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Diagnosis of Parkinson's Disease by Electrophysiological Methods

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1. Introduction

Effective differential diagnosis of Parkinson's disease (PD) needs in informative indices that objectively reflect the functional state of the extrapyramidal system. And also, when evaluating an efficacy of antiparkinsonian therapy, it is essential to have both, qualitative and quantitative characteristics, permitting to correct treatment and predict a disease course. One of informative diagnostic method in PD is surface (interference) electromyography. As know, a nigrostriatal dopamine deficit results in disturbances of the central supraspinal control over the muscle tonic activity and voluntary movements (Valls-Solé & Valldeoriola, 2002). Electromyographically, the extrapyradimal insufficiency shows itself by a high level of bioelectrical activity of muscles at rest, changes of motor unit conduction velocity and synchronization (Farina et al., 2004; Semmler & Nordstrom, 1999). The traditional methods to evaluate surface electromyograms (EMGs) are based on amplitude and spectral analysis. However, myoelectric signals are nonlinear by its nature (Nieminen & Takala, 1996). A surface EMG is formed by the summation of a number of single muscle fiber action potentials. Therefore different world clinics have been searching for new relevant methods based on nonlinear time-series analyses of EMG to quantify the motor features of the disorder in PD (Del Santo et al., 2007; Meigal et al., 2009). Some other novel EMG characteristics, such as dimensionality based on fractal analysis or higher order statistics of EMG distribution have also proved to be sensitive to neuromuscular status (Swie et al., 2005).

Although the cardinal symptoms of the disease are movement disorders the manifestations of PD also comprise a variety of diverse abnormalities including disturbance of sensory gating and cognitive decline (Lewis & Byblow, 2002). Several authors suggested that movement disorders in PD might be also developed because of dysregulation of sensory processing that affects sensorimotor integration (Abbruzzese & Berardelli, 2003). This is an important issue because one of the proposed key functions of basal ganglia is the gating of sensory input for motor control (Kaji, 2001). Numerous studies have demonstrated marked changes in the somatosensory (Rossini et al., 1998), acoustic (Teo et al., 1997;) and visual (Sadekov, 1997) evoked potentials in PD patients. Evaluation of brain evoked potentials may have potential in the assessment of the severity of PD. In contemporary neurophysiology,

studies of the central mechanisms underlying the organization of motor function and its impairments increasingly involve analysis of endogenous cortical event-related potentials, a set of potentials which includes contingent negative variation (CNV). The CNV extent depends on the level of attention, motivation, and volitional effort (Deecke, 2001). The magnitude of this potential is known to decrease in diseases accompanied by motor disorders, including PD (Aotsuka et al., 1996; Pulvenmuller et al., 1996). CNV has been shown to display significant increases after administration of levodopa in patients with Parkinson's disease, suggesting a role for the central dopaminergic system in its generation (Oishi et al., 1995).

Although electrophysiological methods objectively reflect motor and sensory dysfunctions, they are still used rather rarely in the clinical evaluation of PD. We carried out systematic and detailed research of surface EMG characteristics in PD patients in comparison with age-matched healthy subjects, paying the special attention on the correlation associations between EMG parameters and subitems of the Unified Parkinson's Disease Rating Scale (UPDRS). Amplitude and spectral features, statistics of distribution, fractal dynamics of the EMG signals were investigated. Separate research was dedicated to the study of EMG characteristics of clinically healthy kinsmen of the patients suffering from PD in order to detect latent symptoms of extrapyramidal insufficiency that can be considered genetic determinants of the risk of development of the above disease. Since the question of the relationship the early and late phases of CNV with the mechanisms controlling motor functions in PD has received inadequate study we conducted such research in patients with this disease. With the purpose of evaluation of the brain inhibitory processes in PD patients the study of cortical evoked potentials upon paired-click auditory stimulation was performed. The results of these investigations are presented below.

2. Surface electromyography

Surface EMG is a simple and noninvasive method that permits to estimate the severity of symptomatology in patients and also may help to exposure of the hidden manifestations of the disturbed muscles activity on the presymptomatic stage of the neurodegenerative process (Kryzhanovsky et al., 2002; Lukhanina et al., 2010). In PD patients the EMG characteristics of the tonic and phasic shoulder muscle activities at rest, during voluntary contraction and under tonic muscle strain were studied. In kinsmen of the patients, suffering from PD, EMGs in the resting state and under conditions of two functional tests (retention of load and retention of arms in the elevated and outstretched state) were recorded.

2.1 Amplitude and spectral analysis of EMGs in patients with Parkinson's disease

One of the informative EMG sign of extrapyramidal insufficiency appears to be the resting EMG amplitude values that reflect the muscle ability for relaxation. Spectral analysis of resting EMGs is used for assessing the burst muscle discharges with a frequency of 4-8 Hz reflecting parkinsonian tremor. Amplitude values of the EMGs recorded during the voluntary muscle contraction serve to calculate the phasic activation coefficient. This coefficient clearly reflects the competitive relationships between the tonic and phasic processes. Study of the reflex agonist/antagonist muscle involvement under tonic strain is valid for establishing coordinating muscle relationships.

2.1.1 Methods

Studies were performed in two groups: 48 patients with PD, 1.5-3.5 Hoehn-Yahr scale (23 men and 25 women, mean ± SE age 62.2 ± 1.6, range 49-75 years) and 42 age-matched healthy controls (20 men and 22 women, mean ± SE age 65.8 ± 1.43, range 58-74 years). All of them were right-handed persons. The study patients, who regularly underwent treatment at the Parkinson's Disease Centre of Institute of Gerontology, gave their written informed consent to participate in this investigation. They had 4-13-year history of an idiopathic PD and received an antiparkinsonian medication (an individual dose 0.250-12g of levodopa/carbidopa, daily). All patients were studied in the OFF state. For the quantitative evaluation of levodopa therapy 20 patients (in which the clinical "ON-OFF" phenomenon was verified) were studied also in the ON state, one hour after an intake of the single individual dose of levodopa/carbidopa. The motor activity of PD patients was evaluated in ON state, according to sections II-III of the UPDRS.

For each subject, we recorded the surface EMG from the flexors and extensors (mm. biceps and triceps brachii) of the right and left arms. The subject lay on his back, with the arms lying on the horizontal surface. The EMGs were recorded using four bipolar skin electrodes (0.5x1.0 cm) with an interelectrode distance constant of 1.5 cm. Bioelectrical potentials were amplified with a band pass of 10 Hz - 10 kHz. The amplified analogue signals were fed to a computer, which digitized them at a sampling rate of 1000 Hz and then stored the data for further measurements. The time of each recording was 10 sec. EMG recordings were made:

1. At a resting state, being cautious that the subject is relaxed.
2. During a voluntary m. biceps brachii contraction started after a command to bend the arm at the elbow, fingers touching the shoulder. The sound signal served as a command to initiate arm bending, and it was simultaneously registered on EMG. An electrical contact enclosure marked the start of arm lifting, being recorded simultaneously with the EMG on a free channel.
3. During a tonic m. biceps brachii strain under weight holding (2 kg) in the hand, with arm lifted upward and stretched forward, for 5 sec.

In resting EMG recordings, the average and maximal EMG amplitudes were calculated to evaluate the muscle ability for relaxation. An artefact-free section on the EMG record was selected by the experimenter. The single EMG wave amplitude was defined as the difference between the values of upper and lower peaks. The oscillations with no less than 2 μV amplitude were considered. The resting average EMG amplitude was calculated based on minimum 100 measurements. The maximum amplitude value was calculated on the same EMG section. The amplitude distribution histograms were constructed.

The resting EMG recordings were also used for assessing the burst muscle discharges For this purpose, the Fourier spectrum diagrams for the low frequency area were constructed. In doing this, part of the data with negative EMG amplitude meanings were discarded. Data with the positive EMG amplitude meanings underwent a Butterworth digital sinus low pass filtering with a band pass of 0-20 Hz As a result, the envelope of EMG amplitude was formed, which then served as the data array for fast Fourier transformation. The data for each lead were divided into several successive sections, each containing 512 points, which underwent the fast Fourier transformation. The obtained spectra were averaged, and the envelope of EMG amplitude frequency with a maximal power was determined (Fig 1). The statistical significance of the frequency peak was determined by means of constructing the 95% confidential intervals (M ± 2 S.D).

The EMG recordings made during the voluntary m. biceps brachii contraction served to calculate the phasic activation coefficient (PhAC), from a formula :

$$PhAC = (AVCa\text{-}ARa)/AVCa \quad (1)$$

where AVCa is the average EMG amplitude on a section with most marked changes in the muscle activity under voluntary contraction, and ARa is the average amplitude of resting EMG. In the conditions of low tonic muscle activity at rest the phasic muscle activation during voluntary movement is facilitated and the PhAC value is close to 1. On the contrary, when the resting tonic activity increases, the PhAC falls.

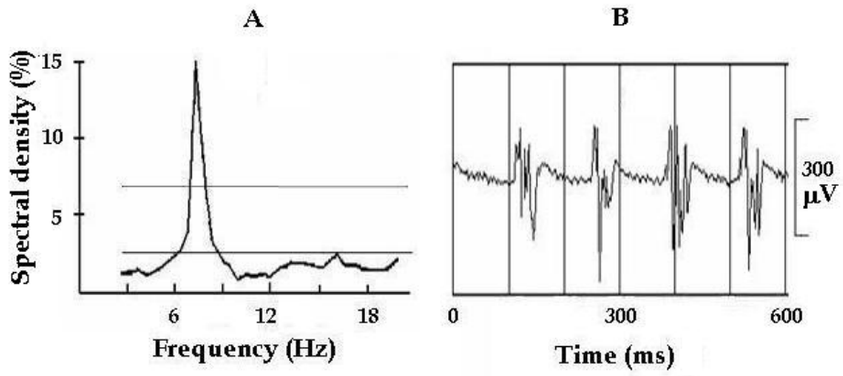

Fig. 1. The spectrogram of the power of EMG envelope frequency with 95% confidence intervals (A) and the corresponding resting EMG pattern of m. biceps brachii in a patient with Parkinson's disease (B). Peak deviation on the spectrogram reflects the frequency of the rhythmic burst muscle discharges.

The functional test with weight holding served for study of the reflex agonist and antagonist involvement during tonic muscle strain. We calculated the coefficients of reflex involvement of the muscles of the opposite arm, which characterized "distant" synergies. The coefficients of reflex involvement, respectively for the m. biceps brachii and m. triceps brachii of the opposite upper limb were obtained by calculation of the ratio of the mean amplitude recorded from the m. biceps (or triceps) on the resting side and mean amplitude recorded from the m. biceps on the side of retention of a load; the latter value was taken as 100%. In the norm, the value should not exceed 15%. An increase in this index is indicative of abnormal intensification of muscle coordinative interactions; if the coefficient of reflex involvement value exceeds 50%, such a disorder is qualified as gross.
Statistical analysis of the obtained data was performed using Statistic 8 software. Dispersion analysis ANOVA and a non-parametric two-tailed Mann-Whitney criterion were used in the course of comparison of the values observed in the different groups of the tested persons. Data obtained from the same patients before and after Levodopa treatment were compared using two-tailed paired t-test. The nonparametric Spearman test was used to evaluate possible correlation between above EMG parameters and subitems of UPDRS. Differences were considered to be significant at $P < 0.05$.

