COMPLEMENTARY METHODS OF DIAGNOSIS AND TREATMENT IN MOVEMENT DISORDERS

L. Popa, C.D. Popescu

School of Medicine, "Gr. T.Popa" University of Medicine and Pharmacy, Iasi, Romania

ABSTRACT

The cortical and subcortical regions are functionally connected, and normal well-coordinated movement results from their interaction. Abnormal movements are the consequence of a lesion or malfunction in the basal ganglia (BG) and their interconnections. Movement disorders are usually corrected by medication, but there are some techniques not-included into regular medical practice, which improve the symptoms by their neuromodulatory effects. In this review we discuss the uses of Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), Transcranial Sonography (TCS), Transcranial Magentic Stimulation (TMS) and Electrooculography (EOG) in paraclinical diagnosis, and the potential of Deep Brain Stimulation (DBS), Extradural Cortical Stimulation (ECS), transcranial Direct Current Stimulation (tTDS), repetitive Transcranial Magnetic Stimulation (rTMS) and Functional Electrical Stimulation (FES) as a therapeutic tool in patients with movement disorders.

Key words: movement disorders, Parkinson's disease, Single Photon Emission Computed Tomography, Transcranial Magnetic Stimulation, Deep Brain Stimulation, Functional Electrical Stimulation

NOTIONS OF ANATOMY AND PHYSIOPATHOLOGY

The preparation and planning of movement occur in premotor (PM) and supplementary motor area (SMA), the execution is commanded by primary motor area (M1) and made by brainstem nuclei and spinal motoneurons, while the control of movement is assured by basal nuclei, ventroanterior and ventrolateral nuclei of the thalamus and the cerebellar paravermis (1).

From a phylogenetical standpoint, *the system involved in movement control* is the oldest central motor system. Together with the cerebellum, it makes up a set of structures involved in motor skills control and regulation, being involved in all its aspects – tonus, posture and movement. It includes *cortical areas* (4s, 6, 8, 8s in the frontal lobe, 1, 2, 2s, 3, 5 and 7 in the parietal lobe, 21 in the temporal lobe, 18, 19, 19s in the occipital lobe, sections of the gyrus cinguli, gyrus orbitalis and gyrus insularis), *subcortical structures* (caudate and lentiform striate body nuclei, extrapyramidal ventral anterior and ventral lateral intermediary nuclei of the thalamus, and center median nucleus of Luys; subthalamic and sublenticular nuclei – subthalamic nucleus of Luys, Reichert's substance and zona incerta) and *brainstem structures* (red nucleus and substantia nigra, descending reticular formation nuclei, bulbar olives and paraolives, vestibular nuclei). In 1991, De Long and Alexander described *5 neuronal circuits*: a motor circuit (projected on the SMA and involved in movement programming and performance), an oculomotor circuit (projected on the frontal oculomotor area, which is involved in saccades occurrence), an anterior cingulate or limbic circuit (involved in regulating moods and emotional behavior) and two associative circuits towards the prefrontal dorsolateral and orbitofrontal lateral areas (involved in regulating spatial and non-spatial object-oriented behavior) (2).

Movement disorders result either from excessive motor program facilitation (hyperkinesia related to chorea, athetosis, ballismus, tremor, myo-

Author for correspondence:
L. Popa, School of Medicine, "Gr. T. Popa" University of Medicine and Pharmacy, Universitatii street No. 16, Iasi, Romania
e-mail: livintz@yahoo.com

clonus, dystonia) or from motor program inhibition (hypokinesia related to Parkinsonian syndromes).

CLASSIFICATION OF MOVEMENT DISORDERS

- Paleostriatal (nigropalidal) syndromes: Parkinson's disease (PD) and Parkinsonian syndromes;
- Neostriatal (putamino-caudate) syndromes: acute chorea (Sydenham), chronic chorea (Huntington) and choreic syndromes;
- Pan-striatal syndromes: hepatolenticular degeneration (with Wilson's and Westphall-Strümpell's variants), athetosic and dystonic syndromes;
- Neurological manifestations probably related to extrapyramidal lesions: essential tremor (ET), myoclonus, tics;
- Movement disorders in neurological diseases having infectious, toxic, metabolic, vascular, degenerative or tumoral etiologies (2).

DIAGNOSIS

1) Radioisotopic methods (***Single Photon Emission Computed Tomography-SPECT***, ***Positron Emission Tomography-PET*** and ***PET-CT***) are the only investigations able to reveal modifications specific to Parkinson's disease, multiple system atrophy (MSA), progressive supranuclear palsy (PSP).

