COMPARISON OF LONG-LATENCY REFLEX AND MIXED NERVE SILENT PERIOD RESPONSES IN VARIOUS HYPOKINETIC MOVEMENT DISORDERS

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Background and purpose – Long-latency reflex and mixed nerve silent period responses are electrophysiological methods to study the sensorimotor functions of the central nervous system. Here we aimed to study long-latency reflexes and mixed nerve silent period responses in different types of hypokinetic movement disorders in order to find an electrophysiological landmark to distinguish them.
Methods – We included 39 patients with idiopathic Parkinson's disease (IPD), 12 patients with multiple system atrophy (MSA), 10 patients with corticobasal syndrome (CBS), 5 patients with progressive supranuclear palsy (PSP) and 26 healthy participants. We recorded the segmental reflex, the long-latency reflexes and the mixed nerve silent period responses for each participant.
Results – C reflex, long-latency reflex-I and long-latency reflex-III responses were not obtained in any patients with PSP. Long-latency reflex amplitude/ F amplitude ratio was significantly lower in patients with IPD and PSP compared to healthy individuals (p=0.036, p=0.006 respectively). The mixed nerve silent period end latencies were significantly longer in IPD, MSA, CBS groups compared to the healthy individuals (p=0.026, p=0.050, p=0.008 respectively).
Conclusion – We suggest that recording long-latency reflex, particularly C reflex responses may provide promising results in distinction of CBS and MSA from PSP. Prospective studies with clinical findings and brainstem reflexes may offer more information.

A HOSSZÚ LATENCIÁJÚ REFLEXVÁLASZOKNAK ÉS A KEVERT IDEGEK CSENDES PERIÓDUSAINAK ÖSSZEHASONLÍTÁSA KÜLÖNBÖZŐ HIPOKINETIKUS MOZGÁSI RENDELLENESSÉGEKBEN

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Háttér és cél – A hosszú latenciájú reflexválaszoknak és a kevert idegek csendes periódusainak elektrofiziológiai módszerekkel való vizsgálata lehetővé teszi a központi idegrendszer szenzomotoros funkcióinak tanulmányozását. Jelen vizsgálatunk célja a hosszú latenciájú reflexválaszok és a kevert idegek csendes periódusainak összehasonlítása volt különböző hipokinetikus mozgási rendellenességekben, annak érdekében, hogy olyan elektrofiziológiai jeleket találjunk, amelyek alkalmasak megkülönböztetésükre.
Módszerek – 39 idiopathiás Parkinson-kórban (IPD), 12 multiszisztémás atrófiában (MSA), 10 corticobasalis szindrómában (CBS), 5 progresszív szupranukleáris paresisben (PSP) szenvedő beteget és 26 egészséges kontrollszemélyt vontunk be a vizsgálatba. Minden résztvevő esetében rögzítettük a szegmentális reflexet, a hosszú latenciájú reflexeket és a kevert idegek csendes periódusait.
Eredmények – C-reflex-, hosszú latenciájú reflex-I- és hosszú latenciájú reflex-III-válaszokat nem kaptunk PSP-ben szenvedő betegeknél. A hosszú latenciájú reflex-amplitúdó/F-amplitúdó arány szignifikánsan alacsonyabb volt az IPD- és a PSP-betegeknél, mint az egészséges kontrollszemélyeknél (p=0,036, p=0,006). A kevert idegek csendes periódusának végén jelentkező latenciák szignifikánsan hosszabbak voltak az IPD-, az MSA- és a CBS-csoportokban, mint az egészséges kontrollszemélyeknél (p=0,026, p=0,050, p=0,008).
Következtetés – Véleményünk szerint a hosszú latenciájú reflexválaszok, különösen a C-reflex-válaszok rögzítése

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ígéretes eszköz lehet a CBS és az MSA PSP-től való megkülönböztetésében. A klinikai leleteket és az agytörzsi reflex válaszokat egyaránt tartalmazó, prospektív vizsgálatok további információt nyújthatnak.

