REPORT

Intralimb and Interlimb Incoordination: Comparative Study between Patients with Parkinsonism and with Cerebellar Ataxia

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Abstract. Dysfunction of limb coordination may be divided into two categories; intra and inter-limb incoordination. To make clear differential character in these two limb incoordination, we measured 13 patients mainly with cerebellar ataxia and 27 patients mainly with parkinsonism during pedaling of an ergometer with left and right pedals that can be rotated independently. As a result, interlimb incoordination was predominantly observed in patients with parkinsonism, while patients with cerebellar ataxia showed relatively preserved interlimb coordination but intralimb incoordination. We concluded that impairment of intralimb coordination was a character in patients with cerebellar ataxia, while impairment of interlimb coordination was a character in patients with parkinsonism.

Key words: parkinsonism, ataxia, interlimb coordination, intralimb coordination, strength ergometer, cluster analysis

Coordinated limb movements require accurate timing of activity onset in different muscles and can be distinguished by the pattern of coordination between limbs or between limb segments1,2). “Interlimb coordination” as coordination between the left and right limbs and use a term “intralimb coordination” as coordination among two or more joints in the same limb. A survey of the literature has led us to hypothesize that intralimb incoordination may be a key clinical feature of cerebellar ataxia patients1), and thus needs to be distinguished from “interlimb incoordination”, which is typical of patients with parkinsonism3-5). To obtain the results reported here, we measured intralimb incoordination in patients with cerebellar ataxia by using an ergometer with left and right pedals that can be rotated independently, and compared it with interlimb incoordination in patients with parkinsonism.

Methods

Subjects

Thirteen patients with ataxia were included in this study. They comprised 6 women and 7 men with a mean age 54.2 ± 16.5 years (range: 29–80) and a mean duration of illness of 4.9 ± 4.1 years (range: 0.6–13). They consisted of 7 patients with clinical possible multiple system atrophy (MSA6), 2 patients each with dentate-rubral pallido-luysian atrophy (DRPLA), and Machado-Joseph disease (MJD), and one patient each with cerebellar cortical atrophy (CA) and spinocerebellar atrophy type 8 (SCA 8). The diagnosis of patients with DRPLA, MJD, CA and SCA 8 was based on DNA analyses. Twenty-seven patients with idiopathic parkinsonism, who were studied in a previous investigation of ours4), were also referred. They comprised 14 women
and 13 men with a mean age of 65.7 ± 9.0 years (range: 39–78) and a mean duration of illness of 4.7 ± 4.8 years (range 2–10 years). The severity of parkinsonism ranged from stage 2 to 4 on the Hoehn and Yahr scale and the mean Unified Parkinson’s Disease Rating Scale (UPDRS) motor score (part III) was 18 ± 8.9 when they were on, and 32 ± 14 when they were off. All patients with parkinsonism were measured in on. All subjects were free of orthopedic, psychological, or other neurological constraints that could affect the study. Fifteen normal volunteers, 5 women and 10 men with a mean age of 40.5 ± 5.2 years (range: 20–69) participated in the same exercise protocol. All subjects gave informed consent for the protocol, which was in accordance with the declaration of Helsinki and ethically assessed and approved by the Human Studies Committee of Osaka University Graduate School of Medicine.

**Measurements**

We measured rotational velocities of pedals during pedaling movements with a bicycle ergometer that has newly been developed by Mitsubishi Electric Engineering (Nagoya, Japan). This bicycle ergometer (Strength Ergo 240W) has a servomechanism maintaining rotational velocity of each pedal at a desired constant value and can keep velocity constant regardless of the limb position even when a patient cannot pedal actively. This assist pedaling system does not affect profiles of pedaling in each patient. Patients were instructed to pedal the bicycle ergometer at a constant velocity of 40 rpm. If a patient cannot pedal and made passively pedal, the rotational velocity is almost constant. Rotational velocities of the left and right pedals were recorded at 0.005 sec sampling interval. All data were filtered by a zero phase-lag second-order Butterworth lowpass filter with cutoff frequency 6 Hz. Times of every peak of the oscillatory velocity profiles were carefully detected to determine each of successive pedaling cycles which was defined by the interval between one peak and its adjacent (next) peak in the right pedal’s velocity profile. The amplitude of the rotational velocity in waveform and the relative phase between the left and right lower limbs were used to analyze the pedal performance. A peak rotational velocity of each of the left and right pedals for one pedaling cycle was referred to as the amplitude of that cycle. A time series data for single 6 min pedaling exercise gives rise to two sets of the amplitude time series (i.e., for the left and right pedals) as the functions of the pedaling cycle.

