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Research Article

Parkinson's Disease Diagnosis with ^{123}I Ioflupane (DaTSCAN)

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Abstract

The authors of the paper statistically evaluated the results of single photon emission computed tomography (SPECT) brain scans in 1050 patients with suspected Parkinson's disease. The control group consisted of patients with other neurological diseases who underwent SPECT brain scans. Diagnosis of Parkinson's disease based on clinical examination is not always straightforward. An examination of the transport dopaminergic route by Ioflupane (^{123}I) helps to refine the diagnosis. Based on the obtained results, the authors believe that in the differential diagnosis of Parkinson's disease (or Parkinson's syndrome), SPECT brain imaging is of unmistakable importance, both from a clinical, therapeutic and socioeconomic point of view. In Parkinson's disease, the functional state of the autonomic nervous system (ANS) changes. Examination of the ANS can help both in the differential diagnosis of Parkinsonian syndromes and in determining the degree of impairment; it is a prognostic indicator. Results of Single Photon Emission Computed Tomography (SPECT) examinations were statistically evaluated in the group of 1050 patients with suspected Parkinson ś disease. SPECT examinations of patients with other neurological diseases were used as a control group. Diagnosis of Parkinson's disease based on clinical examination is not always straightforward. An examination of the transport dopaminergic route by Ioflupane (^{123}I) helps to refine the diagnosis. After statistical evaluation of these results authors believe that in the differential diagnosis of Parkinson's disease (or Parkinson's syndrome), SPECT brain imaging is of huge importance from a clinical, therapeutic and socioeconomic point of view. In Parkinson's disease, the functional state of the autonomic nervous system changes. Examination of the autonomic nervous system can help both in the differential diagnosis and in determining the degree of impairment.

Keywords

Parkinson's Disease, Parkinson's Syndrome, SPECT of the Brain, Autonomic Nervous System

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1. Introduction

In recent decades, we have witnessed a rapid development of functional imaging methods also in neurology. These methods are able to visualize pathological metabolic changes of the central nervous system with great accuracy at an early stage. For a patient, this means the initiation of optimal therapeutic procedures.

In nuclear medicine, imaging methods are based on the use of radionuclides. Imaging methods are Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) or the fusion of nuclear medicine and radiology images SPECT/CT, PET/CT, PET/MR of the brain, which by combining physiological and anatomical views brought a new level of quality [1, 2]. Other brain imaging options are Computed Tomography (CT), functional magnetic resonance imaging (fMRi), MR spectroscopy, etc. [3].

The autonomic nervous system (ANS) plays a very important role in the regulation of the activity of the cardiovascular system. Sympathetic dysfunction is present in many diseases, including Parkinson's disease. By examining the state of the ANS, we can reveal the asymptomatic stage of cardiovascular autonomic neuropathy. The severity of these changes correlates with increased mortality.

2. SPECT

Single-photon emission computed tomography (SPECT) uses gamma radiation from radionuclides, which are administered into the body as radiopharmaceuticals. The examination enables the evaluation of disease processes based on information about the metabolic state of cells, tissues, and organs [1, 4]. The radionuclide emits gamma radiation, which is captured by the device's detector during the examination. The detector moves around the patient and records measured data at certain time intervals. In this way, the relative level of perfusion in individual parts of the brain can be investigated, immediately after the application of the radiopharmaceutical. By combining SPECT and CT examinations (or PET and CT, PET and MR), the anatomical details are supplemented with the functional state of the brain tissue [1, 5-7].

To determine regional cerebral perfusion (rCP) by the SPECT method, the radiopharmaceutical ^{99m}Tc-HMPAO (hexamethylpropyleneaminooxime) is used, commercially supplied as an inactive kit under the name Ceretec®, Stabilized Ceretec®. The radiopharmaceutical is administered parenterally into a vein. In the brain, it passes through the blood-brain barrier and is absorbed in the brain tissue, depending on the current blood supply of individual areas (Figures 1, 2). It is used for the examination of resting cerebral circulation, changes in metabolic activity due to circulatory disorders after a stroke, mapping of the speech-activated cerebral area, etc. [8].

