Electroneurography abnormality in Parkinson’s disease: a potential biomarker to help diagnosis

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Abstract

Parkinson’s disease (PD) is a common neurodegenerative disease, pathologically characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra. Although various biomarkers and imaging criteria for PD have been established, objective and reliable evaluation methods are still lacking. Electroneurography, as an objective measurement of evoked compound muscle action potentials, is used to assess the integrity of the peripheral nerve and is important in the diagnosis and differential diagnosis of PD with neuromuscular injury. Moreover, it provides references for the evaluation and quantification of the motor function in PD. Here, we summarize recent advances in clinical research of electroneurography in PD, including the peripheral nerve conduction velocity, needle electromyography, surface electromyography, and motion unit number estimation. The potential values of electroneurography in PD diagnosis are also involved.

Keywords: Parkinson’s disease, electroneurography, needle electromyography, surface electromyography, motor unit number estimation
INTRODUCTION

Parkinson’s disease (PD) is a common neurodegenerative disease in middle-aged and elderly people. Currently, it is believed that the main pathological change of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra. The prevalence rate of people over 65 years old in China is 1.7%, and the incidence increases with aging\textsuperscript{1}. PD is clinically characterized by motor deficits including rest tremor, bradykinesia, myotonia, and postural balance disorders, as well as non-motor symptoms such as sensory disturbances, autonomic dysfunction, and mental and cognitive disorders. PD diagnosis is primarily based on history and physical examination\textsuperscript{2}. In the early stage of the disease, there is still a lack of objective or reliable diagnostic measurements. Although several auxiliary examinations have been established including olfactory test\textsuperscript{3}, transcranial B-mode sonography of substantia nigra\textsuperscript{4}, positron emission tomography with 18-fluorodeoxyglucose examination\textsuperscript{5}, and autonomic nervous function examination such as ventricular variation rate detection\textsuperscript{6}, these methods lack sensitivity and specificity in the early stage of the disease. Meanwhile, with recent advances in the understanding of the non-motor symptoms of PD, increasing lines of evidence show that peripheral neuropathy (PN) caused by neuroinflammation, oxidative stress, environmental toxins, and apoptosis may play an important role in the pathophysiological process of PD. Axonal or myelin sheath injury caused by these factors often manifests as peripheral nerve conduction velocity, including the prolonged latency, decreased compound muscle action potential amplitude, altered conduction velocity, conduction block, or waveform dispersion.

As an objective examination method, electroneurography has been widely used in the diagnosis and differential diagnosis of PN, muscular diseases, neuromuscular junction, and other diseases. This article reviews the research progress in the clinical application of electroneurography in PD.

THE MECHANISM OF PERIPHERAL NEUROPATHY IN PD

Peripheral nerve conduction velocity (NCV) examination includes motor nerve conduction velocity, sensory nerve conduction velocity, and F-wave, which can objectively reflect the integrity of myelin sheath. According to the traditional view, PD lacks epidemiological correlation with PN, and it is limited to patients with rare gene mutations such as PARK2, FMR1, ATXN3, and \textit{ATP13A2}\textsuperscript{7} or mitochondrial disease. In recent years, it has been demonstrated that PN can also be found in idiopathic PD. Damage affecting medium to large fibers was found in PD in lower limbs, which can be confirmed by NCV as a new clinical fact, and the most common nerve found was the superficial fibular nerve, followed by the sural\textsuperscript{8}.

Axonopathy in PD, as shown by the decreased amplitude of sural nerve\textsuperscript{9,10}, may also be due to long-term treatment with levodopa. Levodopa is methylated by catechol-O-methyltransferase to produce S-adenosyl homocysteine in central and peripheral tissues, which is immediately cleaved to form homocysteine (HCY). Folate and vitamin B12 as cofactors are required to convert HCY back to S-adenosylmethionine (SMA). Therefore, with the increase of levodopa, vitamin B12 consumption increases, and PN associated with vitamin B12 deficiency occurs\textsuperscript{11}. On the other hand, HCY induces inflammatory responses by increasing brittleness to mitochondrial toxins and increasing free radicals, impinging on DNA repair mechanisms\textsuperscript{12,13} and RNA methylation\textsuperscript{14}, leading to terminal degeneration of sural nerve axon. The incidence rate of large fibrous lesions in PD is 16.3%, and in small fibers, confirmed by biopsy is 56.9%\textsuperscript{15}. However, the literature does not exclude the possible influence of other factors such as diabetes and age-related factors on peripheral nerve damage. Levodopa is not the initial factor of PD with peripheral neuropathy, but the treatment exacerbates the progression of neuropathy.
A third mechanism of the causal relationship between PN and PD is the massive accumulation of α-synuclein in peripheral nerve terminal and damaged axon transport, resulting in small fibers\cite{[16]}.