2.1.2 Results and discussion

In the group of age-matched healthy subjects, the EMG amplitude of the shoulder flexors and extensors during muscle relaxation showed low values (Fig 2, Controls 1, 2). The

average EMG amplitude values for mm. biceps and triceps brachii varied across the subjects within 3-12 μV and the maximal amplitude values within 4-34 μV. For the whole group of healthy subjects, mean ± SE average amplitude did not exceed 5.9 ± 0.2 μV and mean ± SE maximal amplitude was no more 12.8 ± 2.3 μV (Table 1).

	Healthy controls (n = 42)	PD patients (n = 48)
Average EMG amplitude (μV)		
m. biceps dexter	5.3±0.8	19.5±3.8 ***
m. biceps sinister	5.5±0.7	21.4±7.4 ***
m. triceps dexter	5.9±0.2	13.1±1.7 *
m. triceps sinister	5.4±0.8	12.5±3.1
Maximal EMG amplitude (μV)		
m. biceps dexter	12.5±2.1	74.0±17.9 ***
m. biceps sinister	12,8±2.3	73.8±15.6 ***
m. triceps dexter	11.9±1.3	60.1±7.4
m. triceps sinister	12.3±2.1	61.9±12.0

Table 1. Resting EMG amplitudes of shoulder muscles in healthy controls and patients with Parkinson's disease. Notes: values are Mean ± Standard Error; n - number of subjects in each group; *, *** significant difference compared to healthy controls according to Mann-Whitney test, $p < 0.05$ and $p < 0.001$, respectively.

There were no statistical differences in EMG amplitude values between men and women. A significant positive correlation ($p<0.05$) was found for the resting activities of the antagonist muscles of the upper extremities in the age-matched healthy subjects (Table 2). The use of the envelope EMG construction technique demonstrated the presence of rhythmic burst muscle discharges in those cases where they were badly visualized on the EMG. Low amplitude burst discharges were occasionally identified in healthy subjects with the help of this technique (Fig 2, Control 2). Of EMG recordings taken from flexors and extensors on both sides in 42 persons of the control group, 11 recordings (6.5%) made in eight subjects displayed the burst discharges, with a mean ± SE frequency of 6.1 ± 0.3 Hz. The maximal amplitude of burst discharges in control subjects did not exceed 11-18 μV (mean ± SE = 14.3 ± 1.1 μV).

Healthy controls		PD patients, OFF state		PD patients, ON state	
right side	left side	more impaired side	less impaired side	more impaired side	less impaired side
0.42**	0.40**	0.27	0.33*	- 0.26	0.32*

Table 2. Correlation coefficients between average EMG amplitudes of the antagonist shoulder muscles (mm. biceps and triceps brachii) at rest in healthy controls and PD patients. * significant correlation, $p < 0.05$; ** is . $p < 0.01$.

In the group of PD patients, we observed a significant increase in the resting EMG amplitudes, which was ascribed to muscle relaxation disturbances. The mean average amplitude values for various study muscles, estimated for a whole PD group, were 2-3 times

greater compared to control values, and the mean maximal amplitude values were approximately 5-6 times greater (Table 1). In some patients, average amplitude from a more impaired side reached 44-123 μV and maximal amplitude - 210-508 μV

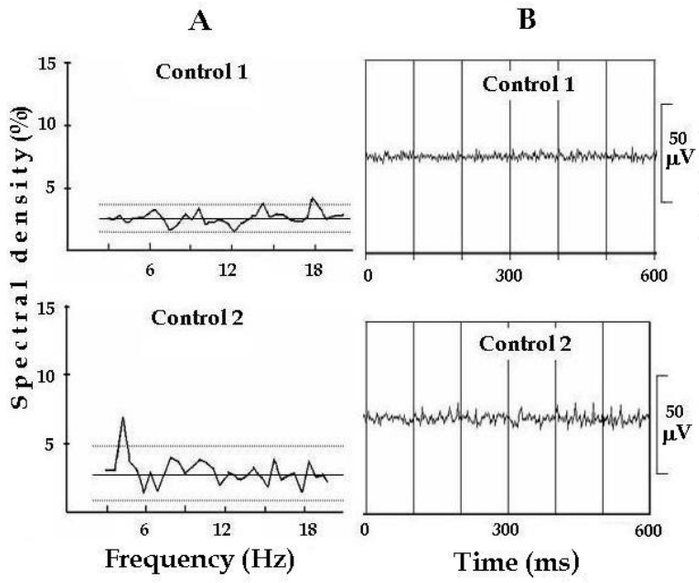

Fig. 2. The spectrograms of the power of EMG envelope frequency with 95% confidence intervals (A) and the corresponding resting EMG patterns of m. biceps brachii (B) in healthy controls (Control 1 and 2) Peak deviation on the spectrogram reflects the frequency of the rhythmic burst muscle discharges. Control 1: the absence of the burst muscle activity. Control 2: low amplitude burst muscle discharges with a frequency of 4 Hz in a healthy control subject.

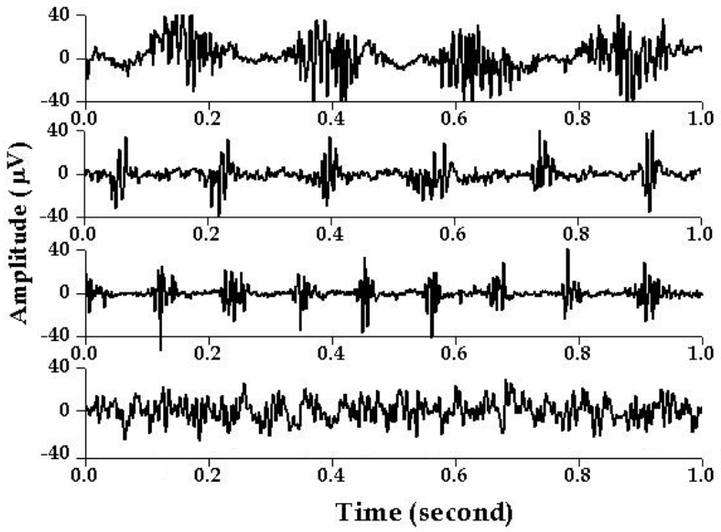

Fig. 3. Typical examples of EMGs registered in the resting state from three patients with the akinetic-rigid trembling form of Parkinson's disease (three upper records) and a patient with the akinetic-rigid form of this disease (low record).

Of interest is the fact that PD patients did not show a significant correlation between resting activities of the antagonist mm. biceps and triceps brachii on the dominant side, as has been true in the cases of the right and left sides in healthy subjects (Table 2). On the EMGs taken from PD patients with the akinetic-rigid-trembling form of the disease burst muscle discharges occurred as a rule with a frequency of 4-8 Hz. The mean ± SE frequency of the burst discharges was 5.2 ± 0.2 Hz. They had high amplitude (Fig.3). The maximal amplitude of burst discharges varied from 30 to 508 μV (mean ± SE = 89.8 ± 15.6 μV). Of special note, no significant correlation was found between resting EMG amplitude values and the occurrence of burst muscle discharges.

When comparing the data in OFF-state and ON-state, we observed a noticeable decrease in amplitude values. Mean ± SE average EMG amplitude of different muscles decreased to 8.2 ± 1.9 – 12.3 ± 5.1 μV and mean ± SE maximal amplitude decreased to 20.1± 5.3 – 32.1± 7.1 μV In this respect, the amplitude histograms made for the same patient during both states were very illustrative (Fig.4).

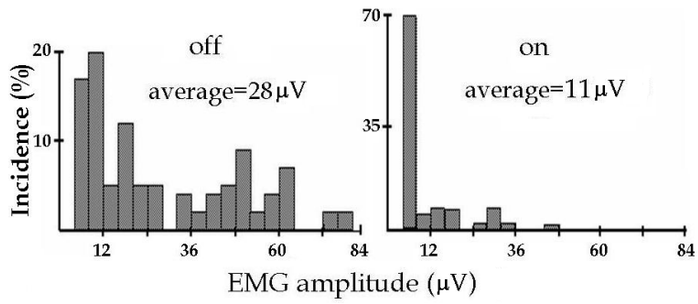

Fig. 4. The decrease of resting EMG amplitude values (calculated from peak to peak) of m. biceps brachii in a PD patient after intake of single dose of levodopa/carbidopa. OFF: the histograms of distribution of EMG amplitude values during the off-medication state; ON : one hour after drug intake. The bin of histograms is 4 μV.

But the treatment with levodopa did not result in the normalization of correlations between resting activities of the antagonist shoulder muscles (Table 2). Following a single dose of levodopa/carbidopa the number of cases displaying burst discharges with a frequency of 4-8 Hz decreased. In some patients the rhythmic discharges disappeared, as is shown in Figure 5, top records. In the other patients who displayed discharges after a dose of levodopa, an increase occurred in the discharges frequency (Fig. 5, lower records).

EMGs recorded during the performance of voluntary arm bending were found to differ considerably in healthy subjects and PD patients. In the healthy subjects, we clearly distinguished an onset of muscle phasic activation on the EMG (Fig. 6, Control). Means ± SE of average EMG amplitude of the mm. biceps brachii during their voluntary contraction was 49 ± 8 μV from the right and 44 ± 2 μV from the left, the maximal amplitude – 189 ± 31 μV and 137 ± 30 μV, respectively. In view of the low resting EMG amplitude value in healthy subjects, the coefficient of phasic activation in most cases was equal to 0.7-0.9; mean ± SE was 0.77 ± 0.04.

In contrast, in the PD patients it was often difficult to locate a site on the EMG at which the muscle phasic activation started because of increased resting tonic muscle activity and a very delayed rise in EMG amplitude after the delivery of a command to move (Fig. 6, PD). During peak voluntary flexor contraction, some patients showed a noticeable reduction of

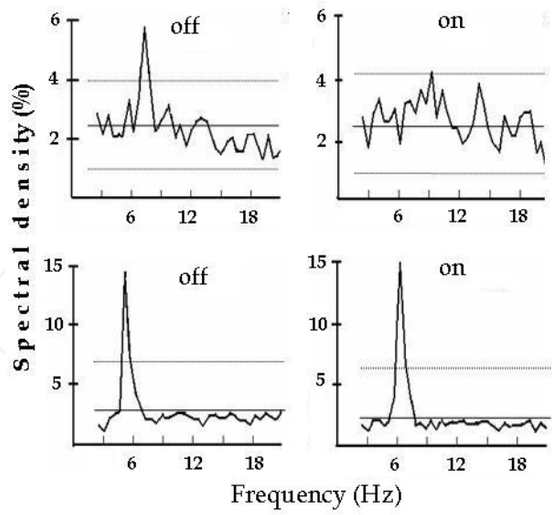

Fig. 5. Changes in the rhythmic (4-7 Hz) burst muscle discharges in patients with Parkinson's disease after the intake of an individual single dose of levodopa/carbidopa. The spectrograms of the power of EMG envelope frequency in two patients in an off-medication state (OFF) and one hour after drug intake (ON). After the drug intake, burst muscle discharges disappeared in one patient, while their frequency somewhat increased in another patient. For other notes see Fig. 1.