The main dopaminergic neurons are found within the substantia nigra pars compacta and the ventral tegmental area; the neostriatum is their main target area (3). The dopamine is stored in presynaptic vesicles. The D2 receptors are the most widely expressed receptor in the central nervous system (CNS), and they are present at the pre- and postsynaptic dopaminergic regions. SPECT allows assessment of presynaptic dopaminergic function and postsynaptic dopamine receptors (3,4). The dopamine transporter (DAT) is a sodium chloride-dependent protein on the presynaptic nerve terminal, which controls dopamine levels by active reuptake of dopamine following action at the postsynaptic receptor. ***DAT-SPECT*** gives an indirect measure of dopaminergic neural degeneration. Presynaptic radioligands used in imaging include FP-CIT (18F-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-N-tropane) β-CIT ([3H]2β - carbomethoxy-3β([4-iodophenyl] tropane), IPT (N-((E)-3-iodopropen-2-yl)-2β-carbomethoxy-3β(4-chlorophenyl tropane and TRODAT (^{99m}Tc[2[[2-[[[3-(4-chlorooheny) - 8 - methyl -8 - azabicyclo [3.2.1] oct-2-yl]-methyl](2-mercaptoethyl)amino]ethyl]amino]ethane-thiolato-(3)-N2,N2,S2,S2]oxo-[1R-(exo-exo)]) (3). *The radiotracer used to assess striatal postsynaptic* D2 *receptors binding* is IBZM (123I-(S)-2-hydroxy-3-iodo-6-methoxy-N-[1-ethyl-2-pyrrodinyl)-methyl]bemzamide (5). DAT-SPECT demonstrates asymmetrical reduced striatal uptake of radioligands even in early PD. The striatal uptake of radioligands has also been shown to correlate with disease duration and motor severity. Bradykinesia is strongly correlated with striatal DAT binding while tremor is not (3). The PD patients with postural instability and gait difficulty have a lower presynaptic uptake ratios in putamen than patients with tremor-dominated symptoms (6). Although, DAT imaging is very usefull in differential diagnosis of monosyptomatic tremor (dystonic tremor, essential tremor, Parkinson tremor) (7). It is normal in ET, in witch no dopamine deficit is found (3, 8). Parkinson-plus syndromes, such as MSA, PSP and corticobasal degeneration (CBD), all demonstrate reduced striatal uptake on DAT-SPECT. Combining DAT imaging with postsynaptic receptor D2 imaging (FP-CIT), which is also abnormal in each of these conditions, may assist their diagnosis from PD (where D2 is normal) (3). Adding MIBG (meta-(123)I-iodobenzylguanidine) scintigraphy, for assessing myocardial adrenergic innervation, the diagnostic accuracy increase (5). Furthermore, a normal DAT-SPECT is helpful in supporting a diagnosis of drug-induced-, psychogenic- and vascular parkinsonism by excluding underlying true nigrostriatal dysfunction (7). 123I-FP-CIT-SPECT shows similar DAT binding in PARK6 patients compared to idiopathic PD, but an increased DAT binding in heterozygous PARK6 carriers, which can be a very early preclinical finding (9). DAT imaging is considerated safe, giving approximately the same radiation dose as a computerized tomography (CT) brain scan. It also has much wider availability then PET scanning (3).

Like SPECT, ***PET imaging*** allows the *in vivo* assessment of the nigrostriatal system. One presynaptic (18F-dopa) and two postsynaptic radiotacers (11C-raclopride for D2 receptors and 11C-SCH 23390 for D1 receptors) are commonly used. PET scanning can detect preclinical stages of PD, can monitor the response to different therapies in this disease (ropinirole *vs.* levodopa, thalamothomy, deep brain stimulation- DBS, transplantation of human embryonic mesencephalic tissue) and can observe the changes in receptor occupancy which may determine peak-dose dyskinesias. Despite its superior sensitivity and resolution compared to SPECT (10), PET remains a research tool in movement dis-

orders, because it involves more time and effort and more personnel exposure than radiolabeling by chelation with 99mTc (brain perfusion SPECT) (3, 10).

2) Magnetic Resonance Imaging (MRI) contributes to the diagnosis of atypical Parkinsonism (PSP, MSA, CBD) and of some inherited hyperkinetic conditions including neurodegeneration with brain iron accumulation and fragile-X tremor/ataxia syndrome. In the first case, MRI reveals characteristic patterns of regional atrophy combined with signal changes and microstructural changes in the basal ganglia (BG), pons, middle and superior cerebellar peduncles, and cerebral subcortical white matter. In the second conditions, it shows characteristic symmetric signal changes in the basal ganglia and middle cerebellar peduncles, respectively (11).

3) Transcranial sonography (TCS) is a cheap, easily available and non-invasive imaging technique that may assist diagnosis and screening for PD. Substantia nigra hyperechogenecity (SN+) is the most characteristic feature in PD. The reason for the change of echogenicity is suggested to be an increased tissue iron content causing oxidative stress and neuronal damage. In a series of 112 patients with clinically probable PD, TCS detected hyperechogenicity of the substantia nigra in 103 (92%) of patients (Berg, 2001). Increased signal was most noticeable contralateral to the most clinically affected limbs, but findings did not correlate with disease severity. It seems that the abnormal echogenicity reflects a predisposition to the disease rather the architectural changes as a result of cell loss (3). This hypothesis was confirmed in a study published in 2011 by the same researcher. Those, 1847 healthy older persons, having a neurological assessment and a initial transcranial sonography, were followed-up 37 months. At the end of this interval, 1535 participants could undergo reassessment. There were 11 cases of incident PD during the follow-up period. In subjects with SN+ at baseline, the relative risk for incident PD was 17.37 times higher compared with normoechogenic subjects (12). The frequency of SN+ appears to be homogeneous in white and Asian populations, as shown in a recent study (Go, 2012), made on 71 healthy adult German participants and 30 age-and-sex-matched Filipino participants (13). However, this hyperechogenicity is not patognomonic for Parkinson's disease. It occurs in multiple sclerosis, probably in relation with microglia activation (like in PD), but also in non-neurodegenerative disorders (14). In PD patients with depression, the substantia nigra hyperechogenecity is associated with the hypogenicity of the mesencephalic midline (15). TCS can be used to differentiate PD from Parkinson-plus syndromes. SN+ is predictive for PD whereas a hypoechogenic substantia nigra, especially when combines with a hyperechogenic lentiform nucleus, suggests a Parkinson-plus disorder (3). This technique can detect trace metal accumulation in deep brain structures with higher sensitivity than conventional MRI. Especially, increased iron content in the sunstantia nigra in Parkinson's disease, increased copper content in the lenticular nucleus (LN) in Wilson's disease and idiopathic dystonia, and increased manganese content in the LN in manganese-induced Parkinsonism were detected with TCS, even in subjects with normal MRI (16). The sensitivity and specificity of transcranial ultrasound for the diagnosis of PD is 81% and 97% respectively (17).

4) Neurophysiology and neuroimaging have had a spectacular development over the last decades. Nuclear medicine explorations have been enriched by ***Transcranial Magnetic Stimulation (TMS)***, a modern cortico-spinal activity recording and modulation method.