**Fig. 1.** Definition of the amplitude: Solid and dashed curves represent time profiles of the rotational velocities of the right and left pedals, respectively. $A_i$ is the time interval between the i-th and (i+1)-th peaks of the velocity profile of the right pedal. $B_i$ is the time interval between the i-th peak of the right pedal’s velocity and the peak of the left pedal’s velocity located between the i-th and (i+1)-th peaks of the right pedal’s velocity profile. A peak rotational velocity of each of the left and right pedals for one pedaling cycle was referred to as the amplitude of that cycle. A time series data for single 6 min pedaling exercise gives rise to two sets of the amplitude time series (i.e., for the left and right pedals) as the functions of the pedaling cycle.

**Definition of the relative phase:** The relative phase between the left and right sides during the pedaling exercise was defined as follows. The relative phase of the i-th pedaling cycle $\phi_i$ was defined by the relative location of a peak of the velocity profile of the left pedal that falls between the i-th and (i+1)-th peaks of the rotational velocity of the right pedal. This gives rise to another time series, the relative phase time series. In equation form, the relative phase was defined as;

$$\phi_i = B_i / A_i \times 360 \, \text{degree}. \quad (1)$$

where $A_i$ is the time interval between the i-th and (i+1)-th peaks of the velocity profile of the right pedal and $B_i$ is the time interval between the i-th peak of the right pedal’s velocity and the peak of the left pedal located between the i-th and (i+1)-th peaks of the right pedal’s velocity profile. Non-oscillatory rotational velocity profiles were observed for some periods during the exercise. It was happened more frequently for the affected side than for the less affected side. When the peak of the left pedal’s velocity between the i-th and (i+1)-th peaks of the right pedal’s velocity profile could not be detected, the relative phase $\phi_i$ was not defined for the cycle.

**Statistical analyses**

All data sets for the single 6-min exercise included one set of velocity profiles of the left and right pedals and two associated time series of the amplitude and relative phase. For characterization of coordination during the exercise, five indices were defined, comprising variance of amplitude modulation (vam), mean relative phase (mrp), variance of relative phase (vrp), mean slope of regression lines (mrl) and variance of slope of regression lines (vrl).

The indice vam represents the intensity of amplitude modulation. The obtained two variances were compared to take a larger one as vam. For example, when the amplitude modulations of both sides were small, the vam took small
value. The indices mrp and vrp for the patients might represent how much their relative phase time series were deviated from the ones for normal subjects. The indices mrl and vrl were defined in order to extract information reflecting cross-correlation between the left and right velocities. (For further explanation, see appendix and reference 4). These values were calculated from a set of time series for rotational velocities of the left and right pedals, amplitude and relative phase. Detailed definitions and implications of these indices are explained in the relevant references 3-4).

A set of the five indices for each data set was considered as a point located in the five-dimensional index space and this space was used for a cluster analysis. Furthermore, we used unpaired repeated two-way ANOVA to differentiate between parkinsonism, ataxia and control at each index. Statistical significance was defined as p<0.05.

**Results**

As was described in our previous paper 4, sets of recorded values from the 27 patients with parkinsonism, were divided into four clusters. Validity of the clustering was statistically tested. In this test, for every cluster generated in the cluster analysis, the distances from the center of the cluster to all value points belonging to the cluster as well as the distances to the remaining values points were calculated. Statistical significance of differences between the two sets of distances was evaluated with Welch’s test. All values could be classified into four clusters (Fig. 2). In cluster 1, the amplitude on each side was constant and the relative phase was locked at 180°. In cluster 2, the amplitude on each side was constant, but the relative phase was locked at 90°. In cluster 3, the amplitude on each side was modulated, and the relative phase fluctuated regularly from 0° to 360° (=0°) during pedaling cycles. In cluster 4, the amplitude on each side was synchronously and irregularly modulated, and the relative phase fluctuated with intermittent spike-like decrement.

Example text: Fig. 2. The velocity waveforms exhibited different characteristics among patients with parkinsonism. In cluster 1, the amplitude on each side was constant and the relative phase was locked at 180°. The pattern was the same as seen in normal subjects. In cluster 2, the amplitude on each side was constant, but the relative phase was locked at 90°. In cluster 3, the amplitude on each side was modulated, and the relative phase drifted monotonously from 0° to 360° (=0°) during pedaling cycles. In cluster 4, the amplitude on each side was synchronously and irregularly modulated, and the relative phase fluctuated with intermittent spike-like decrement.

