

Clinical Study of Dyskinesias and Other Complications in Parkinson's Disease Treatment

Mancheva-Ganeva Velina¹, Manchev Lachezar², Ganev Iordan³, Manchev Ivan¹

¹Department of Neurology and Psychiatry, Trakia University, Faculty of Medicine, Stara Zagora, Bulgaria

²Department of Radiology, Trakia University, Faculty of Medicine, Stara Zagora, Bulgaria

³Clinic of Psychiatry, Military Medical Academy, Sofia, Bulgaria

Abstract: 293 patients suffering from Parkinson's disease, randomly picked, were studied. The patients' condition was assessed by the Unified Parkinson Disease Rating Scale–UPDRS. The modified Hoehn and Jahr scale and the Schwab and England Activities of Daily Life Scale were also used. Electromyography studies of tremor were conducted as well. The results obtained were processed with the help of statistical methods. The patients, included in the study showed the following complications as a result of the treatment conducted: dyskinesias, morning dystonias, sleep disorders, predictable and unpredictable "off" periods, etc. Sleep disturbances had the highest frequency—in 153 patients (52%), with an insignificant prevalence in women as compared to men. Day dyskinesias came second—in 50 patients (17%), occurring with almost equal frequency in both genders. 47 patients (16%) had severely and moderately restricted movements, with equal incidence for both genders. 40 patients (13,6%) had moderate and severe pains, accompanying dyskinesias, equally distributed between men and women diagnosed with Parkinson's disease. The percentage of the predictable and unpredictable "off" periods were one and the same for men and women.

Keywords: Parkinson's disease, dyskinesias, sleep disturbances

1. Introduction

Dyskinesias are clinically heterogeneous. They are often manifested as chorea or choreoathetosis, myoclonus, akathisia, ballism and other abnormal movements. Chorea causes involuntary rapid irregular and unstoppable movements that seem to flow from one body part to another. The severity of these movements is different and they disappear at rest and during sleep and appear during active limb movement. Choreoathetosis usually affects some body parts as the trunk, head and neck, limbs and speech or respiratory muscles. Dystonia is the second most common disorder which is characterized with persistent muscle contractions, manifested independently or in combination with chorea.

Some less frequent movement disorders include akathisia /excessive muscle restlessness/, rapidly alternating leg movements / RAM/, blepharospasm, etc.

Types of levodopa-induced dyskinesias:

- **Peak-dose dyskinesia.** This is the most common form, which is related to peak plasma levels of levodopa and involves the head, trunk and limbs, and, in certain cases, the respiratory muscles as well. The reduced dosage of levodopa may improve dyskinesias, frequently at the cost of deteriorating the symptoms of the main disease.
- **Diphasic dyskinesias.** They occur when plasma levodopa levels are rising or falling without reaching the peak levels. They are also called D- I- D/ dyskinesias - improvement-dyskinesia/ and do not respond to levodopa dose reduction and may rather improve with high dose of levodopa / Ruzicka K, Zaburova J, Nutt G, 2011/.

"Off" period dystonias. They occur when the plasma levels of levodopa are low / for instance during the night and in general occur as painful spasms in one foot/. There is no universally accepted method for dyskinesias assessment. UPDRS is the most commonly used scale, as the patients may not be relied upon to give an accurate account of the severity of dyskinesias, especially when they are milder. The assessment of dyskinesias, therefore, remains largely subjective and often inaccurate. The indicators of severity of dyskinesias include amplitude, duration, the number of body parts affected and the cause for their occurrence.

Aim

Study of the frequency of dyskinesias and other complications in the treatment of patients, diagnosed with Parkinson's disease.

Material and Methods

293 patients with Parkinson's disease (129 man and 164 women) aged 58-79 years, randomly picked over an 8-year period (2005-2012) were studied. The study used the following assessment tools:

- 1) Unified Parkinson's disease rating scale – UPDRS
- 2) Modified Hoehn and Yahr scale for assessment of clinical symptoms
- 3) Schwab and England Activities of Daily Living Scale
- 4) Electromyographic studies of tremor (tremorograms) performed with EMG equipment
- 5) Statistical methods for processing the data received – SPSS statistics software was used

2. Results

Day dyskinesias were observed in 50 patients of both genders with almost equal frequency and duration. No statistically significant gender and number related differences in the frequencies were found. /Table 1/.

Table 1: Duration of dyskinesias in Parkinson's disease

Clinical symptom – stage of impairment	men	Gender women	Total
Duration / what proportions of the waking day are dyskinesias present/	n %	n %	n %
0= zero%			
1= 1- 25% of the day	6 4,6	8 4,8	14 4,7
2= 26- 50% of the day	8 6,2	7 4,2	15 5,1
3= 51- 75% of the day	10 7,7	6 3,6	16 5,4
4= 76- 100% of the day	3 2,3	2 1,4	5 1,7
TOTAL	27 20,9	23 14	50 17

Disabling dyskinesias were found in 47 patients - 27 men and 20 women. Severely and moderately restricted movements were most commonly observed for both genders /Table 2/.