TMS was first used by Anthony Barker in 1985, and it relies on the principle of electromagnetic induction postulated by Michael Faraday in 1831. The stimulation device has a coil run through by high intensity (5000 amperes) and very short (200-300 μs) electrical currents. It is placed either on the scalp or paravertebrally, and it induces the formation of a magnetic field having a 0.7-2 Tesla strength, which will induce the formation, in the conductive tissue media, of an electrical field capable of modulating the neuronal activity in the subjacent areas (18). This magnetic field has a penetrability of about 3-4 cm in the intermediate consistency tissues (skin, muscles), and much lower in the osseous structures (1.5-3 cm through the skull bones) (19). Also, medullar stimulation is more difficult to achieve then cortical stimulation (vertebral arches and spinal apophyses diminish significantly the strength of the magnetic field on the skull bones, which are a few millimeters thick); radicular stimulation is achieved instead (the roots of the spinal nerves are more accessible). The method has two major advantages: it is non-invasive and pain free. Several types of magnetic stimulation are used in clinical practice and research: single-pulse, paired-pulse, repetitive, computer-assisted, multichannel, electroencephalography (EEG)-associated TMS.

By motor cortex and descending tracts stimulation, ***single-pulse TMS*** determines the occurrence

of motor evoked potentials (MEPs) on the electromyographic path (EMG), which correspond to the upper and lower limbs characterized by the following parameters (table 1).

Paired-pulse stimulation brings about information on the intracortical excitation and inhibition level, supplementing the neurophysiological diagnosis of diseases involving an imbalance between the exciting and inhibiting mechanisms. ***Paired-pulse TMS*** uses two magnetic stimulation devices connected to a single coil, which discharges paired pulses every few milliseconds. Depending on the intensity (threshold, suprathreshold or subthreshold) and interstimulus interval (ISI), the first stimulus (conditioned stimulus) has an inhibitor or facilitator effect on the second stimulus (test stimulus), which induces a motor response (MEP). Paired pulses may also be applied using two coils, which allows stimulating two different areas in the brain and analyzing intracortical connections. A series of parameters are also defined in this case (table 2).

Most of the studies conducted in Parkinson's disease revealed no motor threshold (MT) change; however, the *resting MT* may drop in very rigid patients, whereas the *active MT* may be higher in bradykinetic patients. A low motor threshold was found in patients with obsessive-compulsive disorders and tics, while in Huntington's disease, dystonia, myoclonus and essential tremor the MT is normal (20).

Central motor conduction time is normal in PD, CBD, Huntington chorea, ET, dystonia, myoclonus, Gilles de la Tourette's syndrome, and it may be extended to patients with MSA, PSP and to Parkin gene carriers (20, 21, 26).

MEP amplitude is higher and *MEP area* is larger in PD patients than in healthy subjects (27).

The ortical electrical silent period (cSP) is shorter in PD, dystonia, myoclonus or tics, normal in ET and variable in chorea (20, 23).

The ipsilateral electrical silent period (iSP) is shorter in CBD and PSP (morphometric MRI studies revealed corpus callosum atrophy), normal in PD and MSA, and longer in focal hand dystonia (indicating a transcallosal inhibition increase) (20).

In Parkinsonian patients, *the short-interval intracortical inhibition* is reduced at rest, and it improves under dopaminergic medication, deep brain

Table 1. *Parameters obtained by magnetic stimulation of the motor cortex and pyramidal tracts*

No.	TMS parameter	Description
1.	Motor threshold (MT)	= the minimum motor cortex stimulation intensity sufficient to trigger, in the target muscle, at least 5 motor evoked potentials, with amplitudes ≥ 50 μV, out of 10 consecutive stimulations (20)
2.	Latency of motor evoked potential (L_{MEP})	= time interval between the stimulation artifact and the occurrence of the MEP on the elecromyography (first positive wave) (21) - depending on the stimulated area, it may be central (cortical) or peripheral (medullar= cervical or lumbar)
3.	Central motor conduction time (CMCT)	= latency difference of MEP produced by motor cortex and motor nerve roots stimulation, respectively (21): CMCT = Cortical MEP latency (contralateral) – Medullar MEP latency (ipsilateral)
4.	Size of motor evoked potential	- it is defined by 3 parameters: amplitude, duration and area of motor evoked potential (22)
5.	Contralateral Silent Period (cSP)	= the interval which lacks any electrical activity and which follows a magnetic stimulation on the background of a submaximal voluntary contraction (20-50%) (23) - on the electromyography, it is measured between the last MEP wave and the voluntary electromyographic activity reoccurrence (21, 23) - it is considered a probe of motor cortical inhibition (23); the lower the intracortical inhibition, the lower the cSP value
6.	Ipsilateral Silent Period (iSP) or Transcallosal inhibition (TI)	= contralateral motor center activity suppression by means of the corpus callosum - it may be proven by TMS applied during a tonic contraction of at least 50% of the small hand muscles ipsilateral to the stimulated hemisphere; the neurons in the stimulated motor cortex inhibit the contralateral pyramidal neurons (in the unstimulated hemisphere) by means of the callosal fibers; temporary suppression of the tonic activity of contracted muscles is recorded on the EMG path (21) - both latency and TI duration are measured; for a proper assessment, calculate the mean of the values read after 20 consecutive stimulations