EMG amplitude, while other patients had the same meanings as healthy subjects. The coefficient of phasic activation of a voluntarily contracting mm biceps brachii in PD patients was generally decreased to 0.1-0.6 and, sometimes (when amplitude values at rest exceeded those that were observed during phasic activation), even had negative values; mean ± SE was 0.42 ± 0.08. The magnitude of the phasic activation decrease showed a distinct dependence on the side which was most affected. Reduction of the coefficient of phasic activation in the OFF patient group compared to healthy individuals was statistically significant ($p<0.01$).

Disturbance of coordinative muscle interactions was one more typical feature of the EMG recorded in Parkinson's patients. This was manifested in increased reflex involvement of the muscles of the opposite arm (distant synergy) at tonic tension of the m. biceps brachii at one of the sides within the period of retention of a load. In this group, the mean values of the coefficients of reflex involvement for the m. biceps brachii and m. triceps brachii of the opposite side exceeded 50%. As was already mentioned, these phenomena should be considered a gross disturbance of coordinative interactions. In control group the mean values of the coefficients of reflex involvement were 20-26%.

The dose of levodopa/carbidopa in PD patients produced a decrease in resting muscle activity parallel to an increase, more often, to normal values (0.8-0.9) of the coefficient of phasic activation during voluntary contraction of flexors. With regard to the reflex activation of the agonist and antagonist muscles during weight holding, a noticeable reduction of the coefficients of reflex involvement was only observed in some of the patients who took levodopa/carbidopa treatment. In seven patients, after medication even more marked enhancement developed in the agonist or antagonist muscles, and was registered during the performance of the functional test.

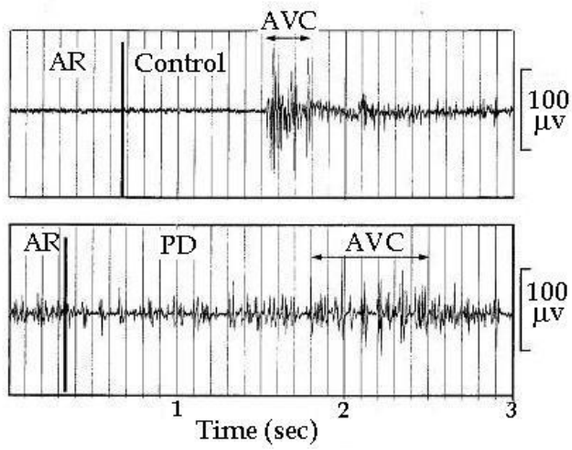

Fig. 6. The phasic activation of m. biceps brachii dexter during voluntary movement in healthy control and off-medication patient with Parkinson's disease. Two sections of native EMGs in a healthy 64-year old subject (Control) and in a 53-year old patient (PD). The vertical thick lines designate the moment of experimenter's command. The horizontal lines over EMGs designate the periods, at which the amplitude measurements of maximal muscular activity during voluntary contractions (AVC) were taken. The resting EMG amplitudes (AR) were measured during 5 s prior to command presentation.

The described quantitative EMG parameters added fundamentally to the clinical motor characteristics of PD patients and correlated selectively with definite UPDRS subitems. Thus, the most significant increases in the resting average and maximal EMG amplitude and decreases in the coefficient of phasic activation were observed in patients whose part III UPDRS scores exceeded 50. At the same time, the greatest involvement of the reciprocal muscles during the functional test was noted in patients with high part II UPDRS scores on the upper extremity daily activity. These patients also, had the greatest dyskinesia (disability) scores. We established the following statistically significant correlations (see Table 3). The resting muscle amplitudes from the more affected side correlated positively with the upper extremity rigidity and general motor scores. We found negative correlations between the phasic activation coefficient of m. biceps brachii from the more affected side and the upper extremity rigidity and general motor scores. The antagonist muscle involvement during the tonic strain holding a weight correlated positively with the handwriting, cutting food, dressing score and dyskinesia (disability) score. Levodopa intake did not influence essentially on the correlations between the reflex muscle involvement and UPDRS scores.

We found the present computer EMG analysis to be a sensitive tool for the objective evaluation of PD symptoms and to quantify the efficacy of levodopa therapy. One of the most useful EMG signs of extrapyramidal insufficiency appears to be the resting EMG amplitude value. In PD, the resting EMGs in the OFF state were characterized by the splashes of high muscle activity in contrast to the flat EMGs seen in age-matched healthy subjects. The average resting EMG amplitude was 2-3 times and the maximal amplitude was 5-6 times greater in PD patients than in the control group. Of interest are our data indicating the statistically significant correlation between levels of resting activity in the antagonist muscles (m. biceps and triceps brachii) in healthy subjects and the lack of such a correlation in PD patients on the most affected side. These findings appear to be an objective EMG

manifestation of the disorganisation of the brain's neuronal excitatory-inhibitory processes and the loss of functional balance between the structures which regulate muscle tone, all of which are due to a neostriatal dopamine deficit (DeLong, 1990).

EMG indices		Upper extremity rigidity score (point 22)	Motor score (points 18-31)	Handwriting, cutting food, dressing score (points 8-10)	Dyskinesia (disability) score (point 33)
Average amplitude of m. biceps at rest	ON	0.51 *	0.50 *	ns	ns
	OFF	ns	0.67 **	ns	ns
Phasic activation coefficient of m .biceps during voluntary contraction	ON	-0.49 *	-0.60 **	ns	ns
	OFF	ns	-0.64 **	ns	ns
M. biceps involvement under tonic strain of m. biceps of the opposite arm	ON	ns	ns	0.55 *	0.52*
	OFF	ns	ns	0.52 *	ns
M. triceps involvement under tonic strain of m. biceps of the opposite arm	ON	ns	ns	0.57 **	0.48*
	OFF	ns	ns	0.53 *	0.51*

Table 3. Significant correlations of EMG indices with the UPDRS scores studied in 20 PD patients in which the clinical "ON-OFF" phenomenon was verified. Data on the EMG indices and the upper extremity rigidity score for a more impaired side are presented. *- $p<0.05$; ** - $p<0.01$; "ns "- not statistically significant ($p\geq0.05$).

A distinguishing feature of the bioelectrical muscle activity at rest in PD patients was the presence of burst muscle discharges with a rhythm of 4-8 Hz. It should be noted that no significant correlation was found between resting EMG amplitude value and the occurrence of burst muscle discharges. This fact is consistent with the viewpoint that muscle rigidity and tremor at PD do not constitute symptoms which influence one another, and that different pathophysiological mechanisms underlie their origin (Furukawa et al., 1991; Otsuka et al., 1996).

The brain systems, regulating the tonic and phasic muscle activities, were shown to be antagonistically interrelated: the activation of the phasic processes is accompanied by an inhibition of the tonic impulses and, vice versa, the enhancement of tonic impulsation hampers the phasic activity (Houk, 1979). In PD, due to an increased tonic muscle activity at rest, increment in EMG amplitude during phasic activation was reduced relative to the

norm, and, in addition, a decrease in the active contraction amplitudes occurred in some of the patients. As a consequence, the phasic activation coefficient of the voluntarily contracting m. biceps brachii of the patients was generally reduced to 0.1-0.6 and even had negative values, while in healthy subjects the value of the phasic activation coefficient was in most cases 0.7-0.9. Our study data suggest that phasic activation coefficients represent a sufficiently informative index that may be used to quantify phasic muscle activity in PD.

Involvement of the agonist and antagonist muscles appeared to be useful for establishing coorditating muscle relationships. We demonstrated significantly ($p<0.05$) greater activation of the agonist and antagonist muscles during m. biceps brachii tonic strain in PD patients compared to age-matched healthy subjects. The present findings confirm the results of other investigators who consider this fact to be a consequence of increased excitation in the motor centers, caused by dopaminergic control failure (Kryzhanovsky et al, 2002).

When examining the action of an individual dose of levodopa/carbidopa in PD patients with ON-OFF phenomenon, we observed distinct positive drug effects in the following EMG parameters: average and maximal EMG amplitudes at rest; the number of cases with registered rhythmic burst muscle discharges of 4-8 Hz; value of the phasic activation coefficient during voluntary muscle contraction. However, levodopa therapy didn't appear to be effective in terms of the normalization of coordinating agonist - antagonist muscle relationships, either at rest and during holding a weight. In some of patients on levodopa/carbidopa, we even observed an enhancement of the activation of agonist and antagonist muscles during above functional test. We believe that such an increased coactivation of the agonist and antagonist muscles is an objective indicator of risk for developing levodopa-induced dyskinesia in PD patients. According to the literature data, the latter is the result of hypersensitivity of the dopamine receptors in the nigrostriatal system or of a disturbed balance between the degrees of activation of D1 and D2 dopamine receptors (Jenner, 1994).

2.2 Statistics of EMG distribution in patients with Parkinson's disease

The histograms of distribution of EMG amplitude values at rest are informative characteristic of muscle activity (Meigal, 2009). The histogram sharpness and statistical EMG parameters, such as range, variance and kurtosis reflect the magnitude of bioelectrical muscle signals and the level of motor unit synchronization.

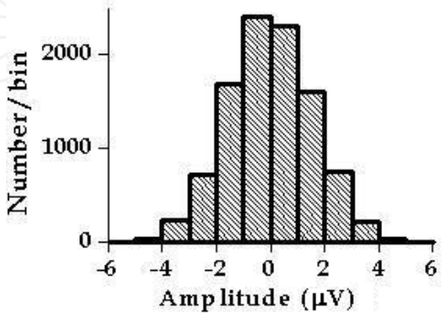

Fig. 7. Example of the histogram of resting EMG amplitudes distribution in healthy subject.

An artifact-free EMG recordings (no less than 10 seconds in duration) from the flexors and extensors (mm. biceps and triceps brachii), registered in 33 patients with PD and 24 age-

matched healthy subjects at rest, were analyzed by the computer programs "Origin 8" and "Statistic 8". EMG in healthy subjects was characterized by low amplitude, flat symmetric histogram (fig. 7) and small values of range, variance and kurtosis (table 4). Range did not exceed 20 μV, variance – 7 and kurtosis – 0.4. In patients with the akinetic-rigid form of the disease, the amplitude of EMG signals was considerably increased because of impossibility of entire muscle relaxation. The mean values of EMG statistical parameters, estimated for this PD group, were significantly ($p<0.001$) augmented as compared to control. In some patients range amounted to 66 μV, variance – 56 and kurtosis – 1.4 (table 4).