Table 2: Frequency of disabilities in patients with dyskinesias

Clinical symptom – stage of impairment	men	Gender women	Total
Disability; How disabling are dyskinesias	n %	n %	n %
0= not disabling			
1= mildly disabling	4 3,1	4 2,4	8 2,7
2= moderately disabling	9 6,9	6 3,6	15 5,1
3= severely disabling	12 9,3	6 3,6	18 6,1
4= completely disabled	2 1,5	4 2,4	6 2
TOTAL	27 20,9	20 12,1	47 16

Dyskinetic disorders are characterized by excess of motor activity that may interfere with normal movement control. In patients with PD the chronic levodopa treatment induces dyskinetic movements, known as levodopa- induced dyskinesias /Bhidayasirik A, Truong D, 2008, Guridi J, Gonsales R, Obeso A, 2012, Thanvi B, Lo N, Robinson T, 2007, Homayoun H, Christopher G, Goetz M, 2012, Defebvre L, 2004, Jankovic J, 2005/. Dyskinesia includes different types of movement disorders such as chorea, ballism, dystonia, myoclonus, tics and tremor. Younger age of Parkinson's disease onset is related to higher frequency of dyskinesias, and the five-year risk for their development is 50% in patients with disease onset between 40-59 years of age as compared to 16% in those with disease onset after 70 years / Rascol D, Brooks A, Korczyn P et al, 2000/. The presence and degree of nigrostriatal damage, the severity of the disease and the levodopa dose play an important role for the appearance of dyskinesias. The other main factor, related to the origin of dyskinesias, is the pharmacokinetics and mechanics of levodopa, which causes intermittent or pulsatile stimulation of dopamine receptors / Olanow C, Shapira A, Rascol O, 2000/. Често пъти тези два фактора се комбинират/ Calabresi P, Felipo M, Ghiglieri N et al, 2010, Irvani M, Mc Creary A, Genner P, 2012/.

In 40 patients /13,6%/ moderate and severe pains accompanying dyskinesias prevailed, the frequency being equal for men and women with PD /Table 3/.

Table 3: Frequency of painful dyskinesias in the patients studied

Clinical symptom – stage of impairment	men	Gender women	Total
Painful dyskinesias. How painful are the dyskinesias	n %	n %	n %
0= not painful			
1= slightly painful	4 3,1	4 2,4	8 2,7
2= moderate pain	5 3,5	9 5,4	14 4,7
3= severe pain	10 7,7	5 3	15 5,1
4= marked pain	1 0,7	2 1,4	3 1
TOTAL	20 15,5	20 12,1	40 13,6

Early morning dystonias were comparatively rare - 23 patients /7,8%/ with equal frequency of occurrence for both genders. The percentage of predictable and unpredictable "off" periods was approximately the same - 20 patients / 6,8% / and 21 patients / 7,1% / for men and women. These periods come on suddenly in a matter of seconds, their frequency being the same. In 12 patients the "off" periods took 51 - 75% of the waking day; in 6 patients- /26-50%/, in 4 patients / 1-25%/.

Gastro-intestinal complications as a result of the treatment of our patients were rare – found in 18 patients/ 6,1%/, with equal frequency for both genders. These symptoms have been found in a number of other studies / Senard J, Rai S, Lapeyre- Mestre M, et al 1997/.

In contrast to the gastro-intestinal complications, sleep disturbances were rather frequent - in 153 patients /52%/. They prevailed insignificantly in women as compared to men. Autonomic and olfactory dysfunctions, psychiatric symptoms and sleep disturbances may represent prodromal markers of PD, but none of these symptoms is specific to the disease since they all may occur as idiopathic disorders or during the course of other neurodegenerative diseases such as Alzheimer's dementia. Thus, the identification of motor signs in patients at risk to develop PD needs to be verified with instrumental methods, proving the damage to dopamine nigrostriatal pathways. Transcranial sonography is such a method, which shows a highly characteristic enlargement of echogenic signal of the substantia nigra in PD patients.

As PD is thought to be due, at least in part, to oxidative stress, some blood markers such as malondialdehyde, superoxide radicals, coenzyme Q10 and others have been measured.

Studies on peripheral blood mononuclear cells have shown the reduction of intracellular concentrations of dopamine and tyrosine hydroxylase and others.

3. Discussion

A number of dopamine agonists are used for prevention of / Voon V, Fernagut J, Wickens et al 2009/. Several placebo-

controlled studies compare the evolution of dyskinesias in patients initiated with ropinirole, pramipexol, cabergoline. The use of ropinirole as monotherapy with later addition of levodopa over 10-year follow-up delayed the onset of dyskinesias by up to 3 years / Watts K, Lyons R, Pahwa R, 2010/.

The CALM-PD is a randomized controlled study that evaluated the risk of developing dyskinesias in patients with early Parkinsonism, treated for 24 months with pramipexol. They had a significantly lower incidence of dyskinesias – 9,9% as compared to the control group - 30,7%/ Holloway R, 2000/.

Another study showed that the administration of low doses of cabergoline was effective in reducing the frequency of dyskinesias / Belanger N, Gregoire L, Tahar A, et al 2003/и клозапин /Durif F, Debilly B, Galitzky M, et al 2004/.

