Accelerometer based analysis of gait initiation failure in advanced juvenile parkinsonism: a single subject study

MITSUAKI ISHII, RPT, PhD1)*, HIDEAKI MASHIMO, RPT2)

1) Department of Physical Therapy, School of Health Science, Bukkyo University: 7 Nishinokyo Higashi-toganocho, Nakagyo-ku, Kyoto 604-8418, Japan
2) Department of Physical Therapy, Maizuru Red-Cross Hospital, Japan

Abstract. [Purpose] This study used an accelerometer placed close to the center of gravity to quantitatively investigate whether unexpected gait initiation aggravates start hesitation (freezing of gait in gait initiation). [Subject and Methods] The subject was a 53-year-old female who had been suffering from juvenile parkinsonism since she was aged 21 years. An alternating-treatment design was used to compare acceleration characteristics under two gait initiation conditions, which were 1) deliberate gait initiation and 2) gait initiation on a sudden “go” verbal command (sudden gait initiation), in the “on” state of the medication cycle. [Results] In six out of eight sessions, a combination of reduced peak positive anterior accelerations and large power percentage in the high frequency band was consistently observed in the sudden gait initiation compared with deliberate gait initiation. In the other two sessions, although a large acceleration just after the “go” signal was observed, subsequent acceleration signals were blocked by sudden gait initiation. [Conclusion] The results suggest that, even in the “on” state, start hesitation is apparent without increased reliance on frontal cortical attentional mechanisms to compensate for impaired automaticity. In advanced juvenile parkinsonism, sudden gait initiation may be an effective paradigm as a provoking test for start hesitation.

Key words: Juvenile parkinsonism, Freezing of gait, Accelerometer

INTRODUCTION

Juvenile parkinsonism (JP) is a neurodegenerative disorder with an onset before the age of 40 years. JP is characterized by L-dopa responsive parkinsonism with a slow, progressive course1). Freezing of gait (FOG) is frequently observed in JP1). When the patient manifests the “wearing-off” phenomenon, FOG is more commonly observed in the “off” phase. Episodes of FOG during “wearing-off” respond to dopaminergic medications. However, as the disease progresses, FOG becomes resistant to L-dopa despite good L-dopa responsiveness of other parkinsonian features2).

FOG during the “on” phase leads to an increased risk of forward falls because the top half of the body moves forward quickly despite the feet being stuck to the ground. In addition, studies have reported that external cues, such as visual cues, are not consistently beneficial in overcoming L-dopa unresponsive FOG3).

When FOG occurs in the “on” phase, the quality of life of the patients may be further affected. However, it is often difficult to clarify the triggers of FOG in a testing environment because provocation of FOG in daily life is influenced by various contextual factors, including psychosocial aspects as well as primary impairments4).

FOG often occurs at gait initiation (start hesitation) as well as on turning (turn hesitation). Start hesitation is common when the patient is, for example, hurrying to answer the telephone or doorbell, entering an elevator, or crossing the street in
response to a traffic signal\(^5\). Therefore, it has been hypothesized that start hesitation is triggered by unexpected gait initiation. In a qualitative study, patients stated that “Waiting for a few moments before setting off to walk is important, as if I am signaling to my feet”\(^6\). This indicates that plenty of time for planning ahead is needed to cope with start hesitation. However, previous assessments of start hesitation have failed to consider the importance of the above features\(^7\)–\(^9\).

Recently, quantitative gait analysis using tri-axial accelerometry has been reported. The accelerometer is placed close to the center of gravity (COG) of the body and can produce a profile comparable to that associated with the ground reaction forces observed during walking\(^10\).

This study used an accelerometer placed close to the COG to quantitatively investigate whether unexpected gait initiation aggravates start hesitation.

**SUBJECT AND METHODS**

The patient was a 53-year-old female. The Hoehn-Yahr stage was grade 3. She was diagnosed with JP at the age of 21 years. At the age of 36 years, “wearing-off” became increasingly significant. In addition, severe rigidity of the left side of the body and mild dyskinesia were reported. FOG became unresponsive to L-dopa when the patient was aged 39 years. She underwent a right posteroventral pallidotomy at the age of 42 years. The operation successfully controlled “wearing-off,” dyskinesia, and rigidity; however, it had no effect on FOG in the “on” state of the medication cycle.

The dosages of her daily medications were as follows: L-dopa/benserazide 0.5 tablet (T) × 6, Ropinirole (dopamine agonist) 0.25 T × 4, Trihexyphenidyl (anticholinergic) 0.25 T × 1, Amantadine 1 T × 1, Droxidopa 1 T × 2, Entacapone (catechol-O-methyl transferase inhibitor) 0.5 T × 2, and Zonisamide 0.25 T × 2.

