stage of PD patients with additional Neurotropin pill treatment. This is also the one of reports on quantitative measurement of pain sensation using VAS score in patient with PD. In lumbago etiologies of case 2 pain correlated with Parkinson's "off" period. The amount of lumbago was maximal in the "off" state. Lumbago was markedly relieved when the patient was in the "on" state. Lumbago related to the "off" state. Parkinsonian lumbago is originated PD. We considered the lumbago was due to parkinsonism.

However, further studies are needed to confirm the efficacy of Neurotropin for PD lumbago. In next study, effect of the combination of ground golf tournament championship, rehabilitation, medication and Neurotropin should be examined. Because currently available therapies are ineffective for neurological manifestations, a strong demand exists for elucidation of the pathological mechanisms and the development of novel therapies. To determine the combination of ground golf tournament championship, rehabilitation, medication and Neurotropin, and explore the pathological mechanism, we suggest that further investigations are needed.

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REFERENCES

1. Harada T, Ishizaki F, Cheng W, Nitta Y, Miki Y, Numamoto H, Yoshikawa N, Nobukuni Y, Hayama M, Ito S, Miyazaki H, Aoi S, Ikeda H, Iida T, Ando J, Kobayashi M, Ito M, Nitta Y, Sugawara T, Nakabeppu K, Nitta K. Relationship between the characteristics of animal-assisted therapy and patients. International Medical Journal 2020; 27(5): 620-623.
2. Nitta Y, Takesaki Y, Yoshino Y. Sequel: The national elementary school in Hiroshima at that time: focusing on the A-bombed trees at schools. Studies in the Health Sciences 2020; 4(2): 1-12. (in English with Japanese abstract)
3. Harada T, Ishizaki F, Miki Y, Nitta Y, Hayama M, Aonaka J, Kodama Y, Ito S, Yamamoto R, Niyada K, Miyazaki H, Aoi S, Ikeda H, Iida T, Hiroto H, Ando J, Nitta K. Relationship between characteristics of genetic study and essential thrombocythemia in aged patients. International Medical Journal 2019; 26(5): 438-439.
4. Nitta Y. Bean sprouts (Pisum sativum L.) accumulate cadmium (Cd) in their foliage. Studies in the Health Sciences 2020; 4(1): 17-24. (in English with Japanese abstract)
5. Yokoro K, Yamamoto O, Niwa O, Seyama T, Nitta Y, Kinomura A. A comparative study on the carcinogenicity in mice induced by radiations of different quality. Nagasaki Medical Journal 1989; 63: 620-627. (in Japanese)
6. Nitta Y, Takahashi S, Tao K, Amisaki M, Nomura M, Harada T, Ishizaki F. Preliminary study of bento-study-part 5 Oyster public relations. Bulletin of the Suzugamine

Women's College 2013; 60: 103-110. (in Japanese)
7. Harada T, Aonaka J, Miyazaki H, Ishizaki F, Kodama Y, Ito S, Nitta Y, Miki Y, Yamamoto R, Niyada K, Aoi S, Ikeda H, Iida T, Suehiro K, Nitta K. Impacts of high-resolution and high-cut music box audio on balance. International Medical Journal 2019; 26(2): 118-121.
8. Nitta K, Cheng WP, Harada T, Ishizaki F, Nitta Y, Miki Y, Numamoto H, Hayama M, Ito S, Miyazaki H, Aoi S, Ikeda H, Ando J, Kobayashi M, Ito M, Sugawara T, Nakabeppu K, Asakura Y. An experimental study of therapy goat. International Medical Journal 2020; 27(1): 58-61.
9. Tsuboi K, Minegishi Y, Harada T, Ishizaki F, Nitta K. A Case of Informed Consent Obtained from a Patient with Terminal Cancer and his Family using Family Function by the Primary Care Physician. Hiroshima J Med Sci 2007; 56(1·2): 11-18.