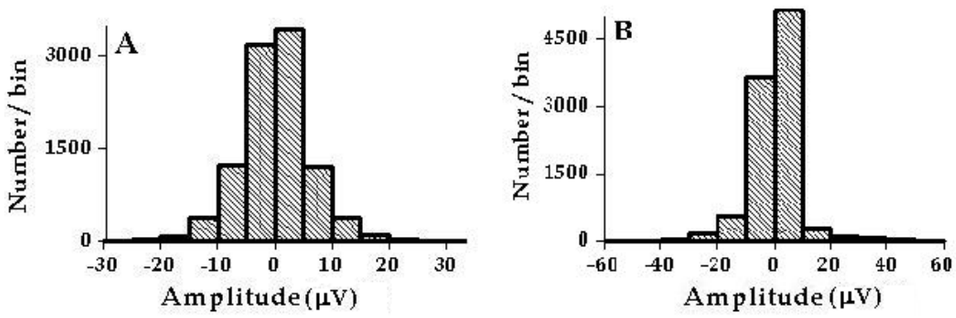

Fig. 8. Examples of the histograms of resting EMG amplitudes distribution in a patient with akinetic-rigid form of Parkinson's disease (A) and a patient with akinetic-rigid- trembling form of this disease (B).

Groups of the tested persons	Statistical parameters		
	Range (μV)	Variance	Kurtosis
Patients with akinetic-rigid-trembling form of the disease n=20	112.75 ± 16.80 *** (24.48 – 381.62)	147.20 ± 44.38 ** (6.91 – 950.63)	4.32 ± 0.51 *** (1.04 – 12.98)
Patients with akinetic-rigid form of the disease n=13	36.81 ± 3.96 *** (21.16 – 66.18)	20.26 ± 4.26 *** (7.89 – 56.16)	0.58 ± 0.14 *** (0.07 – 1.40)
Control group of age-matched healthy subjects n=24	11.18 ± 0.71 (7.08 – 16.46)	2.30 ± 0.31 (0.70 – 5.14)	-0.17 ± 0.03 (-0.10 to -0.30) n = 10 0.18 ± 0.04 (0.01 – 0.33) n = 14

Table 4. Statistical characteristics of EMG in patients with Parkinson's disease and age-matched healthy subjects. EMG characteristics in patients were taken at the side where morbid affection was more expressed; in healthy persons such characteristics were taken at the side where higher values were observed. ** $p<0.01$, *** $p<0.001$ compared to control group. n is number of subjects in each group. In brackets the range of indices in different tested persons is presented.

Patients with the akinetic-rigid-trembling form of PD had the highest values of the EMG statistical parameters. The histograms of EMG amplitude distribution had a sharp peak (fig. 8, B). In some patients of this PD group range reached 382 μV, variance – 951 and kurtosis – 13 (table 4). Correlation analyses revealed statistically significant connection of kurtosis with scores of the point 20 of UPDRS, estimating intensity of tremor of the hand, on which EMG was registered. A coefficient of nonparametric Spearman rank-order correlation between these indices was 0.46 ($p<0.01$). This fact is in accordance with the point of view (Meigal, 2009) that kurtosis well reflects synchronization of motor units responsible for the origin of burst muscle discharges.

2.3 Fractal dynamics of EMGs in patients with Parkinson's disease

Fractal analysis is a new method for biomedical signal processing. Nonlinear analysis techniques are necessary to understand the complexity of the EMG. Study of fractal dynamics of EMG data is based on detrended fluctuation analysis and calculation of Hurst exponent. The Hurst exponent is used as a measure of the long term memory of time series, i.e., the autocorrelation of the time series. (Talebinejad et al., 2010).

Fractal dynamics of EMG signals was studied in 33 patients with akinetic-rigid-trembling form of PD (mean ± SE age 62.1 ± 2.6, range 48-77 years), 30 age-matched healthy subjects (mean ± SE age 65.4 ± 1.9, range 57-78 years) and 20 persons of middle age (mean ± SE age 48.3 ± 1.49, range 45-58 years). EMGs were recorded from m. biceps brachii at the side, where morbid affection was more expressed, at rest no less than 10 seconds in duration.

The rescaled range was calculated for time series. The first step was calculation of the mean. Then mean-adjusted series were created and the cumulative deviate series were calculated from the formula:

$$y(k) = \sum_{i=1}^{k} (z_i - \overline{z}) \tag{2}$$

Where $\overline{z}$ is the mean and $z(i)$ is the value from time series. Then the row of values $y(k)$, $k = 1,\ldots N$ was divided into the segments of length n, and within the limits of each segment the equalization of stright, approximating the sequence of $y(k)$, was defined by least squares method. It is considered that approximation of $y_n(k)$ is the local trend. Further a standard deviation was created from the formula:

$$F(n) = \sqrt{\frac{1}{N}[(y(k) - y_n(k)]^2} \tag{3}$$

Dependence $lg\ F(lg\ n)$ was further built, the angle of slope of approximating line was determined and the value of Hurst index was estimated (Stanley et al., 1999).

We identified three different patterns of surface EMG signals according to fractal dimension (Fig 9, 10): with one, two and three scaling regions, every of which is characteristic by own local exponent. In healthy subjects, the fractal dimension with two exponents was most frequently observed, in 60% among persons of middle age and in 50% among elderly individuals. One exponent was observed in 20% in both groups of healthy subjects and three exponents – in 20% and 30% in middle age and elderly, respectively. In patients with akinetic-rigid-trembling form of PD the fractal dimension of surface EMG signals with three exponents was most characteristic (64%). One exponent did not occur in PD patients (Fig. 11).

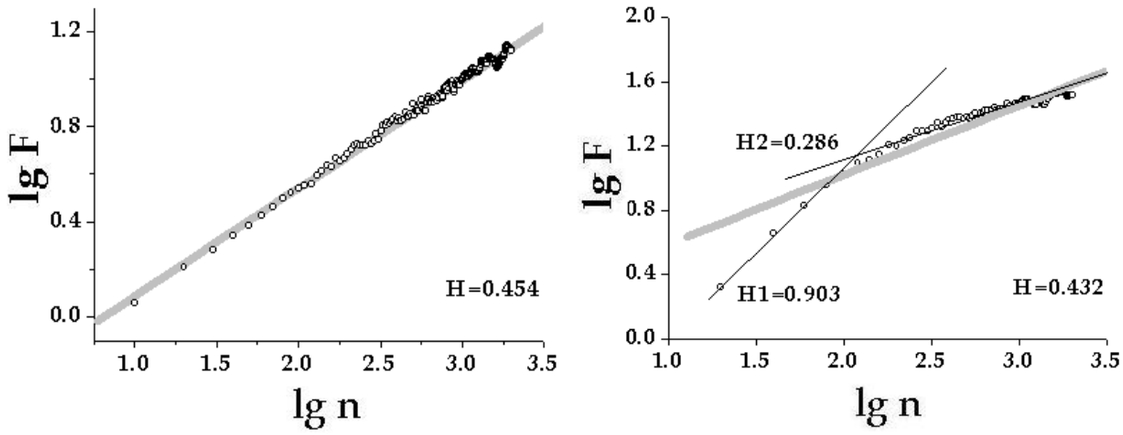

Fig. 9. Patterns of fractal dimension of the surface EMG signals with one and two exponents. Thick line is general exponent, thin lines are local exponents. H is general Hurst index; H1, H2, H3 are values of local Hurst indices.

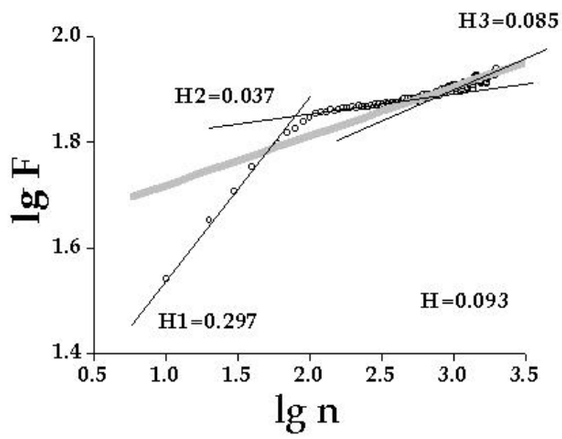

Fig. 10. Pattern of fractal dimension of the surface EMG signals with three exponents. Thick line is general exponent, thin lines are local exponents. H is general Hurst index; H1, H2, H3 are values of local Hurst indices.

Another difference concerned the value of general Hurst index (H). In persons of middle age mean value of H was 0.47 ± 0.02 (range 0.32 – 0.71) and in elderly – 0.44 ± 0.02 (range 0.33 – 0.57). In PD patients mean value of H was significantly ($p<0.01$) lower as compared to elderly subjects – 0.31 ± 0.03 (range 0.09 – 0.49). In PD patients, the value of Hurst index of the third scaling region (H3) in patterns with three exponents also significantly differed from H3 in healthy subjects. H3 was 0.30 ± 0.06 in middle-aged persons, 0.39 ± 0.05 in elderly and 0.14 ± 0.05 in patients with PD ($p<0.05$). It is of interest that the tendency to negative correlation between H and motor scores of part III UPDRS was observed in patients with PD ($r = -0.35$, $p = 0.05$).

Our data showed essential alterations in short and more long-range EMG correlation properties in patients with akinetic-rigid-trembling form of PD. The mean value of H1/H3 in patterns with three exponents in the group of PD patients came up to 27.2 ± 9.5 that

significantly ($p<0.001$) differed from same value in elderly subjects (2.7 ± 0.5). Negative correlation between H1 and H3 ($r = -0.67$, $p<0.01$) was revealed in PD patients.

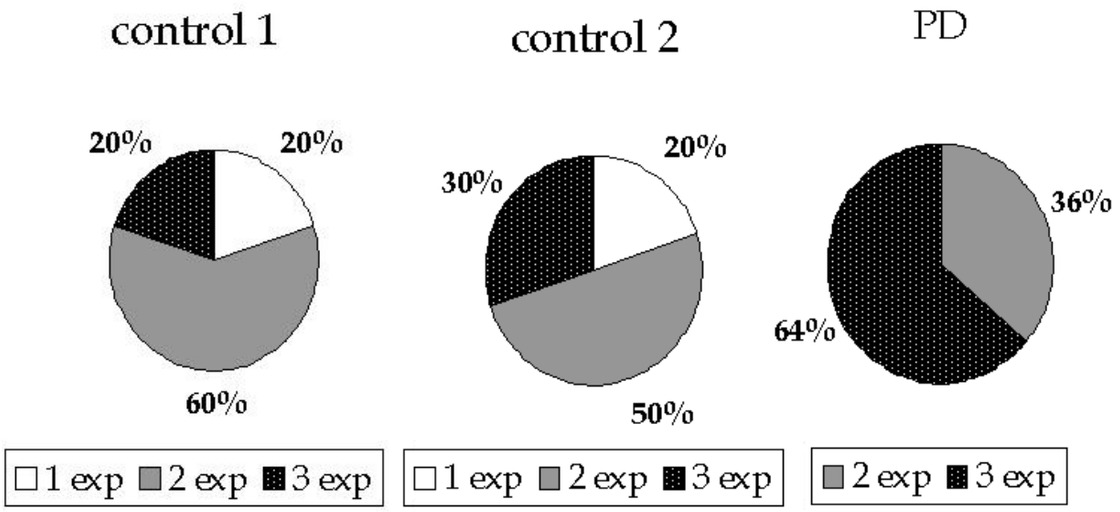

Fig. 11. Comparison of the incidence of different patterns of surface EMG signals fractal dimension (with one, two or three Hurst exponents) in persons of middle age (control 1), elderly subjects (control 2) and patients with Parkinson's disease (PD).