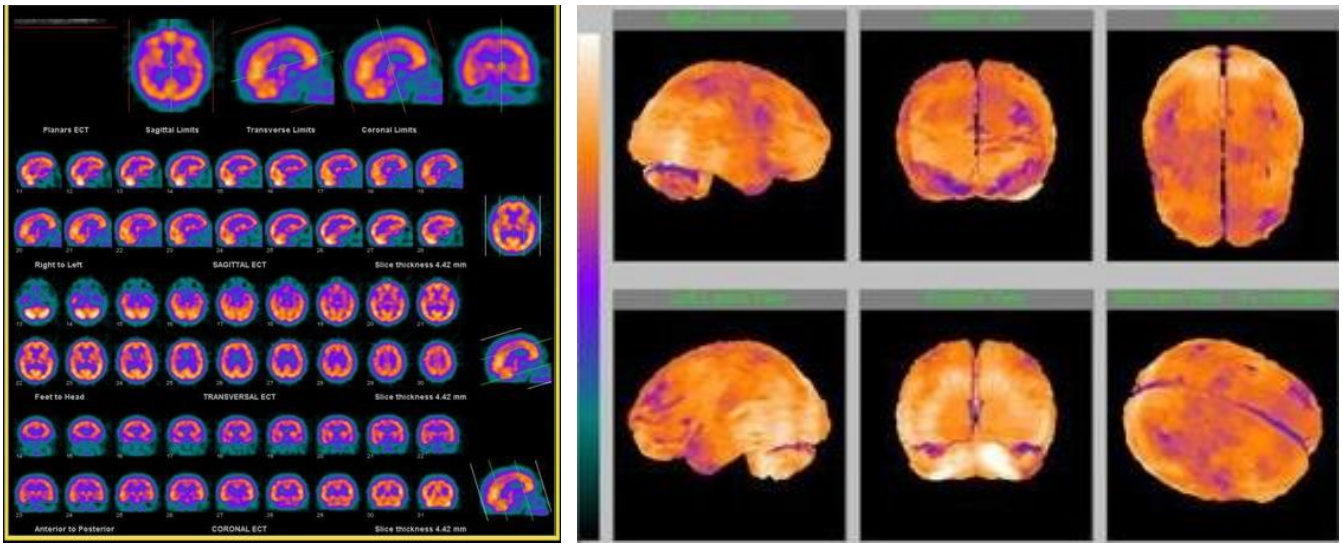


Figure 1. *Normal finding of cerebral perfusion. Sagital, transverse and coronary planes on the left side, 3D Talairach cortical perfusion on the right side.*

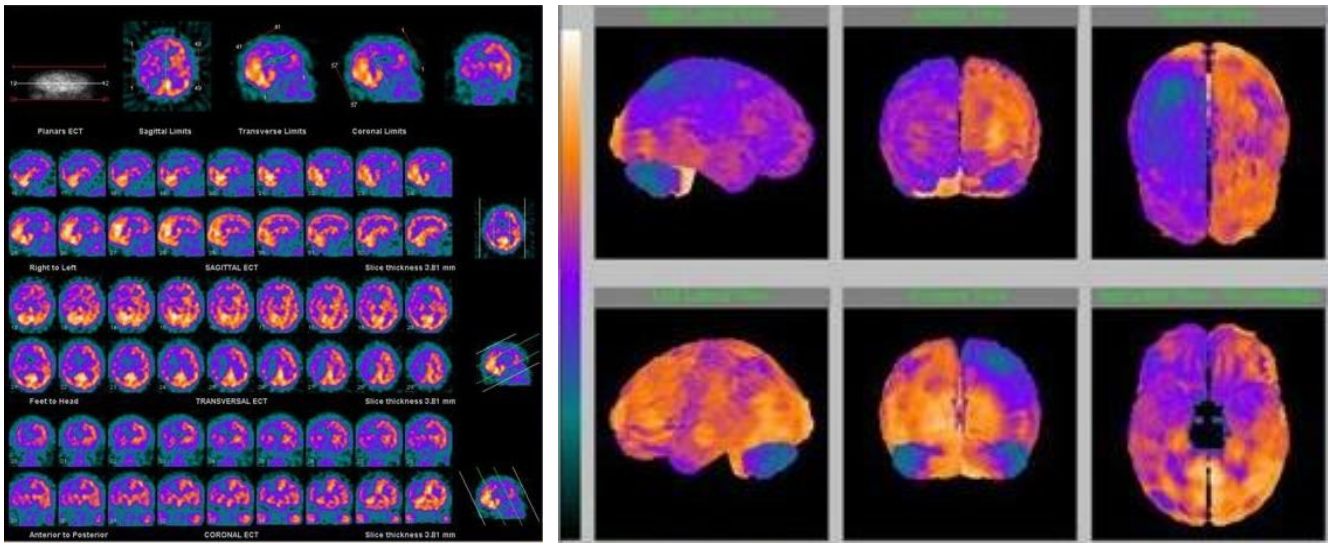
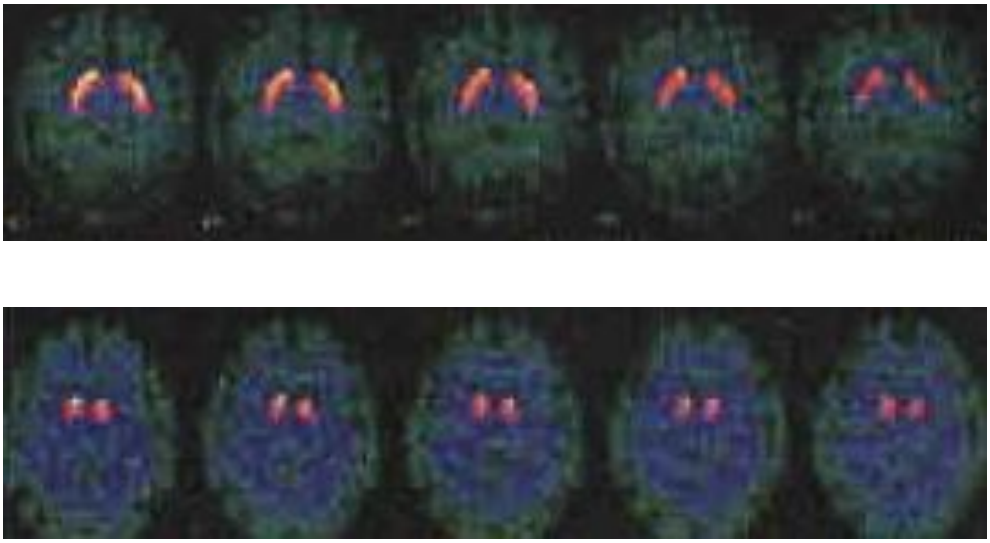