Pathological changes have also been demonstrated in animal models, i.e., the spreading of α-synuclein is associated with sensory nerve degeneration and defective nociception. α-synuclein aggregates in the afferent sensory system, including sensory neurons, axons from the dorsal roots, and spinal dorsal horn neurons, and can reduce NCV through the ultrastructural damaged small and medium myelinated fibers. Meanwhile, α-synuclein, immunoreactive in lamina I of the dorsal horn, modulates pain processing, which is related to the pain of PD\cite{[17],[18]}. PN is a frequent yet underestimated feature of PD. PD patients with PN are older, have a higher levodopa dose, have worse axial motor features, and are independently associated with cognitive impairment. NCV examination can provide an objective diagnostic basis for PD with peripheral nerve damage. PN may be an independent peripheral marker of PD, indicating that there is a long course of disease accompanied by worse axial motion and impairment\cite{[19]}.

**NEEDLE ELECTROMYOGRAPHY**

Needle electromyography (NEMG) is a method to record various electrical characteristics of muscle resting or voluntary contraction by using a concentric needle electrode to determine the localization and type of neuromuscular disease. NEMG inspection is conducted in three parts. The first is the spontaneous activity in the muscle resting state. The second is the contraction [motor unit action potential (MUAP)], which is the sum of synchronous discharges of a group of muscle fibers dominated by one anterior horn cell. The third is the electrical activity during vigorous muscle contraction (recruitment pattern). NEMG is often used in PD with camptocormia and anal electromyography.

**The NEMG in PD with camptocormia**

Abnormal postures are common in PD, mainly including camptocormia, antecollis, Pisa syndrome, scoliosis, and striatal deformity\cite{[20]}. According to epidemiological statistics, the incidence of PD with camptocormia is about 22.5%, also with multiple system atrophy (MSA), dementia with Lewy bodies, frontotemporal lobar degeneration, progressive supranuclear palsy, and Alzheimer’s disease\cite{[21]}. While the exact mechanism underlying the pathogenesis of camptocormia is unknown, it has been recognized that both central and peripheral mechanisms may be involved, including abnormal motor function of basal ganglia-thalamic-cortical circuits\cite{[22]}, sensory afferent dysfunction, muscle and joint proprioception abnormalities\cite{[23]}, acetylcholine-dopamine transmitter imbalance\cite{[24]}, and inflammatory infiltration in paraspinal muscles. The possible pathogenesis can be divided into the following four types\cite{[25]}: those caused by the progression of PD, manifested in the form of PD with dystonia, secondary to paraspinal muscle myogenic diseases, and antipsychotics caused by treatment.

Myopathy, myositis, neurogenic changes, and dystonia can be seen in NEMG in PD with camptocormia\cite{[26]}. NEMG of paravertebral muscles can suggest myopathy-like manifestations, with a narrow duration of multiphase potential and low amplitude, or accompanied by a small amount of spontaneous potential\cite{[27]}, as well as dorsal and ventral trunk muscles (mainly about rectus abdominis, iliopsoas, internal oblique, and external oblique muscles)\cite{[28]}. Distal and proximal limb muscles may also be involved\cite{[29]}.

In some patients, burst discharges were observed in the responsible muscles under electromyography, which usually suggests pathogenesis caused by dystonia. The camptocormia in PD is aggravated when walking or exercising and relieved by standing against a wall. Similar to the “sensory trick” of dystonia, camptocormia can be caused by the strong contraction of abnormal muscles\cite{[30]}. NEMG can be used to guide the treatment of botulinum toxin A when the pathogenesis suggests dystonia to identify the target muscles with the more active potentials. When botulinum toxin A was injected into rectus abdominis muscle and external oblique
muscle for treatment, the abnormal posture and abdominal pain were significantly improved 7-8 weeks after injection\textsuperscript{[31,32]}. 

