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Clinimetric methods for evaluating patients with Parkinson's disease in the context of the latest treatment strategies

Klinimetryczne metody oceny pacjentów z chorobą Parkinsona w kontekście najnowszych strategii leczenia

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Streszczenie:
Wstęp: Choroba Parkinsona jest chorobą neurozwyrodnieniową, polegającą na odkładaniu się złogów alfa – synukleiny w neuronach dopaminergicznych istoty czarnej, w konsekwencji czego dochodzi do obniżenia poziomu dopaminy w ośrodkowym układzie nerwowym i powstaniu objawów ruchowych i pozaruchowych.
Cel pracy: Celem pracy jest wskazanie klinimetrycznych metod oceny pacjentów z chorobą Parkinsona w kontekście współczesnych terapii.
Materiał i metody: Dokonano przeglądu anglojęzycznego piśmiennictwa naukowego z lat 2012 – 2022, pochodzącego z baz danych takich jak PubMed, SCOPUS, Web of Science, Google Scholar. Wyszukiwania przeprowadzono według słów kluczowych: choroba Parkinsona, ocena kliniczna, metody leczenia. Do analizy zakwalifikowano 69 pozycji literaturych.

Wyniki i wnioski: Diagnostyka choroby Parkinsona jest diagnozą z wykluczenia, brak jest dostępnych i tanich metod umożliwiających pewną diagnozę choroby. Ocena klinimetryczna chorego jest więc podstawą nie tylko diagnozy, ale także skutecznego, dostosowanego do potrzeb pacjenta leczenia. Istnieje wiele narzędzi oceny dedykowanych pacjentom z tą jednostką chorobową i to właśnie one zalecane są w tym procesie. Do współczesnych metod leczenia, szczególnie u których skuteczność leczenia farmakologicznego jest niezadowalająca zalicza się: głęboką stymulację mózgu, wlew dojelitowy DuoDopy® oraz wlew/iniekcje podskórne apomorfiny. Włączenie wyżej wymienionych technik zależy w głównej mierze od ocenianego stanu chorego.

Abstract:
Background: Parkinson's disease is a neurodegenerative disease involving the deposition of alpha-synuclein deposits in dopaminergic neurons of the black matter, resulting in a decrease in dopamine levels in the central nervous system and the development of motor and non-motor symptoms.
Aim of the study: This study aims to identify clinimetric methods for evaluating patients with Parkinson's disease in the context of contemporary therapies.
Material and methods: English-language scientific literature from 2012 - 2022 from databases such as PubMed, SCOPUS, Web of Science, Google Scholar was reviewed. Searches were conducted according to keywords: Parkinson's disease, clinical evaluation, and treatment methods. 69 items of literature were qualified for analysis.
Results and conclusions: The diagnosis of Parkinson's disease is a diagnosis by exclusion, there are no available and inexpensive methods to diagnose the disease with certainty. The clinimetric assessment of the patient is therefore the basis not only for diagnosis but also for effective, tailored treatment. There are many assessment tools dedicated to patients with this disease entity, and these are the ones recommended for this process. Contemporary treatment methods, especially for those in whom the effectiveness of pharmacological treatment is unsatisfactory, include deep brain stimulation, enteral infusion of DuoDopa®, and subcutaneous infusion/injections of apomorphine. The inclusion of the techniques depends mainly on the assessed condition of the patient.

Introduction

Parkinson's disease, also known as postictal tremor (Latin: paralysis agitans), is a self-limited chronic disease with a slow progression. The disease is characterized by degenerative changes in the central nervous system (CNS), manifesting, in some patients, problems in recognizing surroundings, people, events, time, etc. [1]–[4].

Epidemiologically, Parkinson’s disease is the second most common neurodegenerative disease of the brain. In Poland, about 2,000 to 2,500 people are diagnosed with Parkinson’s disease each year. Worldwide, nearly 7-10 million have the disease, while the incidence oscillates between 0.1%-0.2% in the general population [5]–[8].

Parkinson’s disease was first described by James Parkinson in 1817. The pathomechanism of this pathology focuses mainly on the atrophy of dopaminergic neurons, due to which the concentration of dopamine in the striatum decreases, and this in turn contributes to the functional predominance of the cholinergic system, disturbances in other CNS neurotransmitter systems. The main cause of the degradation of the aforementioned neurons is the deposition of α-synuclein deposits in the form of Lewy bodies (conglomerates in the pericarya) or Lewy neurites (conglomerates in the axoplasm). A patient diagnosed with the described disease entity is characterized by a triad of symptoms: bradykinesia, resting tremor, and rigidity [9]–[12].