Keywords: *long-latency reflexes, mixed nerve silent period, parkinsonism*

Kulcsszavak: *hosszú latenciájú reflexválaszok, kevert idegek csendes periódusai, parkinsonizmus*

Recording long-latency reflexes (or long-loop reflexes, LLRs) is one of the electrophysiological methods to study the sensorimotor functions of the central nervous system[1]. By definition, LLRs are motor responses that are generated automatically by a somatosensory stimulus.[1] The electrophysiological measurements of this reflex represent the integrity of the network of dorsal column, medial lemniscus, thalamo-cortical and cortico-spinal pathways. Any change in these networks can affect the reflex[1]. LLRs are classified into three different types according to the onset latencies: LLRI, LLRII, LLRIII. They can be obtained during rest or active contraction. If LLRI can be detected at rest, it is associated with cortical excitability. A similar stimulation, which is called mixed nerve stimulation also triggers an electromyographic silent period in the contracted voluntary muscle (mixed nerve silent period, MnSP)[2]. A peripheral silent period is a decrease in the activity of a contracted voluntary muscle in response to a stimulus. It can be triggered electrophysiologically by either a cutaneous stimulation or mixed nerve stimulation.[2] The mixed nerve stimulation seems to be made up of three different parts including collision of antidromic with orthodromic motor impulses, Renshaw cell inhibition activated by antidromic motor impulses and activation of cutaneous fibers in the mixed nerve[2, 3].

LLRs have been studied in movement disorders such as idiopathic Parkinson's disease, Huntington's disease and essential tremor[4–10]. In IPD, LLRs were enhanced that was considered to indicate reduced inhibition of parkinsonian rigidity. Correlation between the parkinsonian symptoms and LLRs were also studied. A correlation with rigidity was not found whereas it correlated with the action tremor[1]. There are also studies concerning LLRs and other parkinsonian syndromes. In corticobasal syndrome (CBS), there was an enhanced LLRI response[1].

Here, we aimed to study LLRs and MnSP responses in different types of hypokinetic movement disorders in order to find an electrophysiological landmark to distinguish them. The institutional review board committee approved this study. We received written informed patient consent to perform this study.

Patients and methods

PATIENTS

We included 39 patients with IPD (n=39), 12 patients with multiple system atrophy (MSA) (n=12), 10 patients with CBS (n=10) and 5 patients with progressive supranuclear palsy (PSP) (n=5), who were admitted to our movement disorder outpatient clinic between January 2018 and January 2020. We also constituted a control group composed of 26 healthy subjects with similar features in terms of age and gender without any comorbidities. Clinical characteristics were retrieved from the medical records. **Table 1** shows demographic characteristics of all groups. We excluded the participants who had a contraindication or a confounding factor for electrophysiological procedures.

Table 1. *Demographic findings of the in all groups*

	Male (n)	Female (n)	Mean Age (±SD)
IPD n=39	17	22	65.3 (9.6)
MSA n=12	5	7	64.5 (7.6)
CBS n=10	3	7	63.9 (7.1)
PSP n=5	4	1	66.7 (9.5)
Healthy subjects n=26	15	11	57.8 (9.6)

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, CBS: corticobasal syndrome, PSP: progressive supranuclear palsy

ELECTROPHYSIOLOGICAL RECORDINGS

We used surface silver-silver chloride recording electrodes placed over the abductor pollicis brevis (APB) muscle bilaterally. All examinations were

performed with a Neuropack Sigma MEB-5504k (Nihon Kohden Medical, Tokyo, Japan). All recordings were done under optimum dopaminergic treatment for IPD patients.

We recorded the following parameters: 1) segmental reflex and long-latency reflexes (LLRs), 2) mixed nerve silent period (MnSPs).