**The external anal sphincter electromyography in PD**

External anal sphincter electromyography (EAS-EMG) is widely used in the differential diagnosis of neurological dysfunction of lumbosacral segment related diseases, such as lumbosacral radiculopathy, tethered cord syndrome, neurodegenerative diseases, and intraoperative monitoring of lumbosacral related operations. In the 1960s, Graham and Oppenheimer\textsuperscript{[33]} proposed that Onuf's nucleus, located in 1/3 of the ventral gray matter of S2-S3 sacral medullary, is a motor nucleus which sends out the pudendal nerve to innervate the external urethral sphincter, anal sphincter, and pelvic floor striated muscle.

Both PD and MSA are associated with the impairment of autonomic nerve function, and their pathological mechanisms are different. Since MSA may be associated with the motor neuron degeneration of Onuf's nucleus, EAS-EMG (including duration, phase, and satellite potential) could efficiently make a differentiation between MSA and PD with a sensitivity of 100% and specificity of 86\%\textsuperscript{[34]}. The prolonged motor unit potentials (MUPs) duration and polyphasic MUPs usually indicate collateral reinnervation, which can be seen in early PD and MSA\textsuperscript{[35]}. Compared with PD, MSA is mainly characterized by a more prolonged mean duration and decreased amplitude during vigorous contraction\textsuperscript{[36]}. Most studies show that the abnormal rate of MSA is about 70%; muscular denervation such as fibrillation potential, positive sharp wave, and the duration of the action potential are widened; and the amplitude and polyphase wave are increased, as can be seen under the electromyography\textsuperscript{[37]}.

Based on EAS-EMG, using the test of the bulbocavernosus reflex (BCR) by stimulating the pudendal nerve can also reflect the degree of damage to the autonomic nerve. The amplitude of BCR in PD is lower than in MSA. It is confirmed that PD can be accompanied with functional impairment of the autonomic nervous, but the degree is less than in MSA. Patients with MSA have a longer latent period and higher amplitude. In some cases, BCR can be used to distinguish MSA from PD\textsuperscript{[38]}. However, it is well known that the amplitude is greatly affected by the individual; thus, latency is more accurate in reflecting the degree of autonomic nerve damage, which is not mentioned in the literature above.

**APPLICATION OF SURFACE ELECTROMYOGRAPHY IN PD**

Surface electromyography (sEMG) is a non-invasive method to record the movement of motor units through the skin surface with electrodes\textsuperscript{[39]}. The characteristics of the signals mainly include linear (amplitude and frequency) and nonlinear (complexity and orderly) indices. It is usually used to evaluate the activity and quantify the function of neuromuscular objectively. Motor neurons are activated when muscles contract autonomously or receive an external stimulus; all recruited motor units produce continuous MUAP, which is transmitted through fat and subcutaneous tissues and finally recorded by surface electrodes\textsuperscript{[40]}. Many researchers have used sEMG technology for gait disorder evaluation, fatigue status detection, tremor analysis, central motor control, and acoustic kinematics in PD.

**Application of sEMG in the assessment of gait disorder in PD**

Gait disorder is a common feature of PD with the main characteristics of reduced shuffling, reduced step length and speed, difficult starting, increased rigidity, and freezing. It is one of the important factors of falls in PD. Some gait disturbances, such as bradykinesia and rigidity, have proven to be due to the decreased output of cortical motor caused by the imbalance of basal ganglia loop or supplementary motor area, as well as the changes in cortical and subcortical connectivity\textsuperscript{[41]}. Some abnormal gait with instability is not only caused by the central factor but also peripheral factors, such as the greater contraction of agonist/antagonist
muscle groups and less effective recruitment of individual muscles\cite{45}. sEMG can describe the walking characteristics of the patient to evaluate the motor function and formulate the next treatment and rehabilitation plan\cite{46} by analyzing the way different muscles in the lower body are recruited. Gait analysis by sEMG should include the phase of stance and swing, two-limb support, and one-limb support\cite{47}. Anterior tibial (TA) is the most frequently assessed muscle as it can receive more projections from the cortex with other limb muscles. Patients with PD always have reduced TA activity during the stance phase\cite{48}. Some patients with freezing have a higher activity of bilateral TA during the swing phase\cite{49}, which reflects the impairment in motor control with the step length. The activity of medial gastrocnemius (MG) in PD is lower than in healthy controls, suggesting the defective function of proprioceptive\cite{50}. MG plays an important role in supporting the body in the vertical direction and stabilizing the ankle joint to maintain the balance of walking speed and posture\cite{51}. The asymmetric activities of TA-MG in PD are higher, which is an early feature of PD, as they have reduced muscle activity\cite{52}. The increased EMG variability usually indicates a high risk of falls in PD\cite{53}, and it is an important trigger factor with frozen gait. Different walking modes, such as straight walk, U-turn, and point turn, require high energy consumption and therefore limit walking speed and flexibility\cite{54}. Kugler et al. used a classification algorithm based on data collected from sEMG and accelerometers for step segmentation\cite{55}. The proposed step detection method reached 98.9% sensitivity and 99.3% specificity for the classification accuracy of distinguishing between PD and healthy subjects. The reduced step length seems to be a specific feature of PD gait that can be detected early in the disease and can be a useful marker of disease progression. Co-activation is another feature of gait in PD, which can stabilize the joints and increase rigidity\cite{56}. Interventions for gait disorders must modify the activities and patterns of individual muscles, changing the coordinated contraction on the basis of gait impairment in PD.