A fully certain diagnosis can only be made during a post-mortem pathological examination (autopsy). A test that can help patients with a questionable diagnosis is single-photon emission computed tomography (SPECT), also known as DaTSCAN. It uses a tracer for dopaminergic neurons in the striatum, imaging presynaptic dopamine reuptake in the black matter. Nowadays, the diagnosis of Parkinson’s disease is a clinical diagnosis, which is why it is so important to know the clinimetric methods of evaluating patients to implement treatment early and thus prevent complications[13]–[17] .

The gold standard in the treatment of Parkinson’s disease since the 1960s has been substitution therapy in the form of oral administration of levodopa (L-dopa). Benserazide or carbidopa, which are inhibitors of obligatory levodopa decarboxylase, are used to reduce the formation and accumulation of dopamine in tissues, and catechol-O-methyltransferase inhibitors (e.g., tolcaptone, entacapone) can also be used. Other oral drugs used in Parkinson’s disease are dopamine agonists (bromocriptine, pergolide, pramipexole, ropinirole, rotigotine), amantadine, selective monoamine oxidase B inhibitors (selegiline, rasagiline), anticholinergics

(benzotropine, trihexyphenidyl). Contemporary treatments include DBS (deep brain stimulation), subcutaneous infusions of apomorphine, and enteral infusions of levodopa (described later in this paper) [18]–[27].

Aim of the study

This study aims to identify clinimetric methods for evaluating patients with Parkinson's disease in the context of contemporary therapies.

Material and methods

Information on the methodology of the study is shown in Figure 1. The number of publications included in the review, along with their source and methodology, are summarized in Table 1.

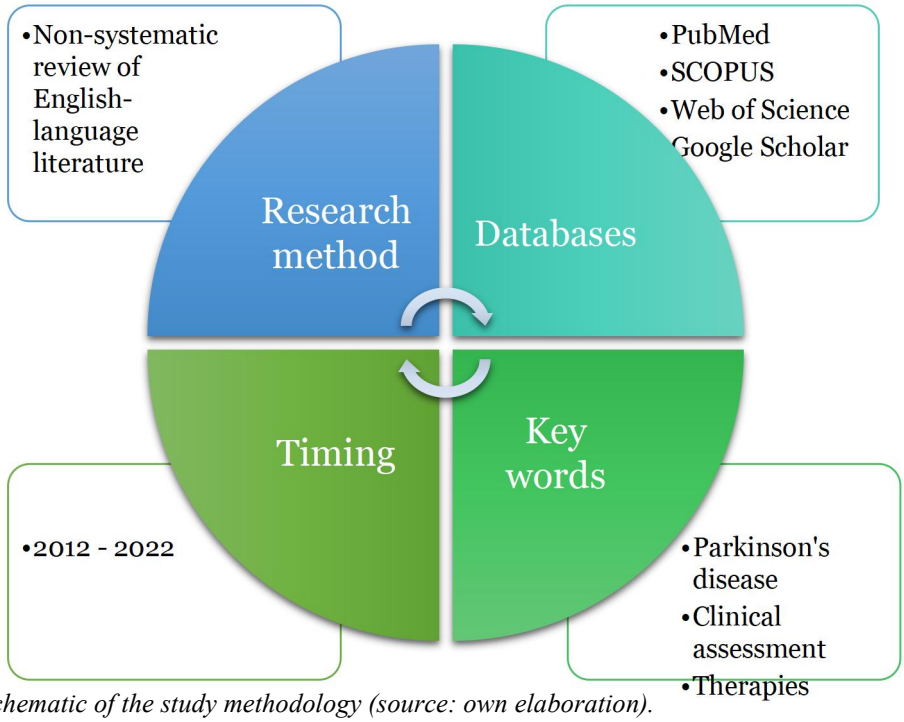

Figure 1. *Schematic of the study methodology (source: own elaboration).*

Database	Number of searches	Publications included in the review	Research methods
PubMed	4 212	30	systematic reviews, metanalyses, cohort studies, case-control studies, clinical trials literature reviews
SCOPUS	2 952	25	
Web of Science	813	35	
Google Scholar	18 500	45	

Table 1. *Analysis of searches in databases (source: own elaboration).*

Results

As mentioned in the introduction of the paper, the diagnosis of Parkinson's disease is a diagnosis by exclusion, and as a result, international bodies of researchers and clinicians working on this neurodegeneration have developed unified diagnostic criteria. Among the most common are the Queen Square criteria implemented by the United Kingdom Parkinson's Disease Society Brain Bank. In their structure, they contain 3 domains. The first is the stage for the diagnosis of parkinsonism, based on the finding of bradykinesia (an obligatory criterion) and at least one of two symptoms: resting tremor (with a frequency of 4 - 6 Hz), postural instability (after excluding other causes). The other two domains are exclusion criteria, divided into data indicating symptomatic or atypical parkinsonism and criteria supporting/supporting the diagnosis of Parkinson's disease. A detailed description of the clinical manifestations is provided in Figure 2 [28]–[32].