Table 2. *Parameters recorded by paired-pulse TMS (24, 25)*

No.	TMS parameter	Definition
1.	Interstimulus interval (ISI)	= interval between the conditioned stimulus and the test stimulus
2.	Short-interval intracortical inhibition (SICI)	= suppression of a test MEP by applying a subliminal stimulus 1-5 ms earlier - it shows $GABA_A$ interneurons activation, which has an inhibiting effect on pyramidal cells
3.	Long-interval intracortical inhibition (LICI)	= suppression of a test MEP by applying a subliminal stimulus 100-200 ms earlier - it shows $GABA_B$ interneurons activation, which has an inhibiting effect on pyramidal cells
4.	Interhemispheric inhibition (IHI)	= suppression of a test MEP by applying a supraliminal stimulus 10-40 ms earlier in the contralateral motor cortex
5.	Short-interval intracortical facilitation (SICF)	= facilitation of a test MEP by applying a supraliminal stimulus 1-1.5 ms/2.5-3 ms/ 4.5 ms earlier - the shorter the ISI, the more significant the facilitation
6.	Intracortical facilitation (ICF)	= facilitation of a test MEP by applying a subliminal stimulus 10-15 ms earlier

stimulation in the subthalamic nucleus and repeated magnetic low-frequency stimulation of the motor cortex; this interval remains unchanged while the patient is active. Some studies revealed an extension of the *long-interval intracortical inhibition*, whereas others documented its drop; in both cases, it became normal further to dopaminergic therapy. The SICI drop and LICI increase may be accounted for by the fact that LICI inhibits SICI (28,29).

SICI also decreses in CBD (this considerable drop was proposed as a diagnostic test), in other Parkinsonian syndromes (MSA, PSP), and in Gilles de la Tourette's syndrome, where it is correlated with motor hyperactivity.

In dystonia (upper limb dystonia, cervical dystonia, blepharospasm, L-Dopa responsive dystonia) and in asymptomatic DYT1 gene mutation carriers, SICI is reduced both at rest and in movement, and it temporarily increases to normal after botulinum toxin has been injected in the dystonic muscles; however, this has not yet been found in the writer's cramp. Also, LICI was high in dystonic patients, except for those suffering from the writer's cramp, in whom it was low (20).

In Huntington chorea, the SICI and LICI results were conflicting, whereas in essential tremor the values of the two intervals were within normal limits.

Interhemispheric inhibition and *intracortical facilitation* are lower in Parkinsonian patients without mirror movements (20,30).

5) Head-mounted infrared binocular eye traking system and ***electrooculography (EOG)*** are used for capturing oculomotor data. In Parkinson's disease, the increase in the activities of basal ganglia output nuclei excessively inhibits the thalamus and superior collicus (SC) and causes preferential impairment of internal over external movements. A recent Japanese study conclude that there are three major drives converging on SC determine the saccade abnormalities in PD. The impairment in visually and memory guided saccades may be caused by the excessive inhibition of the SC due to the increased BG output and the decreased activity of the frontal cortex-BG circuit. The impaired suppression of reflexive saccades (saccades to cue) may be explained if the excessive inhibition of SC is "leaky". Changes in saccade parameters suggest that frontal cortex-BG circuit activity decreases with disease progression, whereas SC inhibition stays relatively mild in comparison throughout the course of the disease. Finally, SC disinhibition due to leaky suppression may represent functional compensation from neural structures outside BG, leading to hyper-reflexivity of saccades and milder clinical symptoms (31). Other three articles, published in 2011, give evidence that saccadic eye movements are age-related in healthy subjects and patients with Parkinson's disease (32), the small saccades restrict visual scanning area in PD (33) and the turning performance in PD may be negatively influenced by saccade dysfunction (34).

6) Clinical neurophysiology in tremors consists of ***surface electromyography*** and ***acclerometric recordings*** from the affected limbs. Fourier/spectral analysis of these data can determine the exact tremor frequency- an important diagnostic hint. Correlating these results with other paraclinical and clinical aspects, we can differentiate the Parkinsonian tremor of the essential, cerebellar, dystonic, orthostatic, physiologic and psychogenic tremor (35). Adding to EMG the ***myotonometry*** and the ***mechanomyography***, the passive stiffness in the

muscle belly and tendon can be assessed. Compared with controls, PD patients have higher passive passive stiffness in the muscle belly and tendon (36). ***Laryngeal electromyography*** and ***acoustic voice analysis*** allow to measure the oral communication impairment which occurs in 75% to 90% of Parkin sonian patients. A study on 26 subjects exhibited a rest hypertonicity, meaning that patients with PD presented with spontaneous intrinsic laryngeal muscle activity during voice rest, which occurred in 73% of the individuals. The vocal tremor was detected in 69.5% of the subjects, while not a case of laryngeal tremor was registred by EMG (37). ***The electromyographic testing of the anal or uretral sphincters*** is applied to distinguish between idiopatic PD and multiple system atrophy. The anterior horn cells innervating the sphincters are located in Onuf's nucleus in the sacral cord. This nucleus is among CNS sites affected by neural cell loss in MSA, but not in PD. Consequently, the MSA patients have an abnormal sphincter EMG (38). By combining EMG with ***EEG*** or ***polysomnography (PSG)***, arousals from rapid eye movement (REM) sleep can be sense in patients with REM sleep behaviour disorders (RBD) (39).

7) Olfactory testing, as Brief Smell Identification Test (B-SIT), UPSIT (University of Pennsylvania Smell Identification Test (UPSIT) or Sniffin Sticks olfactory test, is usefull in identifying olfactory dysfunction in patients with PD or other neurodegerative conditions. It seems that olfactory deficit is present as a prodromal sign 11.2 years before the diagnosis of PD (40), and it commonly coexists with psychotic symptoms, poorer memory and executive performance. The relationship between hyposmia, psychosis, and specific cognitive impairments may reflect the anatomic distribution of Lewy pathology and suggests that olfactory dysfunction could be a biomarker of additional extranigral disease (41). Some patients with PARK2 mutations have increased thresholds of olfactory function and myocardial sympathetic dysfunction as nonmotor symptoms (42); on the other hand, olfactory and cardiac impairment are less prevalent in PD associated with Leucine-Rich Repeat Kinase (LRRK2) (43).