Overall, the present investigation has demonstrated the following distinctive features of surface EMG signals fractal dimension in patients with akinetic-rigid-trembling form of PD: 1) correlation behavior of the resting EMG time series in patients was more complex compared to healthy subjects and often suggested three scaling regions; 2) the value of Hurst exponent was significantly lower in patients, its value may descend to 0.1 - 0.2 that indicates a time series with negative autocorrelation (e.g. a decrease between values will probably be followed by an increase); 3) considerable degradation of short and longer range correlation properties, that, perhaps, is associated with the loss of integrated physiological responsiveness at this disease (Goldberger et al., 2002).

2.4 EMG characteristics of clinically healthy kinsmen of the patients with Parkinson's disease

According to modern concepts, the genetic factor plays a considerable role in the development of Parkinson's disease. Modifications in several genetic loci responsible for the development of this disease have been identified. The considerable role of the genetic factor for the propensity to Parkinson's disease has been confirmed by the data of epidemiological studies. The frequency of development of this disease in kinsmen of Parkinsonian patients is two to seven times higher than that in persons of the control groups (Elbaz et al., 1999). Symptoms of functional insufficiency of the extrapyramidal system can be identified very early, namely several decades prior to possible onset of the development of the clinical form of Parkinson's disease (Berg et al., 2002). Prevention or deceleration of the development of this disease can be provided by the detection of the early, presymptomatic stage of the neurodegenerative process and identification of informative "biomarkers" of PD (Illarioshkin, 2008). We studied surface EMG in clinically healthy kinsmen of the patients

suffering from PD in order to detect latent symptoms of extrapyramidal insufficiency that can be considered genetic determinants of the risk of development of the above disease. The task of our study included estimation of the frequency of occurrence of muscle activity disorders in kinsmen of the patients, characterization of correlations between the appearance symptoms of extrapyramidal insufficiency and age of the tested persons, and formulation of recommendations for individuals belonging, from the aspect of risk of development of PD, to a risk group.

We examined two groups of persons. The first group consisted of 37 clinically healthy kinsmen/kinswomen of patients suffering from PD (children, brothers, and sisters; 22 women and 15 men aged 30 to 56; mean age 45.6 ± 1.5 years). The second group (control) included 30 healthy young and middle-aged persons (19 women and 11 men; age nearly corresponding to that of persons of the first group , i.e., from 34 to 58 years, mean age 46.9 ± 2.2 years. All examined persons gave informed consent to be involved in the study. We recorded surface EMG at rest using superficial bipolar electrodes fixed on the flexor and extensor of the elbow joint (m. biceps brachii and m. triceps brachii, respectively); an electroneuromyograph NeuroMPF (Russia) was used. The detailed description of method is presented in section 2.1.1.

In 9 (24%) clinically healthy kinsmen of PD patients symptoms of functional insufficiency of the extrapyramidal system were evident. They demonstrated the mean amplitude value of 5.4-12.4 μV, maximal amplitude value of 25-93 μV, and the mean power of EMG oscillations reached 0.85- 1.8 mV/sec. In control group the mean amplitude value varied from 3.4 to 5.0 μV, maximal amplitude varied from 5.6 to 20.6 μV and the mean power of EMG oscillations did not exceed 0.02-0.71 mV/sec. Higher values of the intensity of electrical muscle activity in kinsmen of PD patients positively correlated with their age; it should be noted that, in this respect, age older than 45 years can be considered to be critical. The number of elder (older than 45 years) subjects with values of the mean power of EMG oscillations higher than the mean value of this parameter in persons of control group exceeded significantly the number of elder persons with low values of the mean power of EMG oscillations ($p < 0.05$, χ^2 criterion). The correlation coefficient between the age of the tested persons and the value of mean power of EMG oscillations was 0.40 ($p < 0.05$).

In 6 (16%) kinsmen of PD patients short burst-like discharges consisting of two to three oscillations generated with a frequency of 5-10 Hz were observed within the resting EMG (Fig. 12). As a rule, the amplitude of these potentials did not exceed 52 μV.

For more detailed investigation we used statistics of EMG distribution, namely such parameters as range, variance and kurtosis. Range and variance reflect the extent of bioelectrical muscle signals. Kurtosis characterizes motor unit synchronization. We supposed that statistical methods might appear effective for exposure of pathological signs of muscle activity. In control group of healthy middle-aged persons the extreme value of resting EMG amplitude range was 20 μV, variance – 7 and kurtosis – 0.4. The parameters of range, variance and kurtosis were considered going out outside a norm, if they exceeded the extreme values of these indices in the control group. We found 16 (43 %) kinsmen of patients with PD, who had high statistical parameters of EMG signals. In 14 kinsmen (38 %) range and variance were augmented compared to the extreme values of these indices in the control group. In 11 kinsmen (29 %) kurtosis had higher values than normal, presumably, reflecting enhanced synchronization in activity of motor units (Table 5).

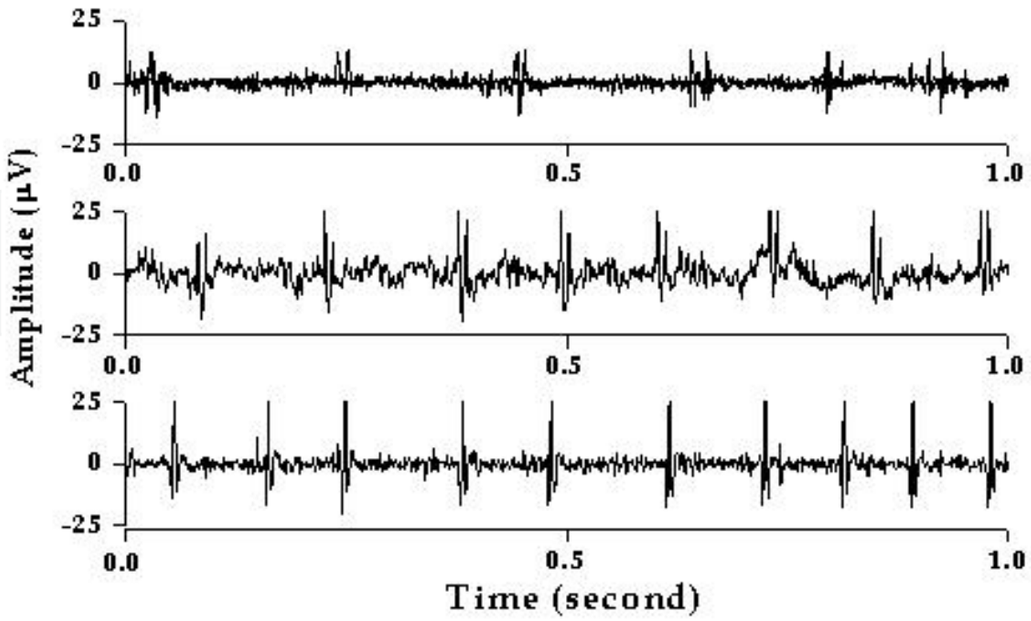

Fig. 12. Types of burst-like muscle discharges with frequency 6, 8 and 10 Hz recorded in three kinsmen of patients suffering from Parkinson's disease.

Statistical parameters	Number of tested persons
Range [22.46 – 113.61 μV] Variance [8.23 – 112.32] Kurtosis [0.43 – 16.30]	9 (24 %)
Range [24.22 – 28.33 μV] Variance [8.08 – 13.55]	5 (14 %)
Kurtosis [0.67; 0.70]	2 (5 %)
Total	16 (43 %)

Table 5. Incidence of resting EMG statistical parameters, going out outside a norm, in kinsmen of patients with Parkinson's disease. In square brackets the range of indices in different persons is presented.

The data obtained in our work agree with findings of other authors who emphasized that data obtained using EMG techniques are of a high informative value in the diagnostics of subclinical manifestations of weakening of the supraspinal control (Robichaud et al., 2009), and that the genetic factor responsible for the propensity for development of the extrapyramidal insufficiency is rather important (Elbaz et al., 1999; Illarioshkin, 2002).
A single common pathogenetic factor, namely conformational modifications of some cellular proteins at a post-translational stage of their synthesis, underlies most neurodegenerative diseases, including PD. Due to the existence of powerful compensatory and detoxication

systems in cells, such units are capable of successfully "overcoming" abnormal protein substrates for many years (Sherman & Goldberg, 2001). Delayed manifestation of clinical symptoms of the above disease is a feature of "conformational" pathologies of the brain. Latent pathological process can run course up to 30 years (Kryzhanovskii et al., 1995). The rate of pathological modifications in nerve cells within the presymptomatic period of PD is relatively low, but neuronal death is intensified significantly with transition to the stage of manifestation of this disease (Antonini et al., 1998). In relation to the above data, it is quite obvious that early diagnostics of the existence of latent extrapyramidal insufficiency is of exceptional importance. To prevent manifestations of PD in persons belonging to the risk group with respect to the development of parkinsonism, certain basic recommendations should be taken into account. They included a description of the rational daily routine, a recommended dietary intake with an increased content of vitamin B6 (pyridoxine, which is the main catalyzer in the synthesis of dopamine), and also a list of the drugs whose long-term administration should be avoided. Among the latter drugs are therapeutic agents whose administration leads either to depletion of the regulatory function of the dopaminergic system or to an increase in the functional activity of this system. Among such agents are haloperidol, the indole reserpine, fluoxetine (Prozac), metoclopramide (Cerucal), clozapine, and Cordarone, as well as derivatives of phenothiazine and butyrophenol, and also lithium preparations.

3. Investigation of contingent negative variation

Endogenous cortical movement-related reaction contingent negative variation (CNV) is a sensitive indicator for the objective evaluation of the severity of PD and quantifying the efficacy of antiparkinsonian therapy. Many authors identify two phases in CNV: an early phase, the Bereitschaftpotential, and a late phase, the negative slope (Filipovic et al., 1997). It has been suggested that these are generated by different brain structures: the cerebellar efferent system is more involved in generating the Bereitschaftpotential, while the basal ganglia are more involved in generating the negative slope (Ikeda et al., 1997). The question of the relationships between each of these phases and higher integrative processes and the mechanisms of direct motor control have received insufficient study. The aims of the present work were to study the extent to which the early and late phases of CNV depend on motor and mental functions and to determine what effect have neurotrophic agents on CNV. Tasks to be addressed were: 1) identification of the individual characteristics of the early and late phases of CNV in patients with PD as compared with subjects of similar age; 2) identification of correlation the measures of the two phases of CNV with clinical characteristics of the PD patients; 3) investigation the effect of the brain-derived peptide drug cerebrolysin on the amplitude characteristics of CNV in PD.