Segmental reflex and LLRs

We placed the recording electrodes on the belly of abductor pollicis brevis (APB) muscle, while the ground electrode was placed on the palm. We stimulated the median nerve at wrist. The electrical stimulus was 0.2 ms in duration and 20-30 mA in intensity. The stimulus was repeated 20 times. For segmental reflex, we used the response with the minimum latency. The gain was predetermined at 100 mV/division with a sweep ranging from 20 ms per division. The band-pass filters were 2 to 2,000 Hz. LLRs were recorded during rest and while subjects were performing a slight (approximately 25% of maximum) contraction of APB muscle.

MnSPs

The recording electrodes were still on APB muscle. The median nerve at wrist was stimulated with an electrical stimulus 25% above supramaximal threshold of the stimulus intensity producing motor response. Visual and audio feedbacks of EMG signals were used to control muscle activity. 12 consecutive recordings were rectified, amplified and averaged.

DATA AND STATISTICAL ANALYSIS

We measured the minimum latency of segmental reflex (F-wave) and the latency of LLRs as distance from electrical stimulus artifact until the first negative deflection after F-wave. LLRs were classified as I, II and III according to the onset latencies. LLRI is also known as 'C reflex'. We also measured the amplitude of F-wave and LLRs. We calculated the percentage of presence of each wave as follows: number of participants with LLRx100/ total number of participants in the specific group. For MnSPs, mean MnSP end latency was measured.

Data were presented as mean ± standard deviation (SD). Groups were compared using Kruskal-Wallis test, and Mann-Whitney U test was used for post-hoc comparisons. Chi-square test was used for comparison of qualitative data. The data analysis was done using SPSS 20.0 statistical package and p value 0.05 was deemed as significant. After Bonferonni correction, the significant p value was 0.01.

Table 2. *Number of subjects with LLRI, LLRII and LLRIII responses during muscle contraction in each group*

	Subjects with LLR I (n)	Subjects with LLR II (n)	Subjects with LLRIII (n)
IPD n=39	4	12	11
MSA n=12	3	7	5
CBS n=10	2	3	2
PSP n=5	0	2	0
Healthy subjects n=26	3	13	5

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, CBS: corticobasal syndrome, PSP: progressive supranuclear palsy

Results

At rest, we recorded LLRI (C reflex) in two (18.2%) patients with MSA, in three (7.7%) patients with IPD and in three (30.0%) patients with CBS. There was no C reflex in the PSP group or in healthy subjects (p=0.039). During active contraction, LLRI response was obtained in 4 patients out of 39 patients with IPD (10.3%), 3 of 12 patients with MSA (25%) and 2 out of 10 patients with CBS (20%). 3 (11.5%) healthy subjects had LLRI. None of the patients from the PSP group had LLRI response (p=0.556). These findings are presented in **Table 2**.

LLRII response was obtained in 12 (30.8%) patients with IPD, 7 (58.3%) patients with MSA, 3 (30%) patients with CBS, 2 patients with PSP (40%) and 13 healthy subjects. The occurrence of LLR was not different between groups (p=0.336). These results are summarized in **Table 2**.

LLRIII response was obtained in 11 patients with IPD (28.2%), 5 patients with MSA (41.7%), 2 patients with CBS (20%) and 5 (19.2%) healthy subjects. Patients in the PSP group had no LLRIII response **(Table 2)**. The LLR amplitudes were not different among the groups (p=0.140).

The presence of LLRI, LLRII and LLRIII response in each group is shown in the **Figure 1**.

The 'LLR amplitude/ F-wave amplitude' ratio was compared between each patient groups with the healthy individuals. It was significantly lower in patients with IPD and PSP compared to the healthy individuals (p=0.036, p=0.006 respectively). There was no significant difference among the other

groups and healthy individuals. The p-value was still significant after Bonferroni correction in PSP group. **Figure 2** represents the 'LLR amplitude/ F-wave amplitude' ratio for each group of the participants.

The F-wave latencies were similar between groups (p=0.133).