In the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)\(^11\) part II, subitem 13, the patient was grade 3 (moderate: need someone else’s help to start walking again after freezing) over the preceding week. When FOG in “on” periods developed, she had severe FOG (more than grade 3) whenever she was walking. However, while this study was being conducted, the frequency of severe FOG became more infrequent (about once a week). Consequently, the freezing of gait questionnaire (FOGQ)\(^7\) subitem 3 improved from grade 4 to grade 2.

The patient’s total score in the MDS-UPDRS Part III (Motor Examination)\(^11\) was 18 points. Tremor and rigidity were well controlled (grade 0). However, postural stability and FOG were resistant to L-dopa. Postural stability in subitem 3.12 was grade 3 (moderate).

In subitem 3.11 (FOG), the patient was grade 2 (mild: freezes on starting, turning, or walking through a doorway with more than one halt during any of these activities but continues smoothly without freezing during straight walking) under conditions without an extra task. However, she was grade 4 (severe: freezes multiple times during straight walking) when a cognitive task was added.

In the Parkinson Activity Scale (PAS)\(^8\), the patient was grade 3 (hesitation lasting up to 2 s) without an extra task, grade 2 (unwanted arrest of movement lasting 2–5 s) with a motor dual task, and grade 1 (unwanted arrest of movement lasting more than 5 s) with a cognitive dual task in both gait initiation and turning.

The results of frontal executive function tests were as follows. The patient’s total score for the Frontal Assessment Battery\(^12\) was 17 points. The time taken to complete the Stroop Test Part III was 36 s. In the Wisconsin Card Sorting Test, the patient scored 5 on the categories that were achieved, and the patient made 5 perseverative errors of the Nelson type. In the Trail Making Test, the patient completed part A in 53 s and part B in 125 s.

Ethical approval was obtained from the Bukkyo University’s Research Ethics and Governance Panel. The subject was informed about the details of the study, agreed to participate in the study, and provided written informed consent.

We used a single-subject, alternating-treatment design to compare the acceleration characteristics in each of the two conditions, which were 1) planned (self-paced) gait initiation and 2) gait initiation on a sudden “go” verbal command (sudden gait initiation). In planned gait initiation, the patient was instructed to initiate gait deliberately, i.e., (1) breaking down complex sequences into the component parts of gait initiation, (2) focusing on performing each part separately, and (3) mentally rehearsing the action sequence before performing it (planning in advance)\(^13\).

Measurements were taken during the "on" state of the medication cycle. A tri-axial accelerometer (UNIMEC, Japan) was used to measure the accelerations. The sensor was attached to the upper sacral area. Acceleration data were sampled at a rate of 1,000 Hz. Sampling data were analyzed using analysis software (WAS, UNIMEC, Japan). Acceleration signals underwent low-pass filtration using a Butterworth filter with the cutoff frequency set at 6 Hz prior to further analysis. Fast Fourier transformation was used to obtain the power spectrum of the averaged acceleration data.

Eight measurement sessions were conducted over a period of two weeks. The two conditions were varied randomly within each measurement session. The mean anterior peak acceleration of the first four steps in each gait cycle was used, and the mean frequency in the first four steps was the object variable. All data were plotted on a graph, and differences in each of the acceleration characteristics between the two conditions were observed.
RESULTS

The anterior-posterior acceleration characteristics in planned gait initiation are shown in Fig. 1-A. In sudden gait initiation, in six sessions, a combination of reduced peak positive anterior acceleration and narrowed distances of peak-to-peak positive accelerations were found (Fig. 1-B).

These sessions were analyzed using an alternative treatment design. Data analyses showed that 1) the peak anterior accelerations in sudden gait initiation were consistently smaller than those in planned gait initiation, and the mean frequency values were consistently higher in sudden gait initiation compared to planned gait initiation.

In the other two sessions, although a large acceleration just after the “go” signal was reported, subsequent acceleration signals were completely blocked on sudden gait initiation (Fig. 1-C).

Fig. 1. Anterior-posterior accelerations as measured by an accelerometer that was attached at the upper sacral area in gait initiation
A: Planned gait initiation obtained at session 2
B: Sudden gait initiation (“trembling” type of freezing) obtained at session 2
A combination of reduced peak positive anterior accelerations and narrowed distances of peak-to-peak positive accelerations
C: Sudden gait initiation (akinetic type of freezing)
Complete block in stepping motion

Fig. 2. The peak anterior acceleration and mean frequency of one subject with advanced JP in two gait initiation conditions
The peak anterior accelerations in sudden gait initiation were consistently smaller than those in planned gait initiation, and the mean frequency values were consistently higher in sudden gait initiation compared to planned gait initiation.
A: Peak anterior accelerations
Range: Planned gait initiation, 0.20 to 0.25 G; Sudden gait initiation, 0.06 to 0.10 G
B: Mean frequency
Range: Planned gait initiation, 1.46 Hz in all sessions; Sudden gait initiation, 4 sessions of 2.93 Hz and 2 sessions of 1.95 Hz
DIFFUSION

Difficulty in initiating movements (akinesia) in the “off” period is considered to be due to decreased activation of the supplementary motor area (SMA) as a result of impaired functional connectivity between the basal ganglia (BG) and SMA. However, as the disease advances, FOG becomes levodopa unresponsive. Although the precise pathophysiology is unclear, it is speculated to result from the progression of the disease process to nondopaminergic circuits, such as the frontal lobe and pedunculopontine nucleus (PPN).