10. Nitta Y, Nomura M. Preliminary study of Bento-study. Bulletin of the Suzugamine Women's College 2009; 56: 33-43. (in Japanese)
11. Nitta Y. Genome science and small animal clinical veterinary medicine (II). Journal of the Japan Veterinary Medical Association 2009; 62(3): 171-174. (in Japanese)
12. Nitta Y. Nutritional components and amino acid composition of the oyster (Crassostrea gigas) cultured in northern part of Hiroshima bay. Studies in the Health Sciences 2018; 1(1·2): 13-23. (in Japanese with English abstract)
13. Harada T, Ishizaki F, Nitta Y, Miki Y, Numamoto H, Hayama M, Ito S, Miyazaki H, Aoi S, Ikeda H, Iida T, Ando J, Kobayashi M, Ito M, Sugawara T, Nakabeppu K, Nitta K. Relationship between the characteristics of therapy goat and children and older people. International Medical Journal 2019; 26: 405-408.
14. Nitta Y, Suenaga M, Nomura M. Preliminary study of bento-study-part 3. Bulletin of the Suzugamine Women's College 2011; 58: 29-45. (in Japanese)
15. Miyazaki H, Harada T, Aonaka J, Ishizaki F, Kodama Y, Ito S, Numamoto H, Yoshikawa N, Nitta Y, Miki Y, Yamamoto R, Niyada K, Aoi S, Ikeda H, Suehiro K, Nitta K. Relationship between autonomic nervous function and high-resolution music box audio. International Medical Journal 2020; 27(1): 13-15.
16. Nitta Y. Oysters (Crassostrea gigas) in the Hiroshima wide area urban districts concentrate cadmium (Cd) in their shells. Studies in the Health Sciences 2019; 3(1): 1-8. (in English with Japanese abstract)
17. Nitta K, Harada T, Ishizaki F, Imamura R, Hirano K, Koide T. Relationship between the characteristics of gastrointestinal symptoms and large esophageal hiatal hernia in aged patients. Int Med J 2001; 8: 211-213.
18. Nitta K, Cheng W, Harada T, Ishizaki F, Nitta, Y, Miki Y, Numamoto H, Yoshikawa N, Nobukuni Y, Hayama M, Ito S, Miyazaki H, Aoi S, Ikeda H, Iida T, Ando J, Kobayashi M, Ito M, Nitta Y, Sugawara T, Nakabeppu K. Status and practice of therapy goat in the world. International Medical Journal 2020; 27(5): 616-619.
19. Harada T, Ishizaki F, Tachiki N, Matsumoto T, Horie N, Nitta Y, Nitta K, Inoue Y, Oikawa K. Circadian rhythm of cardiovascular autonomic function in Parkinson's disease and multiple system atrophy. International Medical Journal (IMJ) 2005; 12: 37-39.
20. Nitta Y, Takahashi K, Suenaga M, Nomura M. Preliminary study of bento-study-part 2. Bulletin of the Suzugamine Women's College 2010; 57: 21-30. (in Japanese)
21. Suenaga M, Nitta Y. Life expectancy of the Hiroshima A-bomb survivors. Bulletin of the Suzugamine Women's College 2007; 41: 1-11. (in Japanese with English abstract)
22. Nitta Y, Araki N, Nitta K, Harada T, Ishizaki F, Cheng W, Ando J. Effects of monoenergetic neutron irradiation on the postnatal development of cochlea in C3H/HeN mouse. JVMS 2005; 67: 577-582.
23. Nitta Y, Araki N. Study of carcinogenesis of monoenergetic neutron irradiation on the cochlea in mouse. Nagasaki Medical Journal 2004; 79: 288-290.
24. Miyazaki H, Harada T, Aonaka J, Ishizaki F, Kodama Y, Ito S, Nozaki M, Tsujimichi N, Numamoto H, Yoshikawa N, Nitta Y, Miki Y, Yamamoto R, Niyada K, Aoi S, Ikeda H, Suehiro K, Nitta K. Study on comparison of 24 with 16 bit headphone high-resolution music box audio. International Medical Journal 2020; 27(1): 55-57.