Fatigue evaluation of sEMG in PD

Patients with PD often have unexplained fatigue as a sense of overwhelming tiredness, which is different from apathy, depression, dementia, or sleepiness, and it has two forms: subjective fatigue and objective fatigue\cite{57}. The incidence rate ranges from 33% to 50%\cite{58}. Some studies have demonstrated that this figure is as high as 70%. Fatigue can be observed in some but not all patients with good motor function, as well as in patients with depression, sleep disturbance, and autonomic symptoms\cite{59}. Basal ganglia dysfunction, such as the extrastriatal dopaminergic projections or frontal striato-thalamo-cortical loops, has been suggested as the pathophysiology, and the reduced blood perfusion in the frontal lobes can also be a contributor to fatigue\cite{60}. Some potential biomarkers such as C-reactive protein, cytokines, and interleukin-6 may be correlated to fatigue. Other researchers have suggested pathophysiological mechanisms including dysfunction of the hypothalamic-pituitary-adrenal system\cite{61}. The demographic characteristics indicate that the patients with fatigue are 1.4 years older on average, more likely to be female, and have a longer disease duration, higher UPDRS motor scores and levodopa dose, worse cognitive performances, and depression\cite{62}. Fatigue is usually measured through scales with no specific biomarkers. The scales are suitable for subjective fatigue. Subjective fatigue and objective fatigue are distinct and independent concepts. sEMG can detect bioelectrical activities associated with muscle contraction and reveal neural changes in objective fatigue. It can be measured based on changes during sustained muscle contraction. Longer periods of vigorous contraction indicate that more activities are required to initiate movement, leading to bradykinesia\cite{63}. Some researchers have indicated that the sEMG pattern of fatigue in PD is not different from that in healthy controls\cite{64}, which might be due to the impacts from patients with subjective fatigue. sEMG can be used as a viable clinical assessment tool to detect the muscle pattern of fatigue and identify the risk during the onset.

The potential mechanism in tremor with PD by sEMG

With the development of the sEMG technology, many researchers have recently used acceleration measurement combined with sEMG to explore the tremor pattern of PD. The diagnosis of PD is...
challenging; to date, sEMG is the gold standard for the analysis and diagnosis of tremors\cite{62}. The movement during tremor and different burst modes of a pair of antagonistic muscles can be recorded by sEMG. The frequency of most pathological tremors is 4-8 Hz, some palatal tremors are below 4 Hz, and orthostatic tremors are 13-18 Hz\cite{63}. Tremor generators are often classified as central or peripheral in origin\cite{64}. An abnormal rhythm of tremor exists in the basal ganglia of PD, while the network of ET is in the lower olive nucleus. The tremor harmonics as a valuable biomarker for tremor is important\cite{65}.

The rest tremor as a typical and unique feature of PD has been considered for a long time, but recent studies have shown that rest tremor is also present in 15% of patients with ET\cite{66}, causing misdiagnosis. For tremor analysis based on sEMG, parkinsonian rest tremor differs from ET as the tremor amplitude is suppressed during initiation of voluntary and target movements\cite{67}. The suppressed rest tremor may have delayed re-emergence when a new posture is sustained (re-emergent tremor), and the rest tremor in PD is usually unilateral in onset with 4-6 Hz\cite{63}. The rest tremor suppression test has demonstrated a very good sensitivity of $\geq 0.92$ and a specificity of $\geq 0.69$ for identifying rest tremor of PD\cite{67}.