A double-blind cross-over trial studied the effect of amantadine. It was found that dyskinesias decreased by 30-40% as compared to the control group, but some side effect of the treatment were observed / Thomas A, Iacono D, Luciano A et al 2004/. Similar results were obtained in another study as well / Varanese S, Howard J, Rocco A, 2010/.

Some opioid receptor antagonists show positive effect on dyskinesias. The joint administration of naloxone and naltrexone, together with dopaminergic agents, led to a significant reduction in the severity of dyskinesias without reducing the antiparkinsonian efficacy / Samadi P, Gregoire L, Bedard P, 2004/. A significant improvement / up to 40%/ in dyskinesias scores in PD patients, treated with a low dose of propranolol, was found / Carpentier A, Bonnet A, Vidailhet M, et al 1996/.

Except being an efficient antiepileptic drug, levetiracetam has been evaluated in the treatment of levodopa-induced dyskinesias. After 60 days treatment with a mean dose of 625 mg levetiracetam, dyskinesias decreased by about 42% / Zesiewicz Z, Sullivan K, Maldonado L, et al 2005/.

The motor symptoms of PD – bradykinesia, muscle rigidity and tremor depend on the degree of degeneration of the dopamine-containing neurons in the compact part of substantia nigra. Recent studies show that the pathological Lewy bodies that are typical for Parkinson's disease accumulate in several structures outside substantia nigra. These accumulations are related to the appearance of the non-motor symptoms of Parkinson's disease. /Braak H, Ghebremedhin E, Rub U et al, 2004, Pellicano C, Benincasa D, Pisani V, et al 2007, Jankovic J, 2011/. Based on the localization of Lewy bodies the following non-motor symptoms may play a role as prodromal markers of the disease:

- Autonomic disturbances
- Olfactory dysfunctions
- Psychiatric symptoms
- Sleep disorders/ REM/ and behavior disorders / RBD/.

Dysautonomia is a key characteristic of multiple system atrophy / MSA/ but occurs with varying severity in Parkinson's disease. The pathophysiology of dysautonomia in PD is complex and includes degeneration and dysfunction of the vegetative nuclei such as the nucleus ambiguus / n.ambiguus/ and other nuclei, which exert control on the sympathetic preganglionic neurons via the respective descending pathways. Additionally, degeneration of cholinergic, monoaminergic and serotonergic nuclei may cause abnormalities of modulatory effects within the central autonomic network.

Subtle vegetative disturbances that can at least partly be related to the degeneration of the vagal nerve are an early and frequent sign of PD. Almost all PD patients suffer from constipation and other gastro-intestinal symptoms / Magerkurth C, Schnitzer K, Braune S, 2005/. Cardiac sympathetic denervation has also been linked to genetic forms of PD, namely with alpha-synuclein mutations.

Autonomic functions in PD can be objectively assessed by several validated methods, including quantitative sudomotor axon reflex test, urodynamic studies, proctography, sympathetic skin response, pilocarpine test, etc.

Olfactory dysfunctions occur frequently in PD. More than 50% of the patients experience anosmia, 35% of them have severe hyposmia, and 14% have moderate hyposmia. The olfactory deficit in PD shows above all an increase of the olfactory threshold and minor changes of identificative and discriminative function. The olfactory dysfunction in PD depends on damage of the dopaminergic neurons in the olfactory bulbs and olfactory nuclei. However, olfactory deficit is not responsive to antiparkinsonian drugs and is not related to the severity of motor symptoms. Such apparent discrepancy may depend on precocious damage in PD, which makes the olfactory dysfunction already advanced at the time of onset of motor symptoms. Further data suggest that olfactory dysfunctions may be a potentially useful test to distinguish PD from atypical Parkinsonism.

Depression is extremely frequent in Parkinson's disease, occurring in 45% of the cases. It is not necessarily related to the severity of motor symptoms and is often misdiagnosed as hypomimia and reduction of voluntary movements, which are common for both PD and pure depression. Therefore, the identification of depression in PD patients is essentially based upon subjective perception of depressive symptoms such as inability to experience pleasure from different events / anhedonia/, reduced reaction to emotional stimuli, etc.

Anxiety is also common in PD. It can be present as panic attack, phobias or generalized anxiety disorder and can be related to drug-induced motor fluctuations in PD.

Virtually all PD patients develop sleep disruption at the very onset of the disease. These disorders have multifactorial etiology but pathological degeneration of central sleep regulation centers in the brain stem plays the main role. RBD is a specific sleep disorder during the REM phase of sleep, characterized by sudden behavioural episodes of violence, usually triggered by different sounds. RBD sleep disorders

are often seen in a number of synucleinopathies such as PD, MSA, diffuse Lewy body dementia, etc. These disorders are between 15% and 58% and in most cases they evolve together with motor symptoms in PD or precede their onset. Recent data suggest that excessive daytime sleepiness may also be a pre-motor marker of PD. It is important to recognize excessive daytime sleepiness as it can substantially affect quality of life in PD. In some cases the combination of sleep deprivation and antiparkinsonian drugs may cause sudden-onset day sleep / Tracik F, Ebersbach G, 2001/.

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