25. Nitta Y, Miki Y, Shimazu T. Preliminary study of bento-study-part 6-Three year oyster public relations. Bulletin of the Suzugamine Women's College 2014; 61: 251-256. (in Japanese)
26. Yokoyama T, Nitta Y. History of open college of Suzugamine Women's College (part 9): from the students. Bulletin of the Suzugamine Women's College 2014; 61: 237-249. (in Japanese)
27. Nitta Y, Nakahara S, Nakamae M. Preliminary study of bento-study-part 7-Four year oyster public relations. Bulletin of the Suzugamine Women's College 2015; 62: 211-217. (in Japanese)
28. Harada T, Ishizaki F, Nitta Y, Nitta K, Shimohara A, Tsukue I, Wu X, Cheng W. Microchips will decrease the burden on the family of elderly people with wandering dementia. International Medical Journal (IMJ) 2008; 15(1): 25-28.
29. Nitta Y, Yoshino T, Abe N, Asao Y, Aoki Y, Shiga A. Text of training of care workers. Bulletin of the Suzugamine Women's College 2016; 63: 193-214. (in Japanese)
30. Harada T, Ishizaki F, Nitta Y, Aoi S, Ikeda H, Ando J, Nitta K, Ito M. Study on epigenetic differences of monozygotic twin atomic bomb survivors in Hiroshima. International Medical Journal (IMJ) 2011; 18(4): 258-260.
31. Nitta Y. Bibliography of Dr. Mary Lyon. Bulletin of the Suzugamine Women's College 2015; 62: 127-150. (in Japanese)
32. Nitta Y, Satoh K, Suga S, Endo S, Nitta K. Comparison of the effectiveness of high and low let radiations for the proportion of survivals with liver tumors at every age in (C57BL/6N x C3H/HeN) F1 Mice. Journal of Veterinary Medical Science 2006; 68(7): 647-653.
33. Nitta Y. Age-dependent contributions of neck circumference to indices of obesity among female college students aged 18 to 20 Years. Studies in the Health Sciences 2018; 2(1): 1-9. (in English with Japanese abstract)
34. Nitta Y. A longitudinal study of the health care of atomic bomb survivors. Studies in the Health Sciences 2020; 4(1): 1-15. (in English with Japanese abstract)
35. Ito S, Harada T, Miyaguchi M, Ishizaki F, Chikamura C, Kodama Y, Niyada K, Yamamoto R, Nitta Y, Shiromoto O, Imaizumi S, Nitta K. Effect of high-resolution audio music box sound on EEG. International Medical Journal 2016; 23: 142-144.
36. Harada T, Nitta Y, Ishizaki F, Ito S, Niyada K, Aoi S, Ikeda H, Shiokawa M, Tamura N, Iida T, Nitta K. Epidemiological study of eating habit of middle-aged and elderly women: Mihara and Hiroshima questionnaire study. International Medical Journal 2017; 24: 214-218.
37. Nitta Y, Kamiya K, Yokoro K. Vitamin E and carcinogenesis. Journal of Toxicologic Pathology 1994; 7(2): 179-190.
38. Ito S, Harada T, Ishizaki F, Yamamoto R, Niyada K, Miyazaki H, Nitta Y, Chikamura C, Suehiro k, Nitta K. Effect of high-resolution audio on function of autonomic nervous system. International Medical Journal 2016; 23(4): 339-341.
39. Nitta Y, Miki Y, Harada T, Ishizaki F. To measure the concentration of zinc and cadmium in wild oyster shells was onformative to evaluate the sanitary environment. Hiroshima Journal Veterinary Medicine 2017; 32: 81-85. (in Japanese with English abstract)
40. Nitta Y. Pteridophytes in the Hiroshima wide-area urban districts concentrate cadmium (Cd) in their leaf and stem. Studies in the Health Sciences 2020; 3(2): 1-8. (in English with Japanese abstract)
41. Harada T, Moriwaki Y, Ito S, Ishizaki F, Yamamoto R, Niyada K, Miyazaki H, Nitta Y, Aoi S, Ikeda H, Iida T, Nitta K. Influences of high-resolution music box sounds on the peripheral vascular system. International Medical Journal 2016; 23: 709-711.