Thirty-nine percent of CBD patients have tremors during the disease course, including rest tremor, postural tremor, and action tremor. They are similar to low amplitude action myoclonus and differ from the typical rest tremor of PD\cite{68}.

Shaikh et al.\cite{69} applied sEMG to differentiate PD from drug-induced secondary parkinsonian syndrome (dopamine receptor blockers such as antiemetic drugs and antipsychotics and DRBA-induced parkinsonism). Intentional tremor amplitude increased significantly in DRBA-induced parkinsonism, and the amplitude of tremor in resting and postural is similar. It may be due to the irregularity in the oscillation waveforms and the disturbance of central oscillator output. Tremor analysis is particularly useful in the diagnosis of various tremors.

The application of sEMG in central motor control of PD
Determinism (%DET), sample entropy (SampEn), and intermuscular coherence provide estimates of the signals of sEMG structure as nonlinear patterns. Higher %DET, lower SampEn, and higher theta, alpha, and beta band intermuscular coherences are observed in PD, which is correlated with MDS-UPDRS scores\cite{70}. This may reflect the oscillatory synchronization between the central nervous system and motor neurons, resulting in the enhancement of motor unit synchronization. The enhanced theta (4-6 Hz) and alpha (8-12 Hz) band coherences contribute to PD tremor. The amplified alpha-band drive in PD is involved in reticulospinal pathways, cortex and corticospinal output to muscles, and cerebello-thalamo-cortical circuit\cite{71}. The above signal analysis process is complex and requires specific mathematical models or analysis software. Further research is needed to verify the reliability and validity of the analysis method.

The use of sEMG in acoustic kinematics
The output of speech includes the cognitive, neuromotor cortex, neuromuscular, and musculoskeletal components. Gómez et al.\cite{72} used sEMG to differentiate the speech kinematic behavior by absolute velocities (dynamic and acoustic) of the joint jaw-tongue in PD, and their amplitude distributions can be used as potential biomarkers. They showed the characteristics of the interaction between the orofacial muscles by sEMG, which suggest that the facial nucleus and perioral muscles are well-preserved in PD. The lower amplitude ratio is consistent with thalamocortical activation, is limited by motor cortex activity, and contributes to bradykinesia and hypokinesia of orofacial muscles\cite{72}.
CLINICAL APPLICATION OF MOTOR UNIT NUMBER ESTIMATION IN PD

The axon of an anterior horn motor cell and all muscle fibers it dominates are called a motor unit. Motor unit number estimation (MUNE) is a non-invasive electrophysiological test for estimating the signs of degeneration of anterior horn cells. Mes found MUNE measurements were smaller in PD with different muscles, suggesting a slight degeneration\cite{74}. Changes in MUNE are also associated with age, due to the degeneration of motor neurons due to physiological aging. It was also confirmed in the model of rats\cite{75} that the threshold of MUAP was lower and recruited less. Neurofibrodegeneration and Lewy body appeared in large- and medium-sized motor neurons of spinal cord anterior horn cells, while small motor neurons were not found.

Some studies showed the increased motor unit amplitude and duration, which means reinnervation of motor units in PD\cite{76}. Asymptomatic motor neuron degeneration may be one of the pathological manifestations of PD, and MUNE has a certain standard deviation which needs to be confirmed by further studies with other electroneurography techniques.

CONCLUSION

PD is a common neurodegenerative disease, the diagnosis of which is based on clinical criteria only due to the lack of biomarkers. Thus, it has become important to detect the disease early. NEMG is an invasive method and poorly accepted by patients, but EAS-EMG is sensitive and specific for PD and MSA. NEMG is necessary for the auxiliary diagnosis of PD with camptocormia and striatal deformity; it can also be used as a guide for the therapy with botulinum toxin A to identify the target muscles for more precise treatment. sEMG is non-invasive with significant value in PD gait analysis and tremor. Especially, tremor analysis technology is simple and reliable in separating PD from other diseases. It may be a choice to be included in the diagnosis criteria. The application of sEMG in central motor control and acoustic kinematics is not widely used in clinical practice, but it is irreplaceable in the research on the development of quantitative biomarkers such as optimized neuromuscular performance and motor neuron activity. Electroneurogram has localization significance in PD with the diagnosis of the damage in peripheral nerve and anterior horn cells, and it needs further research. Therefore, electroneurography plays a certain role in the clinical diagnosis of PD and needs large samples to be further confirmed.

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Made substantial contributions to conception and revised manuscript: Song C
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