Figure 2. *The United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria (source: Lasse Pihlstrøm: The genetics of sporadic Parkinson's disease. Refining the insights from genome-wide association studies* [33]*).*

In both diagnosis and clinical evaluation, it is important to know the symptoms of Parkinson's disease, among which motor and non-motor symptoms are distinguished. The former mainly revolve around tremors and spasticity and the resulting deficits, and limitations in motor function (dyskinesias, fluctuation, dysphagia, dysarthria, falls). The second, on the other hand, includes dysfunction from the autonomic system, and mental and cognitive disorders, listed in Figure 3 [34]–[36].

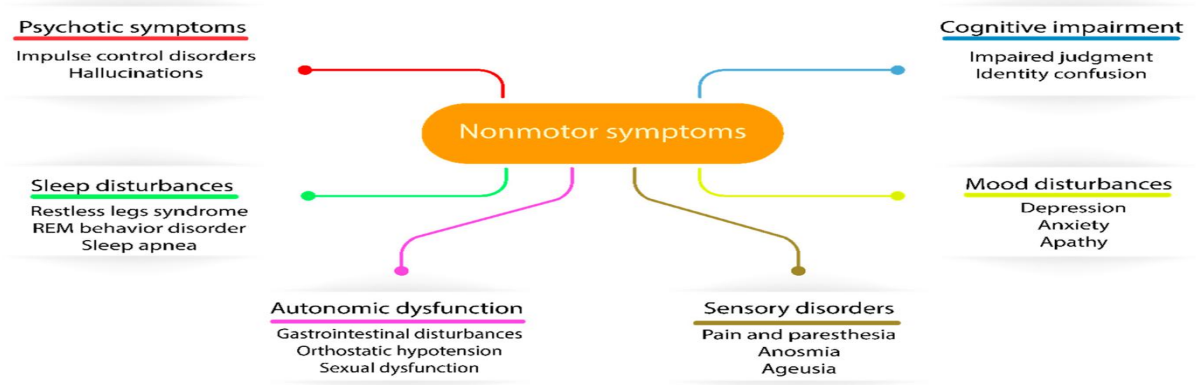

Figure 3. *Nonmotor symptoms of Parkinson's disease (source: Csaba Váradi: Clinical Features of Parkinson's Disease: The Evolution of Critical Symptoms* [37]*).*

A deficit scale that can be used when conducting a physical examination of a patient is the Hoehn-Yahr Scale. This scale describes a five-point cafeteria of symptoms and resulting deficits in functional capacity. It was created in 1967 and is still one of the most widely used tools in the evaluation of Parkinson's disease patients Its development was based on the observation of 856. people. It is presented as follows:
1 – unilateral damage without functional impairment,
2 – bilateral or moderate damage without balance disorders,
3 – impaired balance and function not preventing independent living, disability is slight or moderate,
4 – fully developed disease, disability is significant, although the patient is still able to stand up and walk independently,
5 – the patient is in a wheelchair or in bed [37]–[41]
To standardize the scale, half-points of 1.5 and 2.5 were introduced (*Unified Parkinson's Disease Rating Scale - UPDRS*). The described scale, in determining the severity of the disease is directed at assessing the patient's posture, and for this reason, does not reflect other accompanying dysfunctions of the patient (Figure 4.) [42], [43].