3.1 Methods

Studies were performed using 28 healthy subjects (13 male, 15 female, age 48–73 years, mean age 60.9 ± 1.2 years) and 56 patients with idiopathic PD (23 male, 33 female, age 45–74 years, mean age 61.3 ± 1.1 years). Patients were in stages 1.5–3.0 (2.2 ± 0.1) H-Y (international classification of Hoehn and Yaht, 1967). Patients received basic antiparkinsonism treatment with levodopa-containing agents (levodopa/carbidopa). Individual daily doses of levodopa were 250–750 mg. All subjects were right-handed.

Monopolar recordings were made of CNV from intermediate leads: frontal (Fz), central (Cz), and parietal (Pz). The indifferent electrode was located on the earlobe. The ground electrode was located on the left forearm. During studies, subjects were in a relaxed, calm state with the eyes closed. Bioelectrical signals were passed to an amplifier with a bandpass of 0.08–15 Hz and then to a computer hard disk. CNV was recorded using two sound stimuli of different intensities with a 1-sec interval: the ready signal was at 50 dB HL and the trigger signal was at 80 dB HL. The subject pressed a key in response to the trigger signal. Analysis was performed using computer programs. The sampling frequency was 200 Hz. The analysis time was 3.1 sec, the first 400 ms being a record of the baseline electroencephalogram. Mean initial activity was determined from an artefact-free part of the electroencephalogram trace. Averaging of 30 trials yielded: 1) the duration of CNV measured as the time interval between the start of the negative deviation from the baseline after the ready stimulus and the moment of presentation of the trigger stimulus (ms); 2) the areas of Bereitschaftpotential and negative slope, between the baseline and the negativity curve of the corresponding region $S = (\Sigma Ai) \times \Delta t$ (mV·ms), where Ai is the amplitude of the negative deviation from the initial level at a sampling frequency of 200 Hz and Δt is a time interval of duration 5 ms; 3) the mean amplitudes of Bereitschaftpotential and negative slope defined by $A = \Sigma Ai/n$ (μV). The program also allowed calculation of the simple sensorimotor reaction time (the mean latent period of pressing the key in response to the trigger signal).

Motor symptomatology was assessed quantitatively in patients with PD in points using the unified scale UPDRS. The total score was measured in each of three dimension scales: I (impairments in thought, mood), II (decreased daily activity, impairment of hygiene activities); and III (disturbances of motor function, including bradykinesia, rigidity, and tremor) using four-point subscales for each symptom. General cognitive status of the PD patients was characterized using the standard quantitative scale Mini Mental State Examination (MMSE). The overall assessment of mental functions in normal patients yielded 30 points. Decreases in the total score to less than 25 were regarded as a sign of early dementia.

The state of coordinatory muscle interactions was studied in 29 patients with PD (aged 47–72 years) by assessing the level of reciprocal involvement of the triceps brachii antagonist muscle (the extensor muscle of the shoulder) on functional loading of the biceps brachii muscle (the flexor of the shoulder) on the right side. EMGs were recorded using bipolar skin electrodes (0.5 × 1.0 cm^2) with a constant interelectrode distance of 1.5 cm. Bioelectrical signals were passed to the amplifiers of a Medikor MG440 (Budapest) electromyography with a bandpass of 10 Hz to 10 kHz. Functional loading on the biceps brachii muscle was applied by holding a load of 2 kg on the elevated and forward extended arm for 5 sec. With the patient in the calm, relaxed state and during holding of the load, at least 100 measurements were processed using the computer program to determine the mean EMG amplitude in the triceps brachii at rest (Ar) and loading (Al), the coefficient of reciprocal involvement of the antagonist muscle was calculated as $Al/(Ar + Al)$. This coefficient had a value of 0.5 when the amplitude on loading showed no change. If the amplitude decreased, then coefficient of reciprocal involvement had values of less than 0.5, while increases yielded coefficient of reciprocal involvement values of greater than 0.5.

The effects of cerebrolysin on measures of CNV were studied in 21 patients with PD that were taking antiparkinsonian therapy, which was not changed during one month before cerebrolysin treatment and under the whole cerebrolysin course (intravenously 10 ml, during 10 days). Before and after cerebrolysin treatment we studied clinical scores of UPDRS and CNV.

Data obtained in healthy subjects and patients with PD were compared using the non-parametric Mann–Whitney test. Data obtained in individual patients before and after administration of cerebrolysin were analyzed using the t- test for pairwise dependent variables. Correlations between the amplitudes of the two phases of CNV, the UPDRS and MMSE scales, and the levels of reciprocal involvement of antagonist muscles were identified by calculating the correlation coefficient by the non-parametric Spearman method (rS). Relationships were regarded as moderate at $0.3 \leq rS \leq 0.5$ and considerable at $rS > 0.5$. Differences were taken as significant at $p < 0.05$.

3.2 Results

3.2.1 Characteristics of the early and late phases of CNV in healthy subjects and patients with Parkinson's disease

Repeat studies in individual subjects showed that CNV had the most stable characteristics in the central medial lead (Cz), so data obtained from this lead were analyzed in detail. CNV in healthy subjects could usually be discriminated into two phases: an early phase (Bereitschaftpotential) 505–728 (596.3 ± 12.1) ms before the trigger signal and a late phase (negative slope) apparent as an additional negative deviation 170–365 (230.2 ± 15.4) ms before the trigger signal (Fig. 13). However, the second phase was not always clearly evident; in this situation CNV consisted of an initial drop-off followed by a uniform negative deviation from baseline lasting to the trigger signal. In these cases, the second half of CNV was analyzed as the second phase. In healthy subjects, the mean amplitudes of Bereitschaftpotential and negative slope were 9.0 ± 1.1 and 10.6 ± 1.0 μV respectively, with areas of 2.8 ± 0.4 and 3.2 ± 0.2 mV·ms (Table 6). Unlike healthy subjects, CNV in many patients was poorly evident, in some, no negativity at all developed between the ready and trigger signals (Fig. 14). Statistical analysis of the data revealed significant decreases in the mean amplitudes and areas of both phases of CNV in patients with PD as compared with healthy subjects (Table 6). In addition, patients showed an increase in the simple sensorimotor reaction time for pressing the key in response to the trigger signal, from 240.9 ± 13.7 ms in healthy subjects to 299.6 ± 17.3 ms ($p < 0.05$).

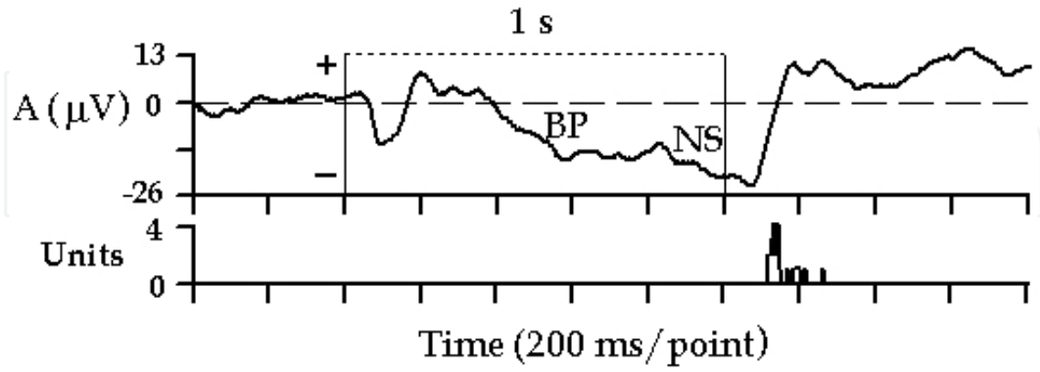

Fig. 13. Characteristic record of contingent negative variation (CNV) in healthy subject aged 64 years. A is the amplitude, μV. BP is the early phase and NS' is the late phase of CNV. Vertical lines show the moments of presentation of the warning and trigger signals, with an interval of 1 sec. Positivity is shown by upward deviations from the baseline and negativity by downward deviations. Low trace is simple sensorimotor reaction times for pressing the key after presentation of the trigger signal. Units show the number of keypresses.

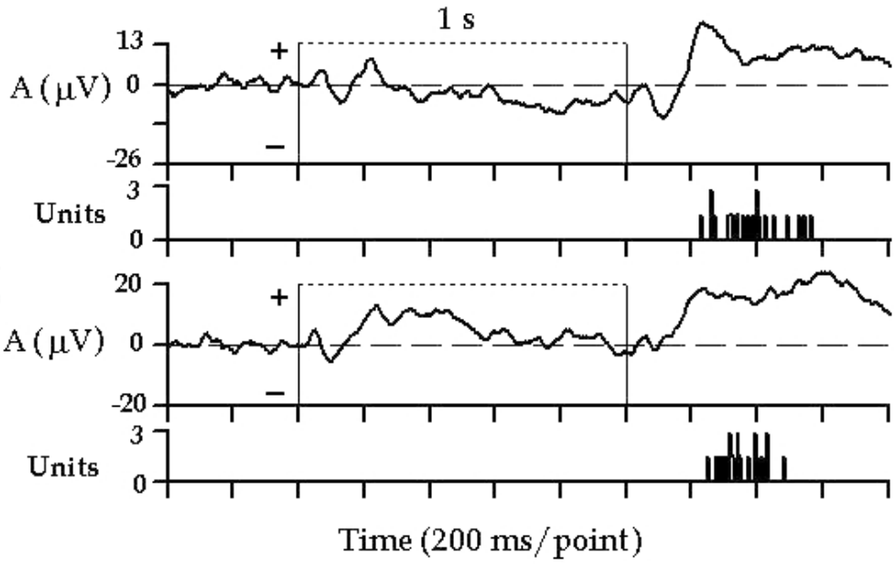

Fig. 14. Example traces of contingent negative variation (CNV) in two patients with Parkinson's disease aged 65 and 54, years. CNV in the first patient was poorly expressed, and the second patient showed no negative deviation. For further details see caption to Fig. 13.

Group	Area of early phase, mV·ms	Mean amplitude of early phase, μV	Area of late phase, mV·ms	Mean amplitude of late phase, μV
Healthy, n = 28	2,8 ± 0,4	9,0 ± 1,1	3,2 ± 0,2	10,6 ± 1,0
Patients, n = 53	1,8 ± 0,2 *	5,7 ± 0,4 *	1,7 ± 0,1 *	6,5 ± 0,5 *
p	< 0,01	< 0,01	< 0,001	< 0,01

Table 6. Differences in measures of the two phases of contingent negative variation in the median central lead (Cz) in healthy subjects and patients with Parkinson's disease. n is the number of subjects in the group.* is significant difference between patients with PD and healthy subjects (non-parametric Mann–Whitney test).