**Discussion**

Characteristic wave forms for cluster 1 or 2 showed relatively preserved pattern of interlimb coordination that was characterized by coordinative movements of right and left pedals, while those for cluster 3 or 4 showed impaired pattern of interlimb coordination 3-5. Six patients with parkinsonism classified into cluster 3 or 4. This may supports that interlimb coordination may be impaired in patients with parkinsonism. All but a patient with cerebellar ataxia classified into cluster 1 or 2, which may suggest that interlimb coordination is preserved in most of patients with cerebellar ataxia.
Based on clinical experiments, we classified coordination patterns into four clusters for patients with Parkinson’s disease\(^4\). These patterns, which included irregular and burst-like amplitude modulations with intermittent changes in the relative phase, correlated with the presence of the freezing phenomenon in patients with parkinsonism. Asai \textit{et al.} suggested that these particular amplitude modulations could be viewed as a typical sign of chaotic behavior in nonlinear dynamical systems\(^3\). These may be characteristic features of interlimb coordination.

Among the five indices, mrp, vrp and vrl may reflect interlimb coordination, while vam and mrl may be associated with intralimb coordination\(^3-5\). The index vam could be related to the effect of unilateral coordination on a more affected limb during pedaling. The index vrl represents time-dependent changes in overall coordination. In our study, vam and vrl for ataxia were significantly larger than those for control, but smaller for ataxia than for patients with parkinsonism. This suggests that, in patients with ataxia, intralimb incoordination may more severely affect coordination impairment than interlimb incoordination. Earhart \textit{et al.} suggested that the cerebellum was the most critical anatomical region for adjusting the relative movement of multiple joints even in a single limb\(^6\). Ataxic patients in their study demonstrated dysfunction in multi-joint coordination. Their results could indicate that the intralimb coordination of lower limbs may also be impaired during ambulation. However, evaluating intralimb incoordination during ambulation is technically complicated, while our study, by using the ergometer, reduced the degree of freedom of movements in associated joints, leading to a successful demonstration of intralimb incoordination in ataxic patients. Doya separately explained roles of the cerebellum and the basal ganglia\(^7\). However, we propose a hypothesis that the cerebellum
mainly control coordination in the ipsilateral limb while the basal ganglia between the limbs. To validate this, we are going to perform physical therapy for patients with parkinsonism and with cerebellar ataxia and evaluate coordinations with the same procedures.

In conclusion, characteristic features of intralimb incoordination may be the inability to keep amplitude and speed of pedaling constant, while characteristic features of interlimb incoordination may be the inability to keep coordinative movements of left and right pedaling.

References

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Appendix

Variance of amplitude modulation (vam)

The index vam was defined as the variance of amplitude time series. More explicitly, the variance of the amplitude time series for each of the left and right pedals was calculated. The obtained two variances were compared to take a larger one as \(vam\). Vam represents the intensity of amplitude modulation.

Mean relative phase (mrp) and Variance of relative phase (vrp)

The indices mrp and vrp were defined as the mean and variance of the relative phase time series. More precisely, \(mrp\) and \(vrp\) were defined by the mean and variance of the absolute value of difference between \(\phi\) and 180 degree (i.e. \(|\phi-180|\)), respectively. Since the value of \(|\phi-180|\) tended to be small (zero) for normal subjects exhibiting anti-phase pedaling with \(\phi\) being close to 180 degree, the indices mrp and vrp for the patients might represent how much their relative phase time series were deviated from the ones for normal subjects.

Mean slope of regression lines (mrl) and Variance of slope of regression lines (vrl)

The indices mrl and vrl were defined in order to extract information reflecting cross-correlation between the left and right velocities. When the velocity time series of the right pedal was plotted against that of the left pedal to form the truncated-ellipse-like object with multiple loops. Each loop corresponds to one pedaling cycle. Such plots were referred to as LR-plots in this sequel. Information involved in a LR-plot can be grasped by the following two examples. Suppose velocity profiles of the left and right pedals were completely identical such as in cases with

Fig. 4. Five figures indicate five indices between ataxia, parkinsonism and control.

*; significant difference (p<0.0001), **; significant difference (p<0.01), #; significant difference (p<0.05)
complete in-phase pedaling. Then the corresponding LR-plot becomes a line segment with slope +1. Similarly, if they were sinusoidal with the same amplitudes and their relative phase was 180 degree, the corresponding LR-plot becomes a line segment with slope –1. The indices *mrl* and *vrl* quantify the shape of a LR-plot based on such slopes. For a LR-plot constructed by whole velocity profiles for single 6 min exercise, however, the shape of single loops may change during the exercise. So, a given data for single 6 min exercise was divided into many segments at every 3 sec interval in which only two or three pedaling cycles were included. Since the corresponding two or three loops in the LR-plot for each segmented data tended to have a similar shape, the shape of the LR-plot could be characterized by the regression line that fits best in the least mean square sense. After obtaining the regression line of LR-plot for every segmented data, *mrl* and *vrl* were defined by the mean and variance of the slopes of the regression lines.