42. Nitta Y, Harada T, Ishizaki F, Iida T, Aoi S, Ikeda H, Shiokawa M, Tamura N, Chikamura C, Nitta K. Dietary patterns and risk of dementia: Two-city cohort study. Medical Consultation & New Remedies 2013; 50(5): 479-485. (in Japanese)
43. Harada T, Ishizaki F, Togo M, Yamashita H, Nitta K, Date Y, Nakazato M, Yamamura Y, Nakamura S. A sporadic case of late-onset familial amyloid polyneuropathy type I (transthyretin Met 30-associated familial amyloid polyneuropathy) inborn habitant of Ehime prefecture. Brain and Nerve. 2002; 54: 615-619. (in Japanese with English abstract)
44. Nitta K, Cheng W, Harada T, Ishizaki F, Nitta y, Miki Y, Numamoto H, Yoshikawa N, Nobukuni Y, Ando J, Ito M, Ito K, Ito S, Nitta Y, Nitta S, Kobayashi M, Sugawara T, Nakabeppu K, Takebayashi K, Yamanaka T. Relationship between the characteristics of Therapy Goat and Goat Keeping. International Medical Journal 2021; 28(6): 629-632.
45. Harada T, Ishizaki F, Ito S, Aoi S, Miyaguchi M, Ikeda H, Nitta Y, Mibu M, Ida T, Chikamura C, Tamura N, Nitta K. Study of objective evaluation of effect of psychological relaxation using classic music. International Medical Journal 2017; 24: 31-33.
46. Nitta Y. Behavioral genetics-1. Contribution of the twin research-. Bulletin of the Suzugamine Women's College 2006; 40: 25-36. (in Japanese with English abstract)
47. Harada T, Kurai R, Ito S, Nitta Y, Aoi S, Ikeda H, Iida T, Miyazaki H, Umei N, Chikamura C, Ishizaki F, Nitta K. Effect of joyful and anxiety-provoking music on autonomic nervous system function. International Medical Journal (IMJ) 2017; 24(2): 211-213.
48. Harada T, Yamamoto S, Fujita Y, Ishizaki F, Nitta Y, Ito S, Niyada K, Aoi S, Ikeda H, Hiroto H, Nakamura S, Takigawa A, Yoshida A, Iida T, Nitta K. Relationship between peripheral vascular metabolic change and handgrip exercise. International Medical Journal 2017; 24(4): 321-323.
49. Harada T, Fujita Y, Yamamoto S, Ishizaki F, Nitta Y, Aoi S, Ikeda H, Hiroto H, Iida T, Nitta K. Impacts of Tai Chi on balance in healthy young adults. International Medical Journal 2018; 25(2): 92-94.
50. Ito S, Harada T, Ishizaki F, Yamamoto R, Niyada K, Miyazaki H, Nitta Y, Suehiro K, Nitta K. Relationship between acceleration plethysmography and headphone high-resolution music box audio. International Medical Journal 2018; 25(5): 327-329.
51. Harada T, Ishizaki F, Murata Y, Mitsuoka K, Kumagai R, Nitta K, Nakamura S. Clinical characteristics of neuroleptic malignant syndrome in Parkinson's disease and other neurological disorders. International Medical Journal 2001; 8: 249-257.
52. Kito S, Miyoshi R, Mizuno K, Nitta K, Matsubayashi H, Yamamura Y. Autoradiographic distributions of neurotransmitter receptors in the brain of patients with Parkinson's disease and MPTP-induced monkey parkinsonism Neurology, edited by Poeck K, Freund HJ, Ganshirt H. Springer-Verlag, Heidelberg, 477-486 1986.
53. Kito S, Miyoshi R, Mizuno K, Nitta K, Matsubayashi H, Yamamura Y, Tahara E. Autoradiographic distributions of neurotransmitter receptors in the human brains of Parkinson's disease and primate models of MPTP-induced parkinsonism Advances in Neurology, edited by Yahr MD, Bergmann KJ. Raven Press, New York, 45 159-165 1986.
54. Harada T, Ishizaki F, Hamada M, Horie N, Nitta Y, Nitta K, Katsuoka H, Nakamura S. Circadian rhythm of heart-rate variability and autonomic cardiovascular regulation in Parkinson's disease. Autonomic Nervous System 2009; 46: 333-340.