3.2.2 Correlation between the amplitudes of the early and late phases of CNV and characteristics of the patients with Parkinson's disease

Correlation analysis revealed moderately significant relationships between the amplitudes of the two phases of CNV and point scores for individual subscales on the UPDRS. Table 7 shows that the mean amplitudes of Bereitschaftpotential and negative slope were negatively related (rS = –0.31 and rS = –0.3 respectively, $p < 0.05$) to the total point score on UPDRS subscale II, which reflects decreases in the activities of daily living (impairments of hygiene habits, cutting and holding food, difficulty dressing and walking). It was interesting to note that there was a selective negative correlation (rS = –0.32, $p < 0.05$) between the magnitude of negative slope and symptoms on subscale II such as gait freezing, while Bereitschaftpotential showed no significant relationships of this type. There were no significant correlational relationships between measures of the two phases of CNV and the total score on UPDRS subscale III, reflecting intrinsic motor functions, or with clinical point scores for rigidity, tremor, or bradykinesia.

Clinical scale points	Mean amplitude of early phase	Mean amplitude of late phase
Total points on UPDRS subscale II; n=56	rS = -0,31 *	rS = -0,30 *
Points on UPDRS subscale II; item 14 (gait freezing); n=56	rS = -0,24	rS = -0,32 *
Coefficient of reciprocal involvement between antagonist muscles; n=29	rS = -0,58 **	rS = -0,51 **
Total score on MMSE (mental functions); n=28	rS = 0,47 *	rS = 0,47 *
Points on MMSE item 4 (memory); n=28	rS = 0,56 **	rS = 0,46 *

Table 7. Relationships between the amplitudes of the two phases of contingent negative variation in the median central lead (Cz) and clinical point scores in patients with Parkinson's disease. n is number of investigated persons. rS is the Spearman correlation coefficient.. * is $p<0.05$; ** is $p<0.01$.

The existence of a link between measures of the two phases of CNV and the state of coordinatory muscle interactions was addressed by studying the relationship between the amplitude characteristics of CNV and the extent of reciprocal impairments between antagonist muscles in patients with PD by calculating the coefficient of reciprocal involvement. Bereitschaftpotential and negative slope were completely absent in those patients in whom the coefficient of reciprocal involvement was high (0.67–0.8), which is evidence for an abnormal increase in the reciprocal involvement of the extensor muscles in the operation of the flexor muscles. Conversely, low coefficient of reciprocal involvement was associated with maximal amplitudes for both phases of CNV. The negative correlations between the extent of reciprocal muscle involvement and the amplitudes of Bereitschaftpotential and negative slope were significant (rS = –0.58 and rS = –0.51 respectively, $p < 0.01$). Comparison of the parameters of CNV and quantitative measures on the MMSE scale revealed an identical moderate positive relationship (rS = 0.47, $p < 0.05$) with the magnitudes of both phases and the state of mental functions in patients with PD (Table 7). The strongest relationship was between Bereitschaftpotential and point 4 of the MMSE scale, which reflects memory (rS = 0.56, $p < 0.01$).

3.2.3 Effects of cerebrolysin on measures of CNV in patients with Parkinson's disease

The results of the present study showed that the course of cerebrolysin treatment combined with levodopa has the positive therapeutic effect, such as: a significant decrease of the part I, II and III UPDRS scores. A decrease of the UPDRS part I scores (improvement in thought, mood) and part II scores (that is an increase of daily activity and ability of more full value selfattendance) was the most expressed. Significant increase of the CNV amplitude value and duration well reflected the enhancement of the brain activity (Table 8).

Time of investigation	Duration of CNV (ms)	Mean amplitude of CNV (μV)	UPDRS part I scores	UPDRS part II scores	UPDRS part III scores
Before CER	423.1 ± 43.3	3.1 ± 0.9	5.6 ± 0.7	14.2 ± 1.3	40.4 ± 3.4
After CER	600.6 ± 38.5*	6.8 ± 1.4***	3.5 ± 0.7***	11.3 ± 1.4***	32.9 ± 3.2*

Table 8. Change of contingent negative variation (CNV) and UPDRS scores in Parkinson's disease patients after cerebrolysin (CER) treatment. Footnotes: * - the significant change after cerebrolysin treatment, $p < 0.05$; *** - $p < 0.001$ (paired t-test).

3.3 Discussion

The results showed that patients with PD, as compared with healthy subjects, had significant decreases in the amplitudes and areas of both the early and late phases of CNV. We established that one significant factor decreasing both phases of CNV in patients with parkinsonism is impairment of coordinatory muscle interactions. Thus, the more significant the coordinatory impairment, apparent as an increase in the reciprocal involvement of the antagonist muscle during functional tests, the smaller the values of Bereitschaftpotential and negative slope in patients (rS = –0.58 and rS = –0.51 respectively; $p < 0.01$). As shown by the present data, a further significant factor affecting both phases of CNV was the state of mental functions. The positive correlation between Bereitschaftpotential amplitude and point 4 on the MMSE scale, characterizing memory (rS = 0.56, $p < 0.01$), was the most marked. This suggests that CNV can be regarded not only as a correlate of the initiation and preparation of motor structures for performing an action, but also as a neurophysiological component of mental functions. This point of view is in good agreement with published data showing sharp reductions in CNV in Alzheimer's-type dementia (Zappoli et al.,1991).

The suggestion (Ikeda et al., 1997), that the nigrostriatal dopaminergic system has a greater role in generating the late phase than the early phase of CNV is supported by our finding of the existence of a selective negative correlation ($p < 0.05$) between the magnitude of negative slope and the severity of symptoms such as gait freezing; there was no such correlation for Bereitschaftpotential. The symptom of "gait freezing" does not correlate with rigidity or bradykinesia (Bartels et al., 2003), is significantly decreased by levodopa (Schaarsma et al., 2003) and depends on the functional state of the globus pallidus: stimulation of its internal zone (the main source of the efferent output of the whole of the striopallidal complex) effectively eliminates the phenomenon of "gait freezing" (Katayama et al., 2000).

The results of the present study enlarge the perspectives in application of cerebrolysin and are in agreement with literature data on the efficacy of cerebrolysin in neurological practice. Thus, it was shown that cerebrolysin might be useful in patients with senile dementia of the Alzheimer type (Ruther, al., 2002). The positive therapeutic effect of the brain-derived peptide drug cerebrolysin can be connected with its ability to increase the expression of BBB-GLUT1 and MAP2 genes, that improves the transport of the glucose through blood-brain barrier and keeps the cytoskeleton wholeness accordingly (Boado, 2001). Cerebrolysin can also reduce the glutamate induced excitotoxicity (Hutter-Pair, al., 1998).

Obtained data proof that CNV appears to be a good tool for the evaluation of the medication efficiency. The parameters of CNV well reflected the improvement of the functional state of the patients after the course of cerebrolysin treatment.

4. Cortical evoked potentials upon paired-click auditory stimulation

It has been previously reported in clinical and experimental studies that movement disorders in PD largely occur due to the imbalance of inhibitory and excitatory processes in motor cortical and subcortical neuronal circuits following a nigrostriatal dopamine deficit (Ridding et al., 1995). A paired-pulse paradigm is usually used to study postexcitatory inhibition effect related to sensory gating mechanisms and synaptic processes in neurotransmitters release (Chu et al., 2009). There are two mechanisms that might explain paired-pulse inhibition phenomena. The first mechanism is the decrease in release probability of excitatory neurotransmitters from terminals of afferent axons (Szabo et al., 2000). Another possible mechanism of the decrement of the second response on paired stimulation is connected with synaptically released GABA from terminals of inhibitory interneurons (Chu & Hablitz, 2003). As the paired-pulse facilitation, paired-pulse inhibition is considered to be a form of a short-term synaptic plasticity. The investigation of cortical evoked potentials to paired-pulse sensory stimulation may provide additional information about mechanisms of neurological disturbances in PD.
The aim of this study was to investigate the postexcitatory inhibition of the N1/P2 complex of the cortical evoked potentials on auditory paired-click stimulation in patients with PD in comparison with age-matched healthy subjects. Our second goal was to evaluate the influence of neurotrophic drug cerebrolysin on postexcitatory cortical inhibition.

4.1 Methods

Studies were performed in two groups. The first group included 58 PD patients, with the severity of the disease corresponding to 1.5 - 3.0 of Hoehn M.M. and Yahr M.D. (1967) scale (28 men and 30 women, mean ± SE age 61.5 ± 1.1, range 45 - 74 years). The second group was control and consisted of 22 age-matched healthy subjects (10 men and 12 women, mean ± SE age 61.4 ± 1.1, range 48 - 73 years).
The study was approved in advance by the Ethical Committee of the Institute of Gerontology and was in accordance with the Declaration of Helsinki. The patients regularly underwent treatment at the Parkinson's Disease Centre of the Institute of Gerontology and gave written informed consent to participate in this study. The diagnosis of Parkinson's disease was determined according to the UK Bank Criteria (Hughes A. et al., 1992). The patients had from 2 to 22 year individual histories of idiopathic PD and were taking antiparkinsonian therapy at individual dose of 187.5 - 750 mg of levodopa / carbidopa daily. Besides levodopa / carbidopa, the patients were using other antiparkinsonian medication: selegiline, pramipexol, amantadine. The neurological status of PD patients was evaluated with Unified Parkinson's Disease Rating Scale (UPDRS; Fahn S. and R. Elton., 1987; Holloway R.G. et al., 2004) in the "ON" state 1 hour after levodopa / carbidopa intake. Mini Mental State Examination (MMSE) was used to study general cognitive status of the PD patients.
Auditory evoked potentials were recorded in the PD patients in their "OFF" state in the morning, after they were free from levodopa treatment and other antiparkinsonian medications for at least 12 hours. During registration of evoked potentials the subjects were sitting comfortably in a semi-reclined armchair in a quiet room with closed eyes. Cortical

auditory evoked potentials were recorded at the vertex (Cz) referenced to a linked-ear electrode. The ground electrode was placed at the left wrist. The impedance of the electrodes was less than 10 kΩ. The electrode signal was amplified using a bandpass filter (0.53 - 30 Hz), digitised with 200 Hz sampling rate and stored for further analysis.
The pattern for double stimulation consisted of paired auditory clicks with 500, 700, 800, 900, 1100 and 2000 ms interstimulus intervals. The identical parameters (duration of 0.15 ms and intensity of 80 dB HL - hearing level) were used for the preceding conditioning click and following test click. Pairs of clicks were delivered once every 7 s for each interstimulus interval. Previous studies have shown that stimulation at faster frequencies can lead to a decrement in the cortical evoked potentials. A 2000 - 3000 ms electroencephalography epoch was recorded for each trial, including a 300 ms pre-stimulus baseline. The recording time depended on interstimulus intervals. The epochs contaminated with blinks or other artefacts were excluded from the data and twenty acceptable artefact-free trials were averaged for each interstimulus interval and used for further analysis. In electroencephalography recordings upon paired stimulation, amplitudes of N1-P2 complex (peak to peak) in the first (A1) and the second (A2) responses were measured. The amplitudes of the components N1 and P2 were estimated in the 60 – 150 ms and 120 - 220 ms ranges of time, respectively. The percent of paired-pulse inhibition of the N1-P2 complex was calculated using the formula: (A1-A2)/A1×100.
The effects of cerebrolysin on the postexcitatory inhibition of the N1/P2 complex of the cortical evoked potentials on auditory paired-click stimulation were studied in 21 patients with PD that were taking antiparkinsonian therapy, which was not changed during one month before cerebrolysin treatment and under the whole cerebrolysin course (intravenously 10 ml, during 10 days).
The results were analyzed statistically. Comparisons between PD patients and control groups were made using a non-parametric two-tailed Mann-Whitney criterion. Data obtained from the same patients before and after cerebrolysin treatment were compared using two-tailed paired t-test.