The MnSP end latencies were significantly longer in IPD, MSA, CBS groups compared to the healthy individuals (p=0.026, p=0.050, p=0.008 respectively). There was no significant difference among the PSP group and healthy individuals (p=0.951). The p-value was still significant after Bonferroni correction in CBS group. The mean MnSP end latencies of each group were shown in the **Figure 3**.

Discussion

We studied segmental reflexes, LLRs and MnSP responses in patients with IPD, MSA, CBS and PSP. The major findings of this study are as follows: (i) C reflex, LLRI and LLRIII responses were not obtained in any patients with PSP and C reflex was common in CBS followed by MSA, (ii) "LLR amplitude/ F-wave amplitude" ratio was significantly lower in patients with IPD and PSP compared to healthy individuals, (iii) the MnSP end latencies were significantly longer in IPD, MSA, CBS groups compared to healthy individuals.

The main mechanism concerning the LLR is the transcortical loop hypothesis that consists of the network of fast conducting group lA afferents along the fast lemniscal pathway, thalamus, the sensory cortex, the prerolandic cortex, then back along the pyramidal tract to the motor neurons[11]. The LLRs are classified into three different types according to the onset latencies: LLRI, LLRII, LLRIII. The pathways for the generation of LLRI and LLRIII are not clear. The LLRI is thought to be a transcortical reflex, the so-called C-reflex that was seen in patients with cortical hyperexcitability such as cortical myoclonus. They both have the same latencies; therefore, C-reflex is an enhanced LLRI response[12].

Changes in LLRI responses are thought to be a result of disinhibited thalamocortical stimulation[10]. Previous studies had shown that LLRI abnormalities are more prominent with myoclonic disorders such as progressive myoclonus epilepsy, in which the main pathology is related with hyperexcitable cortex, especially sensorimotor cortex along with other neurological involvements[13].

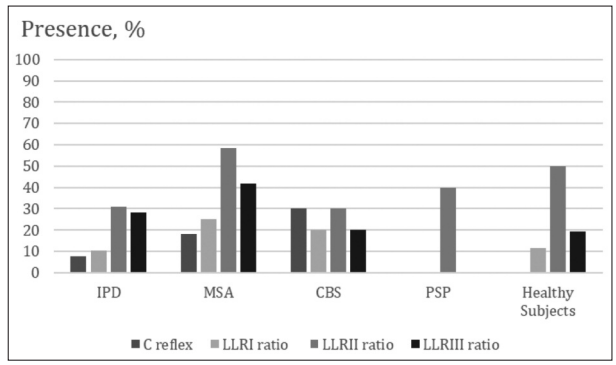

Figure 1. *The percentages of long latency reflexes in each groups of the participants*

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, CBS: corticobasal syndrome, PSP: progressive supranuclear palsy, LLR: long latency reflex

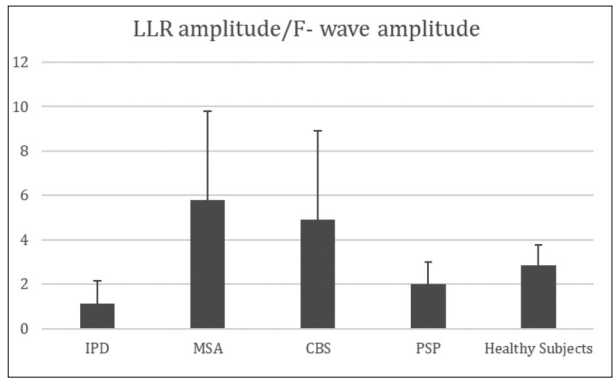

Figure 2. *The 'LLR amplitude/ F- wave amplitude' ratio in each groups of the participants*

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, CBS: corticobasal syndrome, PSP: progressive supranuclear palsy