Figure 2. *Impaired metabolic activity (hypoperfusion) in parieto-occipital region of the right cerebral hemisphere.*

Another method is examination using the radiopharmaceutical ^{123}I-Ioflupane (DaTSCAN). It is used to visualize the density and distribution of dopamine presynaptic transporters. Radiopharmaceutical ^{123}I-Iodobenzamide (IBZM) for evaluating the activity of postsynaptic D2 receptors [4, 9]. Examination with the mentioned radiopharmaceuticals in neurology is most often used to evaluate dopamine transporter proteins on presynaptic endings in the area of the basal ganglia (BG), the postsynaptic dopamine D2 receptor system (Figure 3) [1, 10].



Lower images- pathological findings in BG examination (atypical round shape) in Parkinson's disease during ^{123}I -Ioflupane examination.

Figure 3. *Upper images- transversal cuts. Normal finding in BG examination (semilunar shape).*

We can examine the state of the ANS using ^{123}I-metaiodobenzyl-guanidine (MIBG) (Adreview). It allows determining the concentration of sympathetic receptors in the heart muscle. ^{123}I-Adreview is a metabolic analogue of the adrenergic blocker guanethidine. Unlike in noradrenaline, its enzymatic degradation does not occur in nerve endings. Evidence of the involvement of the sympathetic nervous system (SNS), the renin-angiotensin system, and other neurohumoral factors in the development and course of chronic heart failure led to the formulation of the "neurohumoral model" of the disease. Hyperstimulation of the SNS leads to myocardial ischemia, to a change in the ratio of sympathetic receptors on myocytes, the inotropic response to catecholamines decreases, the mechanism of myocyte apoptosis is activated, and electrical instability of the myocardium increases [11, 12]. Patients with heart failure have an increased level of noradrenaline, there is a reduction of nerve endings in the heart. A reflection of these changes is a significant reduction in the ac-

cumulation of ^{123}I–Adreview in the myocardium. In addition to the reduction of accumulation, the ^{123}I-Adreview washout is accelerated. A denervated but perfused myocardium plays an important role in the development of malignant arrhythmias. This finding in patients points to a high risk of sudden death in patients waiting for a transplant, diabetics with developed cardiac autonomic neuropathy, parkinsonians in whom ANS activity is altered, etc. [12, 13]. Examination of the accumulation of ^{123}I–Adreview allows to detect the presence of arrhythmogenic areas in the myocardium. Such myocardium can be identified by simultaneous imaging of ^{123}I-Adreview distribution and perfusion imaging. If denervation is present and perfusion is preserved, there is a mismatch between the findings during the ^{123}I-Adreview examination and the ^{99m}Tc -tetrofosmin perfusion examination (mismatch) [12, 14]. Another method for determining the state of the ANS is the examination of heart rate variability (HRV) by spectral analysis [14, 15].

2.1. Parkinson's Disease (PD) / Parkinson's Syndrome (PS)

Worldwide, Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. On a global scale, it represents an increasing health, economic and social burden and significantly reduces the quality of patients ´life. It is also one of the most common neurological diseases that gradually leads to a limitation of mobility [16].