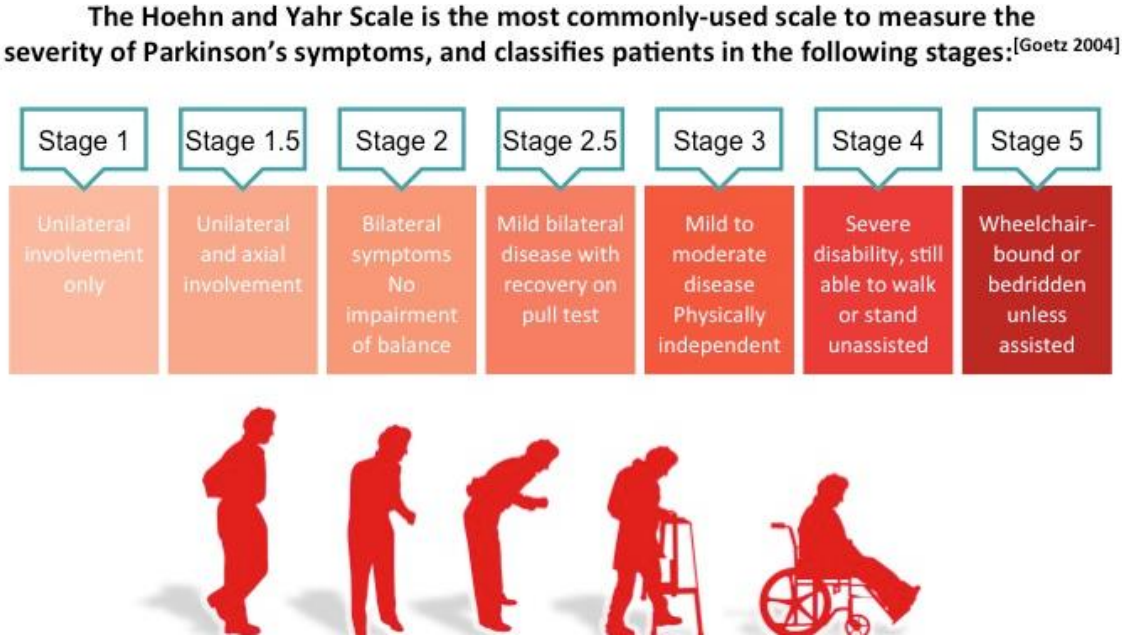

Figure 4. *Unified Parkinson's Disease Rating Scale - UPDRS (source: https://www.personalhealth.ie/helpful-hints-1/exercise-prescription-for-parkinsons-how-the-little-details-make-big-impacts* [44] *).*

In the course of the disease, as already mentioned, cognitive disorders, such as memory and attention disorders, worsen dementia. Therefore, the patient should be systematically assessed and monitored for their occurrence. In this process, the following assessment scales are recommended: the *N-1* and *N-2 tests*, the *"100-7" tests*, the *SCOPA – Cog test*, *The Face - Name - Learning Test (GNL)*, the *Alters Concentration Test (AKT)*. For language proficiency, the recommended tests are *Controlled Oral Word Association Test* (COWAT), *Boston Naming Test* (BNT), *Boston Diagnostic Aphasia Examination* (BDAE) or *Addenbrooke's Cognitive Examination III* (ACE-III) attempts. Despite the plethora of specific tests, current recommendations state that screening should be done using the following scales: *MoCA*, *Parkinson's Disease Dementia - Short Screen* (PDD-SS), *Mini Mental Parkinson's* (MMP), *PD-CRS*, *SCOPA-Cog*, *PANDA*, *Addenbrooke's Cognitive Examination* (ACE), *Mattis Dementia Rating Scale* (MDRS), *DRS-2*, *Mini Cog – Functional Assessment Questionnaire* (MC – FAQ), *Power of Attention* (PoA), *Cambridge Neuropsychological Test Automated Battery* (CANTAB), *Digit Vigilance Accuracy from Cognitive Drug Research* (CDR). It is worth noting that the standard *Mini-Mental State Examination* (MMSE) test used in the diagnosis of dementia is an insufficiently sensitive test for the diagnosis of dementia in Parkinson's disease patients [45]–[52].

Assessment of the disease's progression, along with the lack of effectiveness of oral treatment, is the basis for implementing the latest treatment procedures. They are implemented at late stages of the disease, when: deterioration of response to drug treatment, drug duration is shortened to 30-60 minutes, motor fluctuations and/or dyskinesias appear, there is a lack of effect of the dopaminergic drug at the end of its action (end-of-dose dystonia). Methods include DBS (deep brain stimulation), enteral infusions of levodopa, subcutaneous infusions of apomorphine [53]–[55].