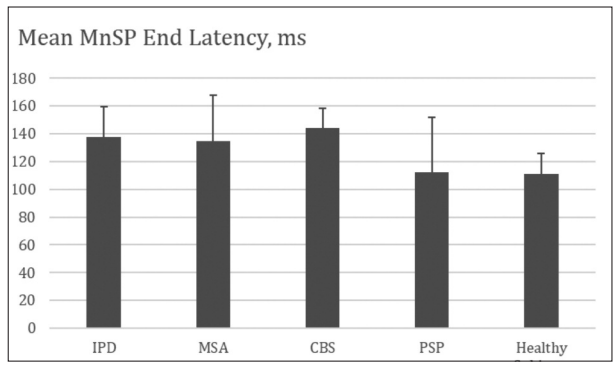

Figure 3. *The mean MnSP end latencies in each groups of the participants*

IPD: idiopathic Parkinson's disease, MSA: multiple system atrophy, CBS: corticobasal syndrome, PSP: progressive supranuclear palsy, MnSP: mixed nerve silent period, ms: millisecond

In our study, patients with CBS and MSA had C reflex, whereas patients with PSP did not. The CBS is a clinical syndrome defined by asymmetric, progressive motor symptoms suggesting basal ganglia involvement (asymmetric rigidity/akinesia or dystonia) and higher cortical symptoms (apraxia, alien limb syndrome, cortical sensory dysfunction and myoclonus). In CBS, the major pathology is in the perirolandic region, however, other cortical regions, which are connected to the perirolandic region, a network of higher-order sensorimotor regions are also affected[14]. This extensive involvement is responsible for some of the cortical symptoms, for example, superior cortical lobule-apraxia. Previous studies have shown the presence of the cortical reflex myoclonus in CBS[15], which is related to the dysfunction of the sensorimotor network. As we mentioned, we did not evaluate the presence of myoclonus in the subjects, however, it is very likely to be accompanied by myoclonus.

Thus, we attribute the presence of C reflex in CBS to the hyperexcitability of the frontoparietal cortex[16]. The clinical course of MSA, a degenerative multisystem disorder mainly involving the frontoparietal cortex and various basal ganglia structures, is much faster compared to IPD and its pathology involves cortical structures at an earlier stage. In MSA-Parkinsonism, the metabolic activity in inferior frontal gyrus, striatum and cerebellum is reduced and the activity in sensorimotor, parietal, temporal and occipital cortices is increased[17]. In IPD, the major pathology is in the striatum and substantia nigra pathway related with the motor symptomatology.

Our study suggested more frequent C reflex in MSA and some of the previous studies also found cortical myoclonus and even large LLR responses with giant somatosensory evoked potentials in MSA patients similar to our study[18]. The higher frequency of traces of cortical excitability in MSA compared to IPD may be secondary to different involvement pattern in IPD and MSA. However, one study showed that there was no LLRI enhancement in MSA[19] and high-amplitude LLRI in patients with IPD predominantly showing tremor and rigidity was shown in another study[19]. Given the anatomical correlates of LLRI, the reduced inhibition may involve sensorimotor cortices in IPD. Although traditionally, Lewy bodies are known to involve cortical regions with advanced disease, there is a sensorimotor network, which plays a central role in the preparation and execution of motor functions[20] and the same network is affected in IPD[21]. In early stages of IPD, there are abnormal connections rather than degeneration in the cortical areas[22]. Thus, we suggest that there is an increase in the sensorimotor cortical excitability in some of the MSA patients.