8) Genetic testing is necessary in some cases of PD, especially for identification of PARK1 (encoding an aberrant α-synuclein, responsable for the formation of Lewy bodies), PARK2 or Parkin (which determine an autosomal-recessive juvenil Parkinsonism), PARK 6 (also implicated in an autosomal-recessive form) and PARK 8/ LRRK2 (the most common gene associated with autosomal-dominant PD, familial or sporadic) (44). In other diseases, genetic testing is imperative for certain diagnosis (*i.e.* cytosine-adenine-guanine (CAG) expansion in Huntington chorea, ATP7B mutation in Wilson's disease) (45).

THERAPY

The therapeutic options currently available for movement disorders include, in addition to drugs, a set of complementary invasive and non-invasive methods.

Invasive methods

1. Stereotaxic procedures- currently less used:
- to control tremor → in the thalamic ventral lateral contralateral nucleus, initially in the posterior ventral lateral globus pallidus;
- for the treatment of all the axial symptoms (akinesia, rigidity, tremor) and L-Dopa induced dyskinesias → posterior ventral lateral pallidotomy (45).

2. Stem cell transplantation – in experimental and clinical research studies.

3. Deep Brain Stimulation (DBS) – successfully used in involuntary movement treatment (tremor, dyskinesia), in certain psychiatric conditions and pain therapy. Brain stimulation may be done in the ventral lateral intermediary nuclei of the thalamus, subthalamic nucleus, internal globus pallidus, centre median-parafascicular complex, motor cortex, periventricular and periaqueductal gray matter. The possible action mechanisms are: depolarization block, local release of inhibitory neurotransmitters (GABA), antidromic inhibitory neurons activation, abnormal discharge scheme disorganization (46).

In *Parkinson's disease*, resting tremor seems to be caused by a neuronal group found in the thalamus and in the basal ganglia discharging simultaneously. In physiological conditions, these neurons discharge chaotically, act as a pacemaker and activate the premotor cortex, supplementary motor area and motor cortex. High frequency thalamic/subthalamic stimulation (periodic high frequency – 4100 Hz – pulses) suppresses this pacemaker activity and, hence, peripheral tremor.

Extradural Cortical Stimulation (ECS) with electrodes located in the epidural space, above the motor area, is a therapeutic alternative for Parkinsonian patients non eligible for DBS. The stimulation current has 3-4.5 V (mA) amplitude, 400-450 μs pulse duration and 10 to 30 Hz frequency (47).

Non-invasive methods

1. Transcranial Direct Current Stimulation (tDCS) consists of applying low intensity (1-2 mA) electrical current directly on the scalp, using two surface electrodes. Although the scalp has high impedance, the current running from the cathode to the anode triggers changes in the resting membrane potential in the subjacent cortical areas: the result is anode activity increase and cathode activity decrease. The primary motor area (M1) is the cortical target in the cortico-subcortical motor circuit. In *PD*, the motor symptoms are the consequence of an affected striato-thalamo-cortical system, which turns the primary motor area into the preferred cortical neuromodulation area, in order to recover thalamocortical conduction.

A study published by Fregni et al. in 2006 revealed a significant improvement of the motor function of Parkinsonian patients further to anodic M1 area stimulation. Cathodic stimulation of the same area and anodic stimulation of the dorsolateral prefrontal cortex (DLPFC) had modest, almost insignificant effects. Also, the tDCS effects were associated with a polarity-dependent effect on motor cortico-spinal excitability in PD: anodic stimulation leads to higher cortical excitability, whereas cathodic stimulation triggers a slight cortical excitability decrease.

Another study of the same group reported a net working memory improvement further to active anodic 2 mA tDCS in the left prefrontal dorsal lateral cortex (48).

Dystonia is associated with an inhibition drop at several nevrax levels (spinal cord, brainstem and cortex). In addition to an inhibitory motor circuit alteration, various functional imaging techniques revealed higher blood flow and glucose metabolism in various cortical areas (prefrontal, parietal and insular lobes, cerebellum and SMA). Excessive and inadequate muscular activation in focal dystonia reflects motor cortico-subcortical circuit disinhibition, which may be an expression of motor sensory integration alteration and maladaptive plasticity. The attempts of controlling the central dystonia-specific disinhibition state have not been very successful so far. Thus, although cathodic tDCS reduces excitability in normal subjects, it tends to increase it in dystonic patients (48).

2. Repetitive Transcranial Magnetic Stimulation (rTMS), a variant of TMS which is used rather for therapeutic than diagnostic purposes, consists of quick and repeated application of 20-2,500 pulse trains in particular brain areas, in order to improve the metabolic status of the neurons in those areas, hence clinically improving related symptoms. Low frequency (≤ 1-Hz) stimulation has an inhibitory effect, whereas high frequencies (≥ 5 Hz) have an exciting effect. The higher the stimulation strength and duration, the longer the effect. Also, magnetic stimulation applied several days in a row may generate effects that last for weeks or even months. rTMS is used both for therapeutic purposes (depression, headache, neuropathic pain, recovery after stroke), and to investigate specific cortical functions (49).

In *Parkinson's disease*, repeated 5-Hz stimulation in the region corresponding to the hand in the M1 area triggers the normalization of the cortical silent period and the improvement of contralateral bradykinesia. FDG-PET revealed improved glucose metabolism in the primary motor area and in SMA. In 2004 Lefaucher et al. proved the positive effect of rTMS in the M1 area both at very low and high frequencies. 0.5-Hz rTMS reduces bilateral rigidity and increases gait speed, whereas 10-Hz rTMS reduces contralateral bradykinesia. Both techniques normalize the silent period, yet the mechanisms are different: 0.5-Hz rTMS normalizes intracortical inhibition, 10-Hz rTMS increases intracortical facilitation. Therefore, rTMS neuromodulation influences both the exciting and the inhibiting circuits.