55. Harada T, Ishizaki F, Horie N, Katsuoka H, Nitta Y, Yamada T, Nitta K, Ito M. Relationship between Characteristics of family care and Alzheimer disease in the Elderly. Medical Consultation & New Remedies 2010; 47(10): 1051-1054.

56. Harada T, Ishizaki F, Horie N, Katsuoka H, Nitta Y, Yamada T, Nitta K, Ito M. Case Study of Successful Surgery for Chronic Subdural Hematoma Associated with Alzheimer's Disease Receiving Warfarin. Medical Consultation & New Remedies 2011; 48(1): 17-18.
57. Harada T, Ishizaki F, Horie N, Katsuoka H, Nitta Y, Yamada T, Nitta K, Ito M. Relationship Between Characteristics of Dementia and Progressive Supranuclear Palsy in the elderly. Medical Consultation & New Remedies 2010; 47(10): 479-485.
58. Harada T, Ishizaki F, Tatiki N, Nitta K, Nakamura S. Evaluation of gastric emptying in Parkinson's disease. Int Med J 2002; 9: 209-213.
59. Harada T, Ishizaki F, Cheng WP, Horie N, Tachiki N, Okazaki M, Nitta K, Nakamura S. Analysis of skin autonomic nervous function in patients with neurodegenerative diseases. International Medical Journal (IMJ) 2002; 9 (4): 275-278.
60. Harada T, Ishizaki F, Tachiki N, Nitta K, Horie N, Matsumoto T, Inoue K, Nakamura S. Evaluation of cardiovascular circadian rhythm in patients with Parkinson's disease. Int Med J 2001; 8: 269-274.
61. Harada T, Ishizaki F, Horie N, Nitta Y, Yamada T, Sasaki T, Nagakane T, Yasumatsu Y, Nitta K, Katsuoka H. New dopamine agonist pramipexole improves parkinsonism and depression in Parkinson's Disease. Hiroshima J Med Sci 2011; 60(4): 79-82.
62. Harada T, Ishizaki F, Nitta Y, Yamada T, Horie N, Hamada M, Yamaoka K, Kanbe M, Nitta K. Circadian rhythm of cardiovascular autonomic nervous function in Parkinson's disease, early-onset parkinsonism and multiple system atrophy. International Medical Journal (IMJ) 2006; 13: 131-133.
63. Nitta K, Harada T, Ishizaki F, Ishizaki M, Nitta Y, Katsuoka H, Nitta S. Relationship between the Characteristics of Goat therapy and Medical Costs. Relationship between the Characteristics of Goat therapy and Medical Costs. International Medical Journal 2023; 30(1): 48-50.
64. Nitta K, Harada T, Ishizaki F, Ishizaki M, Nitta Y, Katsuoka H, Nitta S. Relationship between the Characteristics of Esophageal Hiatal Hernia and Mallory-Wise Syndrome in Aged Patients. International Medical Journal 2023; 30(1): 41-43.
65. Harada T, Ishizaki F, Horie N, Katsuoka H, Nitta Y, Yamada T, Nitta k. Clinical Characteristics of Anhedonia in Japanese Patients with Parkinson's Disease. International Medical Journal (IMJ) 2011; 18(3): 185-187.
66. Harada T, Ishizaki F, Horie N, Katsuoka H, Nitta Y, Yamada T, Nitta K, Aoi S, Ikeda H. Case study of V-P shunt surgery for idiopathic normal pressure hydrocephalus with rigidity and tremor. International Medical Journal (IMJ) 2011; 18(4): 346-347.
67. Harada T, Ishizaki F, Nitta Y, Aoi S, Ikeda H, Iida T, Chikamura C and Nitta K. Relationship between the characteristics of lumbago of Parkinson's disease and efficacy of Neurotropin in aged patient. International Medical Journal 2016; 23: 715-717.
68. Nitta Y, Miki Y, Numamoto H, Matsuzaki M. Research on the domestication of a perilla(Perilla citriodora). Studies in the Health Sciences 2021; 5(1): 33-38. (in Japanese with English abstract)
69. Nitta Y, Miki Y, Numamoto H, Matsuzaki M. Sequel: Research on the domestication of a perilla(Perilla citriodora). Studies in the Health Sciences 2022; 6(1): 1-7. (in Japanese with English abstract)