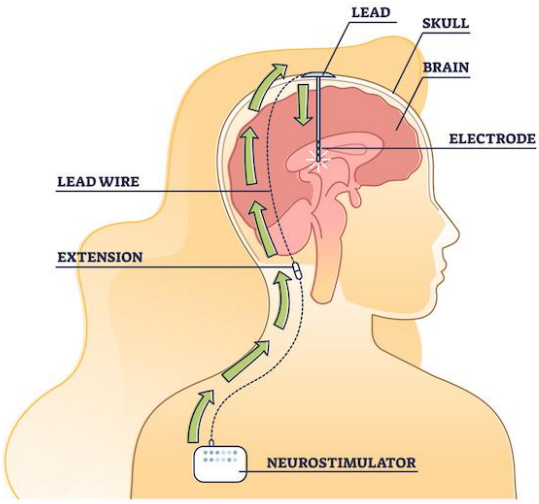

Figure 5. *Deep brain stimulation – simple chart (source: https://www.ohsu.edu/brain-institute/understanding-deep-brain-stimulation-dbs* [69]*)*

DBS involves the surgical, subcutaneous implantation of a brain stimulator, located in the upper thoracic region, which is connected by thin electrodes to the low thalamic nucleus or part of the internal globus pallidus, through which elements of the extrapyramidal system are stimulated to a continuous degree. The simulator is put in place for a period of about 25 years, as this is the life of its battery. DBS allows controlling and adequate change of the parameters of neuronal excitation while modifying the effect of action [56]–[59].

It is worth emphasizing the fact that this method does not limit the progression of the disease but improves the patient's quality of life. Gait disturbances, axial symptoms, and cognitive function are not improved (Figure 5.). DBS is a complementary method to the traditional pharmacological treatment of Parkinson's disease with oral levodopa. It is used because of its ability to reduce the dose of anti-Parkinson drugs and reduce the severity of some motor disorders refractory to drug treatment, such as motor fluctuations and dyskinesias [56]–[58].

Therapy with DuoDopa® consists of enteral administration of levodopa with carbidopa by a route through gastrostomy access using a pump, with the possibility of determining an individual dose of the drug. The advantage of supplying by this route is the stabilization of serum drug levels, which in turn avoids motor fluctuations and dyskinesias. A prerequisite for its implementation is a preserved response to levodopa. It is possible to administer the drug along with nutrition, which is an advantage of the method in long-term care or palliative care patients (Figure 6.) [60]–[64].

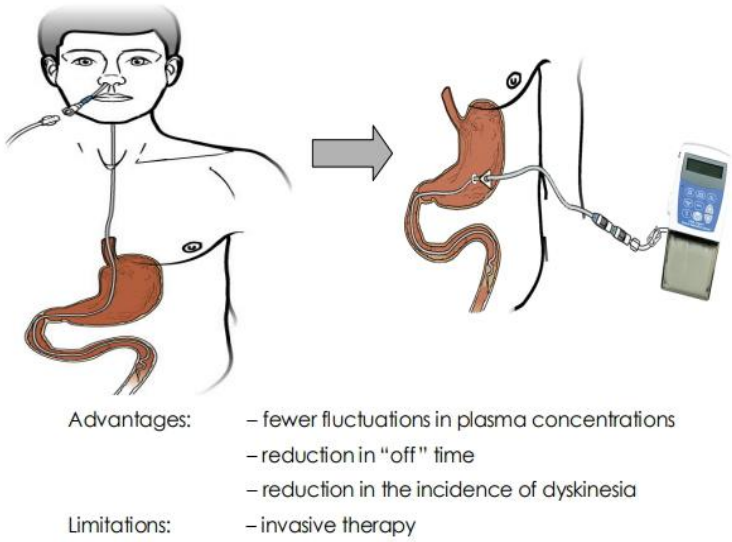

Figure 6. *DuoDopa® pump (source: https://www.e-jmd.org/journal/Figure.php?xn=jmd-2-1-10-3.xml&id=f2-jmd-2-1-10-3&number=94&p_name=1038_94* [65]*)*

Subcutaneous apomorphine infusions are used for continuous administration of apomorphine by the pump. This method is less invasive than the other two, and importantly, if the condition worsens, it is possible to administer apomorphine on an ad hoc basis. An individual pump infusion is used for a period of 16 hours, and if the patient requires it, the total dose is supplemented with an additional subcutaneous injection. This method is associated with the risk of developing tolerance to the drug, so infusions should be interrupted for a period of a minimum of 4 hours. This regimen prevents the development of this undesirable phenomenon [66]–[68].

Conclusions

1. The diagnosis of Parkinson's disease is difficult, relying on diagnosis by exclusion.
2. the progression of the disease should be systematically evaluated, considering the biological, mental, social, and spiritual state.
3. There are many clinimetric tools for evaluating patients diagnosed with Parkinson's disease. The assessment tool should be properly selected, giving priority to tools dedicated to this disease entity.
4. Modern treatments for Parkinson's disease include DBS (deep brain stimulation), enteral infusions of levodopa, and subcutaneous infusions of apomorphine.

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