The dorso-lateral prefrontal cortex is the cortical target in the cortico-subcortical prefrontal circuit, involved in attention, working memory and mood adjustment. Numerous studies revealed improvement in depression further to high frequency rTMS applied in the left DLPFC. SPECT and fMRI revealed an increase in cortical activation or blood flow- rCBF in the left dorso-lateral prefrontal area and in the anterior gyrus cinguli, and an activation decrease in the right symmetrical area, right fusiform gyrus and cerebellum.

Repeated simultaneous stimulation of the M1 area and the DLPFC (25-Hz rTMS, 8 times in 4 weeks) improved gait and hand bradykinesia for a month after the stimulation (Lomarev et al., 2006).

PET and SPECT recorded the changes occurring in the neurotransmitters from various brain regions, thus proving the neuromodulation mechanism. 10-Hz rTMS of the frontal cortex induces focal dopamine release in subcortical structures (basal ganglia), DLPFC stimulation determines higher dopamine secretion in the caudate, and M1 area stimulation accompanies dopamine release in the ventral lateral putamen (48).

A double blind study conducted in 15 centers in Japan in 2009 reported bradykinesia improvement in parkinsonian patients after high frequency (5-Hz) rTMS in the supplementary motor area, as compared to sham stimulation patients (50).

Several studies investigated the effect of repeated magnetic stimulation on *L-Dopa-induced dyskinesia*. Koch et al. noticed, in 2005, that a single 1-Hz rTMS application on the bilateral supplementary motor area decrease dyskinesia severity, and this effect persisted for 30 minutes after the stimulation. rTMS application in the same area and using the same frequency for 5 days did not have a cumulative effect. Also, dyskinesia worsened after 5 Hz frequency stimulation.

In 2007 and 2008, Rektorova proved that 5 days of repeated high frequency (10-Hz) magnetic stimulation in the DLPFC and motor cortex had no positive effect on gait or bradykinesia; the only benefit was a subjective dyskinesia improvement, yet insignificant on the UPDRS (Unified Parkinson's Disease Rating Scale) (24).

In *dystonia*, since this is maladaptive plasticity, motor cortex excitability responds often inadequately, by disinhibition, to rTMS. After 1-Hz stimulation of the M1 area by several trains of suprathreshold, cortical excitability was suppressed in control subjects and facilitated in the writer's cramp. At lower motor thresholds, 1-Hz rTMS in the M1 area does not alter cortical excitability in patients with focal hand dystonia, although this is reduced in the control group. Brief trains of up to 20 pulses at a 1-Hz frequency suprathreshold do not influence excitability, yet if the frequency increases to 5 Hz the result is excessive and long-lasting excitability facilitation (48).

Cortical hyperexcitability specific to *Gilles de la Tourette's syndrome* is the expression of short intracortical inhibition and afferent inhibition reduction; functional imaging detected a supplementary motor area and limbic area activation before the occurrence of tics. Two days of repeated magnetic low frequency (1-Hz) stimulation of the premotor area (PM) had an effect comparable to the placebo effect (sham stimulation), whereas 1-Hz rTMS on SMA for two weeks was followed by a significant score reduction on the tic scale and even by full tic remission in two patients.

In *chorea*, 1-Hz rTMS in the supplementary motor area for three consecutive days led to hyperkinesia improvement on the UHDRS (Unified Huntington's Disease Rating Scale) 15 minutes after the stimulation, which did not happen after 5-Hz rTMS.

Slight improvements of the patients' general state, consisting of basic symptoms diminution, were found in *essential tremor* after low frequency (1-Hz) stimulation of the cerebellar vermis, in *cortical tremor* (myoclonic status associated with progressive ataxia and epilepsy) after 5-Hz rTMS of the premotor cortex, and in *late dyskinesia* after repeated high frequency (17-Hz) stimulation of the dorsolateral prefrontal cortex (24).

3. Functional Electrical Stimulation (FES) with surface electrodes is carried out by discharging an electrical low intensity current through electrodes located along the peripheral nerves, with a view to stimulating related muscles and initiating movement.

In *Parkinsonian patients*, functional electrical stimulation may be useful in correcting motor disabilities. The electrodes are located on the radial nerve path of the upper limbs and on the external popliteal sciatic nerve (common peroneal nerve) path of the lower limbs. The characteristics of the stimulation current are: amplitude = 10-100 mA, pulse duration = 300-350 μs, frequency = 20-40 Hz, waveform = biphasic asymmetric or biphasic symmetric.

A preliminary study conducted in this respect in 2004 by the Functional Electrical Stimulation Center in Salisbury, England, supports FES contribution in gait correction. They started from the assumption that applying an external electrical stimulus on the common peroneal nerve path improves gait and reduces gait freeze episodes. The study included 10 Parkinson's disease subjects in whom the "stimulator acted as a training device" for 8 weeks. At the end of this period, the patients notice the improvement of their gait (better heel stability, longer steps). These improvements persisted at least one month after the stimulation (51).

Another study conducted by the same team on a group of 7 patients suffering from Parkinson's disease in 2007 (and published in 2008) revealed longer average stride length in the 3-minute walk test, without however increasing gait speed or decreasing the number of steps during the 20-m walk with turn test. This gait improvement lasted 4 weeks after electrotherapy was stopped. The number of falls and "freezing" episodes only decreased during treatment, and reached again its initial values after the end of the FES sessions (52).

CONCLUSIONS

Movement disorders are a complex pathology resulting from alteration of cortico-subcortical cir-

cuits. Their diagnosis remains essentially clinical, and their therapy based essentially on drugs. In addition to the radiological methods that provide structural imaging (CT scanning, MRI), the last few years knew a development of modern scintigraphic (PET, SPECT, PET-CT), echographic (TCS) and neurophysiological (TMS, EMG) techniques, which bring precious information on brain functionality. Therapeutically speaking, the widening of the range of drugs used was accompanied by a set of invasive and non-invasive methods which have had promising results.