Patients with FOG reportedly have executive dysfunction. It is thought that FOG becomes apparent when executive function (e.g., set-shifting, conflict-resolution) is insufficient to compensate for the loss of automaticity. However, in this patient, executive function was preserved. Therefore, it is likely that dysfunction or neuronal lesions of the PPN region may underlie levodopa-unresponsive FOG.

The combination of reduced peak positive anterior accelerations and large power percentage in the high frequency band indicates ineffective forward motion superimposed on markedly increased step frequency. These are the characteristics of the “trembling in place” type of freezing. Although this involuntary frequent leg motion is considered to be a compensatory mechanism for ineffective step length or to be associated with repeated ineffective anticipatory postural adjustments (APA) compared to the normal gait, it has recently been hypothesized that the combination of (1) excitatory projections from the subthalamic nucleus (STN) to the internal globus pallidus (GPI) due to increased activity within the STN and (2) inhibitory back projections from the GPI to the STN due to impaired activity within the striatum (absence of inhibitory striatal input) leads to the emergence of oscillatory activity. Complete block in acceleration signals indicates the “akinetic” type of freezing.

In this patient, the “trembling” or “akinetic” type of freezing was elicited in the sudden initiation task in all of the sessions. Therefore, our data support the hypothesis that start hesitation may appear with an unexpected trigger for gait initiation while standing. The results indicate that sudden gait initiation was able to identify the provoking factor for start hesitation in this patient. Conversely, it has been suggested that deliberate gait initiation provides insight into how to overcome start hesitation. Sudden gait initiation may provide an effective paradigm as a provoking test for start hesitation.

Gait initiation requires switching of the motor program from standing to walking. It is also a complex sequential task that comprises two processes: (1) APA and (2) stepping. Because the BG are defective, switching from one motor program to another and automatic execution of a complex action sequence are affected. As shown by the PAS, the patient greatly relied on cognitive function to compensate for her remarkable loss of automaticity. Therefore, it may have been necessary for this patient to become reliant on frontal cortical attentional mechanisms to initiate gait, even in the “on” state. In sudden gait initiation, it can be assumed that the patient might not be able to concentrate on how an action should be performed, such as the timing or the size of each component part of movement in gait initiation. The sudden “go” verbal signal might have distracted her attention from gait initiation due to the breakdown of cognitive compensation. In fact, the patient had acquired insight on potential triggers of FOG. She had overcome FOG episodes in many situations despite severely impaired automaticity. For example, in answering the telephone or doorbell, she implemented preparation time before gait initiation so as not to walk immediately after she heard the ringing. On entering elevators or automatic doors, she was able to predict the timing of the door opening and planned the timing of initiation in advance. Sudden gait initiation may provoke increased activity within the hyperdirect pathway due to increased response conflict, which leads to transient increases in STN firing and increases the inhibitory output of the BG. It is speculated to result from the progression of the disease process to nondopaminergic circuits, such as the frontal lobe and pedunculopontine nucleus (PPN).

Conversely, it has been reported that in APA, peak displacements of the center of pressure posteriorly and toward the stepping leg correlate with peak accelerations of COG forward and laterally over the stance foot and (2) peak accelerations of COG in the APA prior to step initiation are hemiparetic in untreated Parkinson’s disease. However, it is possible that this patient, in sudden gait initiation in two sessions, showed complete block in stepping motion without hemiparetic APA. This may have resulted from the dysfunctional integration of two parallel circuits, i.e., (1) a circuit including the SMA and BG, which generates the APA and (2) a circuit including the primary motor cortex, which generates stepping, within the locomotor area of the brainstem. This force generation to move the COG forward beyond the feet without stepping may indicate the risk for forward falls. Start hesitation in daily life may often be associated with anxiety and feeling rushed. It is well recognized that under time pressure, the more hurried the patient is, the more the feet seem to be glued to the floor despite the intention to move forward. Therefore, in a testing environment, it may be difficult to reproduce completely the start hesitation that is experienced in daily living. This is a major limitation of this assessment. However, this study may indicate that cognitive compensation and resetting through focus on goal-directed behavior are important for L-DOPA unresponsive FOG in advanced JP.

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