4.2 Results

4.2.1 Investigation of the postexcitatory inhibition following paired stimulation

The postexcitatory cortical inhibition in response to auditory stimulation studied with a paired-pulse paradigm was significantly reduced in patients with PD compared to control subjects. Amplitudes of N1-P2 complexes following the second stimulus of a pair at interstimulus intervals of 500, 700 and 900 ms were greater in PD patients. The mean values of paired-pulse inhibition in the group of PD patients were decreased to 29.8 ± 4.8 % ($p<0.01$), 25.4 ± 3.2 % ($p<0.001$) and 15.1 ± 2.6 % ($p<0.001$) for intervals 500, 700 and 900 ms respectively as compared to these values (54.1 ± 4.2 %; 49.8 ± 2.3 % and 42.9 ± 2.7 %) in the group of age-matched controls (Table 9).
The mean amplitude of N1-P2 complex elicited by a single (first) auditory stimulus in the group of PD patients was 16.2 ± 0.8 μV which was less than in age-matched subjects (18.5 ± 1.6 μV) but this difference was not statistically significant ($p>0.05$).

4.2.2 The influence of cerebrolysin treatment on the postexcitatory inhibition

A distinct positive effect of the course of cerebrolysin treatment on the postexcitatory cortical inhibition at paired-click stimulation was observed in the group of 21 PD patients. A noticeable shift of the paired-pulse inhibition value for 700, 800 and 900 ms intervals towards the values of the healthy control was found (Table 10, Fig 15).

Investigated groups	Inhibition in % of the second N1-P2 complex at interstimulus intervals			Averaged
	500 ms	700 ms	900 ms	
Age-matched control	54.1 ± 4.2	49.8± 2.3	42.9 ± 2.7	48.0 ± 2,1
PD patients	* 29.8 ± 4.8	** 25.4 ± 3.2	** 15.1± 2.6	** 21,4 ±2,4

Table 9. Inhibition of the second N1-P2 complex of cortical auditory evoked potentials at paired-click stimulation in age-matched control group and patients with Parkinson's disease (Mean ± SE).
* - P<0.01; ** - P<0.001 compared to control subjects (nonparametric Mann-Whitney test).

Time of investigation	**Averaged value of paired-pulse inhibition** (%) **at interstimulus intervals (ms)**			
	700	**800**	900	**Averaged data**
Before cerebrolysin	29.9 ± 3.9	26.7 ± 3.4	17.1 ± 3.1	24.6 ± 2.3
After cerebrolysin	38.1 ± 3.2	37.1 ±3.3	27.5 ± 4.1	34.2 ± 2.9
P (paired t-test)	<0.01	<0.001	<0.05	<0.001

Table 10. The influence of the course of cerebrolysin treatment on the postexcitatory inhibition following paired-click auditory stimulation in patients with Parkinson's disease (Mean ± SE).

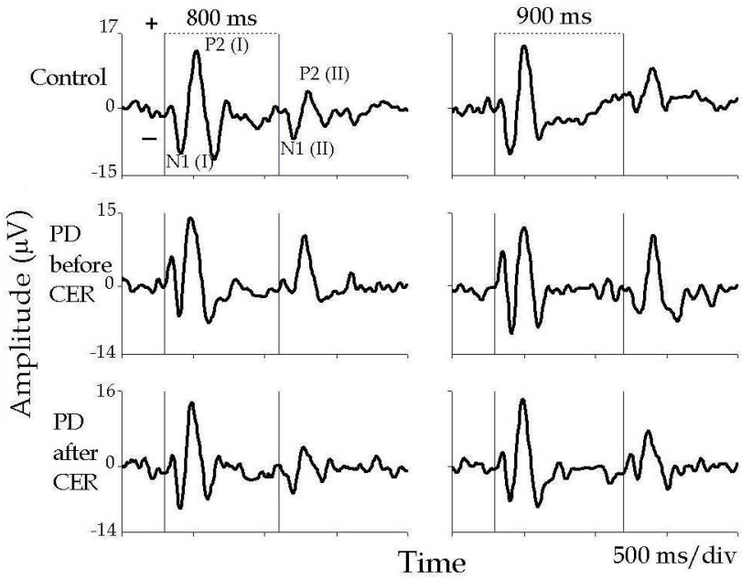

Fig. 15. Cortical auditory evoked potentials at paired auditory stimulation with interstimulus intervals of 800 and 900 ms in healthy control and patient with Parkinson's disease (PD) before and after the course of cerebrolysin (CER). N1(I), P2(I) – the components of cortical evoked potentials on the first conditional stimulus and N1(II), P2(II) – on the second test stimulus. Vertical solid bars on the records correspond to the onset of auditory signals.

4.3 Discussion

The main result of this study showed that PD patients had significantly reduced paired-pulse inhibition of the N1/P2 component of evoked potentials in the auditory cortex for interstimulus intervals of 500, 700 and 900 ms compared to the healthy age-matched subjects. Possible explanation of the reduced cortical inhibition in PD is the functional deficiency of inhibitory interneurons caused by depletion of dopaminergic innervation in the cerebral cortex (Gaspar et al., 1991). As already established (Krnjevic et al., 1966), afferent volleys after initial excitatory postsynaptic potentials (EPSPs) result in inhibitory postsynaptic potentials (IPSPs). A system of GABAergic interneurons, which can be activated by direct and indirect stimulation, may play the major role in the genesis of these IPSPs (Hanajima & Ugawa, 2000). The synaptic release of GABA is regulated by presynaptic GABA receptors of the B-type (Chu & Hablitz, 2003). There is also strong evidence that dopamine regulates inhibitory transmission at the synapses between pyramidal cells and interneurons by activating D1-like receptors located on the presynaptic terminals of GABAergic axons (Gonzalez-Islas & Hablitz, 2001). Dysfunction of cortical interneurons in PD also might be a result of noradrenergic denervation and monoamine terminal loss (Marie et al., 1995), as some investigations showed that cortical GABAergic interneurons can be excited via alpha-adrenoreceptors (Kawaguchi & Shindou, 1998).

Another possible explanation of the reduced inhibition in the auditory cortex in patients with PD may be the loss of dopaminergic transmission in the basal ganglia and the dysfunction of the caudal pallidum that sends its direct projections to the inferior colliculus, medial geniculate nucleus and temporal cerebral cortex (Shammah-Lagnado et al., 1996). The basal ganglia appear to "gate" sensory inputs at various levels and activation of basal ganglia outputs (entopeduncular nucleus and substantia nigra pars reticulate) is able to inhibit sensory responses (Boecker et al., 1999).

Our findings allow to suppose that drugs, which are able to activate cerebral inhibitory GABAergic system, can be useful in medication of PD. Phenibut (noofen) belongs to such drugs (Marshall & Foord, 2010). Application of noofen in complex therapy of PD appeared effective for the improvement of cognitive functions, enhancement of emotional state and increase of social adaptation of the PD patients (Karaban et al., 2006).

This study demonstrated that course of cerebrolysin treatment promotes normalization of the inhibitory brain processes. The positive effect of cerebrolysin indicates that neurotrophic drugs can also be useful in complex antiparkinsonian therapy for advance of the ability of the brain to provide normal inhibition.

5. Conclusion

The present investigation has shown that the surface EMG data add essential information to the clinical characteristics of PD patients. We found that separate EMG indices correlated, in a specific manner, with certain UPDRS sub-items, which could result in a better understanding of the pathogenesis of clinical PD symptoms. Motor disorders in PD (part III UPDRS scores) were found to be predominantly associated with disturbances in regulation of the tonic and phasic muscle activities. At the same time, disorders of the upper extremity daily activity (points 8-10 of UPDRS) and the dyskinesia (disability) (point 33 of UPDRS) are largely conditioned by the disturbance of reflex coordinating relationships between the muscles in PD. EMG analysis seems to be a useful tool for levodopa therapy adjustment and for predicting the course of disease.

In this study critical values of normal statistics of surface EMG distribution at rest were defined. Evaluation of statistical parameters of the EMG signals, to our opinion, appeared to be effective for the detection of signs of the disturbed muscle activity. Range and variance reflect the extent of bioelectrical muscle signals. Kurtosis characterizes motor unit synchronization. These EMG characteristics assist to detect latent symptoms of extrapyramidal insufficiency in clinically healthy kinsmen of the patients suffering from PD that can be considered genetic determinants of the risk of development of the above disease. Formulation of recommendations for individuals belonging to a risk group is of exceptional importance to prevent manifestations of PD.

Novel EMG characteristic is fractal dynamics of EMG data based on detrended fluctuation analysis and calculation of Hurst exponent. Fractal dimension studies the non-linear properties of EMG. The present investigation has demonstrated distinctive features of surface EMG signals fractal dimension at rest in patients with akinetic-rigid-trembling form of PD: 1) fractal dimension in PD patients is more complex compared to healthy subjects; 2) the value of Hurst exponent is significantly less in patients; 3) there is the considerable degradation of short and longer range correlation properties of EMG signals in PD. Fractal analysis has proved to be sensitive to neuromuscular status and may have potential in the assessment of the severity of PD

Evaluation of brain evoked potentials provides additional information about the mechanisms of neurological disturbances in PD. The results obtained in the present study produce evidence for significant relationships between both the early and late phases of movement-related potential CNV and the neurophysiological mechanisms supporting coordinatory muscle interactions and mental functions, including the simultaneous activity of numerous specific and non-specific brain structures (motor cortex, supplementary motor cortex, prefrontal cortex, cerebellar and thalamic projections). The existence of a selective negative correlation between the magnitude of the late CNV phase and the severity of symptoms such as “gait freezing” suggests a great role of efferent system of the basal ganglia in generating this phase of CNV. The investigation of cortical evoked potentials at paired-pulse sensory stimulation shows that inhibitory processes are deficient in PD patients. The findings may suggest that drugs, being the derivates of GABA, can be useful in treatment of PD. The parameters of CNV and the value of postexcitatory cortical inhibition at paired-click sensory stimulation well characterize the state of brain activity. Together with other neurophysiological parameters the brain evoked potentials might be a good tool for quantifying the efficacy of medication of PD patients.

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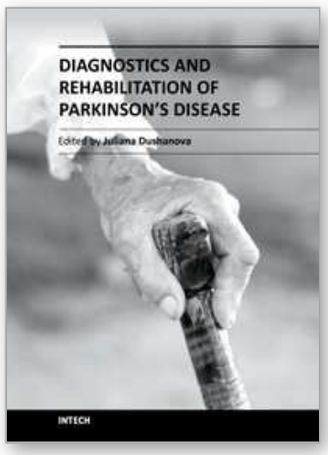

Diagnostics and Rehabilitation of Parkinson's Disease
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Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

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