REFERENCES

1. **Rohkamm R.** – *Atlas de poche de neurology.* Paris: Flammarion-Médicine-Sciences 2005, 42-45.
2. **Ştefanache F.** – *Neurologie clinică*. Iaşi: UMF „Gr. T. Popa" Iaşi, 1997, 296-303.
3. **Grosset D., Newman E.** – Diagnosis and disease monitoring in Parkinson's disease. In: Aquilonius SM, Lees AJ (eds.). *Managing advanced Parkinson's disease: the role of continuous dopamiergic stimulation.* London: ScopeMedical Ltd, 2007, 18-27.
4. **Pifarré P., Cuberas G., Hernández J. et al.** – Cortical and subcortical patterns of I-123 iodobenzamide SPECT in striatal D(2) receptors parkinsonisms. *Cin Nucl Med* 2010; 35(4): 228-233.
5. **Südmeyer M., Antke C., Zizek T. et al.** – Diagnostic accuracy of combined FP-CIT, IBZM, and MIBG scintigraphy in the differential diagnosis of degenerative parkinsonism: a multidimensional statistical approach. *J Nucl Med* 2011; 52(5): 733-740.
6. **Mo S.J., Linder J., Forsgren L. et al.** – Pre- and postsynaptic dopamine SPECT in the early phase of idiopathic parkinsonism: a population-based study. *Eur J Nucl Med Mol Imaging* 2010; 37(11): 2154-2164.
7. **Kägi G., Bhatia K.P., Tolosa E.** – The role of DAT-SPECT in movement disorders. *J Neurol neurosurg Psychiatry* 2010; 81(1): 5-12.
8. **Coria F., Gimenez-Garcia M., Samaranch L. et al.** – Nigrostriatal dopaminergic function in subjects with isolated action tremor. *Parkinsonism Relat Disord* 2012; 18(1): 49-53.
9. **Kessler K.R., Hamscho N., Morales B. et al.** – Dopaminergic function in a family with the PARK6 form of autosomal recessive Parkinson's syndrome. *J Neural Transm* 2005; 112(10): 1345-1353.
10. **Cheng D/, Wang Y/, Liu X/ et al.** – Comparison of 18F PET and 99mTc SPECT imaging in phantoms and in tumored mice. *Bioconjug Chem* 2010; 21(8): 1565-1570.
11. **Mascalchi M., Vella A., Ceravolo L.** – Movement disorders: role of imaging in diagnosis. *J Magn Reson Imaging* 2012; 35(2). doi: 10.1002/jmri.22825.
12. **Berg D., Seppi K., Behnke S.** – Enlarged substancia nigra hyperechogenicity and risk for Parkinson's disease: a 37-month-3-center study of 1847 older persons. *Arch Neurol* 2011; 68(7): 932-937.
13. **Go C.L., Frenzel A., Rosales R.L. et al.** – Assessment of substancia nigra echogenicity in german and filipino populations using a portable ultrasound system. *J Ultrasound Med* 2012; 31(2): 191-196.
14. **Berg D.** – Hyperechogenicity of the substantia nigra: pitfalls in assessment and specificity for Parkinson's disease. *J Neural Transm* 2011; 118(3): 453-461.
15. **Cho J.W., Baik J.S., Lee M.S.** – Mesencephalic midline change on transcranial sonography in early Parkinson's disease patients with depression. *J Neurol Sci* 2011; 310(1-2): 50-52.
16. **Walter U.** – Transcranial sonography in brain disorders with trace metal accumulation. *Int Rev Neurobiol* 2010; 90: 166-178.
17. **Venegas F.P., Miranda G.G., Silva C.M.C.** – Transcranial sonography for the diagnosis of Parkinson's disease. *Rev Med Chil* 2011; 139(1): 54-59.
18. ***** Jalinous R.** – *A guide to magnetic stimulation.* www.home.postech.ac.kr/~neofinet/MagGuide.pdf, 1998.
19. **Rossi S., Hallett M., Rossini P.M. et al.** – Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009; 120 (12): 2008-2039.
20. **Chen R., Cros D., Curra A. et al.** – The clinical diagnostic utility of transcranial magnetic stimulation: Report of an IFCN committee. *Clin Neurophysiol* 2008; 119 (3): 504-532.
21. **Kobayashi M., Pascal-Leone A.** – Transcranial magnetic stimulation. In: Blum AS, Rutkove SB (eds.). *The clinical neurophysiology primer.* Totowa, New Jersey: Humana Press, 2007, 499-517.
22. **Rösler K.M., Magistris M.R.** – The size of motor-evoked potentials: influencing parameters and quantification. In: Wasserman EM, Epstein CM, Ziemann U (eds.). *The Oxford handbook of transcranial stimulation.* Oxford: Oxford University Press, 2008, 77-90.
23. **Wolters A., Ziemann U., Benecke R.** – The cortical silent period. In: Wasserman E.M., Epstein C.M., Ziemann U. (eds.). *The Oxford handbook of transcranial stimulation.* Oxford: Oxford University Press, 2008, 91-102.
24. **Edwards M.J., Talelli P., Rothwell J.C.** – Clinical applications of transcranial magnetic stimulation in patients with movement disorders. *Lancet* 2008; 7 (9): 827-840.
25. **Hanajima R., Ugawa Y.** – Paired-pulse measures. In: Wasserman E.M., Epstein C.M., Ziemann U. (eds.). *The Oxford handbook of transcranial stimulation.* Oxford: Oxford University Press, 2008, 103-118.
26. **Morita Y., Osaki Y., Doi Y.** – Transcranial magnetic stimulation for differential diagnostics in patients with parkinsonism. *Acta Neurol Scand* 2008; 118 (3): 159-163.
27. **Berardelli A., Hallett M.** – TMS in movement disorders. In: Wasserman E.M., Epstein C.M., Ziemann U. (eds.). *The Oxford handbook of transcranial stimulation.* Oxford: Oxford University Press, 2008, 329-336.
28. **Reis J., Swayne O.B., Vandermeeren Y. et al.** – Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol* 2008; 586 (2): 325-351.
29. **McGinley M., Hoffman R.L., Russ D.W. et al.** – Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. *Exp Gerontol* 2010; 45 (9): 671-678.
30. **Vacherot F., Attarian S., Eusebio A., Azulay J.P.** – Excitability of the lower-limb area of the motor cortex in Parkinson's disease. *Neurophysiol Clin* 2010; 40 (4): 201-208.
31. **Terao Y., Fukuda H., Yugeta A. et al.** – Initiation and inhibitory control of saccades with the progression of Parkinson's disease - changes in three major drives converging on the superior colliculus. *Neuropsychologia* 2011; 49(7): 1794-1806.