In our study, we did not get any LLRI, C-reflex and LLRIII responses from any of the PSP patients. PSP is an adult-onset progressive neurodegenerative disorder leading to supranuclear vertical gaze palsy, postural instability with falls, bradykinesia, and axial rigidity[23]. In PSP, there is a predominant midbrain atrophy and a limited involvement of frontal cortex. It has been shown in the literature with somatosensory evoked potentials and transcortical magnetic stimulation studies that there is a predominant motor cortex disinhibition in patients with PSP[24, 25], which may enhance the responses of LLRI, C-reflex and LLRIII. However, we found a decreased response in LLR which was concordant with a previous study in 14 PSP patients finding enhanced LLR response in only one patient[26]. Interestingly, in that study, enlarged cortical somatosensory evoked potential (SEP) responses were found in PSP patients[24]. In PSP, one study showed that the perirolandic region was affected whereas the other parts of a network of higher-order sensorimotor regions were not affected[14]. Thus, we may attribute the presence of C reflex to the involvement of higher-order sensorimotor regions.

Keeping in mind that our PSP patient group was small, recording C reflex and LLR responses could be an easy method to perform, a noninvasive and well-tolerated investigation method to distinguish PSP from CBS and MSA. The sensitivity for the discrimination of PSP from the other types of parkinsonian syndromes may be higher if both of these electrophysiological methods are applied together. This may warrant further studies.

The effect of PSP on SEP and LLR may be different. Though higher centers are also known to be affected in PSP, the well-defined centers that are mainly affected in the disease are the pedunculopontine nucleus and the cholinergic system. Previous animal studies had proved that the neurons in the pedunculopontine nucleus projecting to the basal ganglia structures mainly the substantia nigra pars compacta which has a role on motivational values and sensorimotor/arousal signals[26]. We may hypothesize that the different outcomes of LLR and SEP responses in the same patient group could derive from the changes in the pedunculopontine nucleus in the PSP patients.

The F-wave is a response produced by antidromic activation of motor neurons[27, 28]. Any change in motor neuron activity can cause an alteration in

F-wave amplitudes. For example, in flaccid spinal excitability caused by acute upper motor neuron damage, F-wave amplitudes were decreased[29–31]. F-wave amplitudes are higher in conditions such as spasticity, voluntary muscle contraction and rigidity[32–35]. In patients with IPD who had tremor and rigidity, increased F-wave amplitudes suggested the basal ganglia control over the spinal motor neuron excitability. In our study, "LLR amplitude/ F-wave amplitude" ratio was significantly lower in patients with IPD and PSP compared to the healthy individuals. This was a result of the increased amplitudes of F-waves. Enhanced amplitudes in patients with IPD were concordant with the current literature.

The MnSP end latencies were significantly longer in IPD, MSA, CBS groups compared to the healthy individuals whereas there was no difference in patients with PSP. On the other hand, in patients with CBS and IPD with rigidity reveal cortical hyperexcitability[25]. It is interesting to see that MnSP may also provide a distinction of PSP from other types of parkinsonism syndromes. It is a spinal reflex. As far as we know, the peripherally induced silent periods stand for the complex inhibitory mechanisms of the muscle activity and they are reproducible by the cutaneous or mixed nerve mechanical or electrical stimulations[36]. In 10 patients with IPD[37], investigators had found that on the rigid extremity, the peripheral silent period following ulnar nerve stimulation at the wrist was prolonged. Currently there is no data in the literature concerning the role of the peripheral silent period in distinguishing PSP from the other types of parkinsonism syndromes. Therefore, taking into account our small group of patients with PSP, it is better to evaluate our results with MnSP studies in a more cautious pattern.

There are some limitations of the current study. First, the diagnosis of patients was made clinically without any pathological evidence. Second, except the IPD group, all other patient groups were consisting of small numbers. The groups were not homogenous in certain clinical aspects such as disease duration, which may have an impact on electrophysiological findings. However, considering clinical courses, it is impossible to homogenize these clinical features. The percentage of the reflex is also low in healthy individuals and in each patient groups leading to more difficult comments. However, this is the nature of this recording and we were meticulous while recording. Finally, our results did not have prospective clinical correlations.

To conclude, we suggest that LLRs, particularly C reflex may provide promising results in distinction of CBS and MSA from PSP. However, this is an explorative study and further prospective studies of LLRs with clinical findings and brainstem reflexes are needed and may offer more information.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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