32. **Litvinova A.S,. Ratmanova P.O., Evina E.I. et al.** – Age-related changes in saccadic eye movements in healthy subjects and patients with Parkinson's disease. *Fiziol Cheloveka* 2011; 37(2): 40-47.
33. **Matsumo H., Terao Y., Furubayashi T. et al.** – Small saccades restrict visual scanning area in Parkinson's disease. *Mov Disord* 2011; 26(9): 1619-1626.
34. **Lohnes C.A., Earhart G.M.** – Saccadic eye movements are related to turning performance in Parkinson disease. *J Parkinsons Dis* 2011; 1(1): 109-118.
35. **Raethjen J., Deuschl G.** – Tremor. In: Lisak R.P., Truong D.D., Carroll W.M., Roongroj B. *International neurology: a clinical approach*. West-Sussex: Wiley-Blackwell, 2009, 144-151.
36. **Marusiak J., Jaskólska A., Budrewicz S. et al.** – Increased muscle belly and tendon stiffness in patients with Parkinson's disease, as measured by myotonometry. *Mov Disord* 2011; 26(11): 2119-2122.
37. **Zarzur A.P., Duarte I.S., Holanda G.N., Martins M.A.** – Laryngeal electromyography and acoustic voice analysis in Parkinson's disease: a comparative study. *Braz J Otorhinolaryngol* 2010; 76(1): 40-43.
38. **Palace J., Chandiramani V.A., Fowler C.J.** – Value of sphincter electromyography in the diagnosis of multiple system atrophy. *Muscle Nerve* 1997; 20(11): 1396-1403.
39. **Sorensen G.L., Jennum P., Kempfner J. et al.** – A computerized algorithm for arousal detection in healthy adults and patients with Parkinson disease. *J Clin Neurophysiol* 2012; 29(1): 58-64.
40. **Gaenslen A., Swid I., Liepelt-Scarfone I. et al.** – The patients perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. *Mov Disord* 2011; 26(4): 653-658.
41. **Morley J.F., Weintraub D., Mamikonyan E. et al.** – Olfactory dysfunction is associated with neuropsychiatric manifestations in Parkinson's disease. *Mov Disord* 2011; 26(11): 2051-2057.
42. **Yoritaka A., Shimo Y., Shimo Y. et al.** – Nonmotor symptoms in patients with PARK2 mutations. *Parkinsons Dis* 2011: 473640.
43. **Ruiz-Martinez J., Gorostidi A., Goyenechea E.** – Olfactory deficits and cardiac 123I-MIBG in Parkinson's disease related to the LRRK2 R1441G and G2019S mutations. *Mov Disord* 2011; 26(11): 2026-2031.
44. **Szász József Attila** – Etiopatogenia bolii Parkinson. În: Băjenaru O (ed.) *Actualităţi în diagnosticul şi tratamentul bolii Parkinson*. Bucureşti: Media Med Publicis, 2010, 11-27.
45. **Hufschmidt A., Lücking C.H.** – Neurologie integrală. De la simptom la tratament. Iasi: Polirom, 2002, 165-187.
46. **Popescu C.D., Ignat B., Poboroniuc M.** – Stimularea electricală funcţională în medicină. *Rev Med Chir Soc Med Nat Iasi* 2005; 109(1) suppl 1.
47. **Gutiérrez J.C., Seijo F.J., Alvarez Vega M.A., Fernández Gonzáles F., Lozano Aragoneses B., Blázquez M.** – Therapeutic extradural cortical stimulation for Parkinson's Disease: Report of six cases and review of the literature. *Clin Neurol Neurosurg* 2009; 111 (8): 703-707.
48. **Wu A.D., Fregni F., Simon D.K., Deblieck C., Pascual-Leone A.** – Noninvasive brain stimulation for Parkinson's disease and dystonia. *Neurotherapeutics* 2008; 5 (2): 345-361.
49. **Tsuji S.** – Clinical applications of transcranial magnetic stimulation for the treatment of various neurological diseases. *Rinsho Shinkeigaku* 2005; 45 (11): 831-833.
50. **Hamada M., Ugawa Y., Tsuji S.** – High-frequency rTMS over the supplementary motor area improves bradykinesia in Parkinson's disease: subanalysis of double-blind sham-controlled study. *J Neurol Sci* 2009; 287 (1-2): 143-146.
51. **Mann G.E., Finn S.M., Taylor P.N.** – A pilot study to investigate the effects of functional electrical stimulation on gait in Parkinson's disease. *Proceedings of the 9th Annual IFESS Conference.* Bournemouth, UK, 2004, 62-64.
52. **Mann G.E., Finn S.M., Taylor P.N.** – A pilot study to investigate the feasibility of electrical stimulation to assist gait in Parkinson's disease. *Neuromodulation:Technology at the neural interface* 2008; 11(2): 143-149.