The total number of patients in the population is about 1:1000 inhabitants. For persons older than 60 years, 1:100 inhabitants, i.e. 1% [16, 18]. It shows an increasing prevalence with age, up to 75 years of age. Most often, the onset of the disease is between 58 and 62 years of age. There are approximately 10% of patients with the onset of the disease at a younger age (before the age of 40). There are approximately 10% of patients with the onset of PD after the age of 75. The incidence of the disease in single year is around 10-20 cases/100,000 inhabitants [19, 20]. The disease more often affects men, in whom PD develops approx. one and a half times more often than in women, although not all studies support this. The incidence of PD increases with age, showing a sharp increase after the age of 60 and stabilizing between the age of 70-79 [21, 23]. According to data from the National Centre for Health Information in Slovakia (NCZI), in 2018, almost 25,000 patients suffered from PD. As the level of health care improves, as well as the average life expectancy increases, the prevalence of PD will also increase. It is assumed that by 2030 the number of patients with PD will double. Therefore, the costs of treating PD itself, but also secondary costs related to complications of PD (e.g. falls), as well as the costs of social care for patients will increase [24].

Parkinson's disease is characterized by the progressive loss of specific but heterogeneous neuronal populations. The primary symptoms of Parkinson's disease are a result of the loss of dopaminergic neurons in the substantia nigra, pars compacta. In addition, neurons in the monoaminergic nuclei of the brainstem (catecholaminergic and serotonergic), cholinergic neurons of the nucleus basalis Meynert, hypothalamic neurons, small neurons in the cerebral cortex (specifically in the cingulate and entorhinal cortex), as well as neurons in the olfactory bulb, sympathetic ganglia and parasympathetic neurons in the digestive tract [25]. The disappearance of dopaminergic neurons of the substantia nigra leads to a decrease in the amount of dopamine in the striatum, especially in the dorsal and central regions of the putamen, which contributes to the emergence of akinesia and rigidity. When the first symptoms of PD appear, most (up to 60-80%) cells of the substantia nigra have already died. This assumes an existence of several years to decades of the preclinical stage of the disease [16]. Significant loss of neurons in the medial part of the substantia nigra, especially those projecting to the caudate nucleus, may contribute to the impairment of cognitive functions. Other structures whose dysfunction has been implicated in cognitive impairment in patients with Parkinson's disease include the nucleus basalis of Meynert, the locus coeruleus, and cortical areas, particularly the entorhinal cortex. Neurodegenerative processes in bulbus olfactorius underlie anosmia. Degeneration of neurons in the intermediolateral column of the spinal cord, sympathetic and parasympathetic ganglia (probably also the nucleus centralis amygdalae) causes autonomic dysfunction, while degeneration of serotonergic and noradrenergic nuclei of the brainstem and probably also the amygdala causes behavioural disorders, including depression [25].

Currently, the formation of pathologically altered proteins that damage the functions of neurons is considered to be the pathogenetic basis of the emergence and development of neurodegenerative diseases. This change occurs as a result of a so-called misfolding [26], i.e. (of non-physiological packing - protein molecules must fold into defined three-dimensional structures in order to obtain a functional activity of the protein in a biologically active form (conformation) [26, 27]. The resulting aberrant protein damages the neuron either by losing its physiological function, by creating a new function (toxic) or by accumulating aberrant proteins in the form of aggregates or inclusions. In Parkinson's disease, such a protein is alpha-synuclein [(a major component of Lewy bodies (LB)]. Its physiological conformation is an alpha-helix, which in pathological situations folds into a pathological form, the so-called beta-sheet (folded sheet). this misfolding of alpha-synuclein can be induced by a number of mechanisms, e.g. mutations of the gene for the formation of alpha-synuclein, lack of protective proteins, the so-called chaperones that prevent pathological packaging, also the presence of various substances, such as rotenone or a protein resulting from a mutation in the glucocerebrosidase gene, etc. [26, 28, 29].

Decades of research have identified genetic factors and biochemical pathways involved in the development of neurodegenerative processes and the development of neuro-

degenerative diseases (NDDs) such as PD. Based on these investigations, eight characteristic features of NDD have been identified: pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeleton abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation and neuronal cell death [28, 30].

Clinically, it is an akinetic-rigid or hypertonic-hypokinetic syndrome. Its basic characteristic is the tetrad of main symptoms – bradykinesia, rigidity, tremor and postural instability. However, James Parkinson already stated the fact that the classic motor symptoms of PD are accompanied by a whole range of other symptoms (e.g. sleep disorders, constipation, defecation disorders, sialorrhoea or urinary dysfunctions, etc.), which today we refer to as non-motor (NMS) [16, 17, 21, 22].

In recent decades, our knowledge of PD in terms of the course of the disease has changed to a great extent. The clinical stages of PD based on the latest classification are as follows:

1. Preclinical phase: Neurodegenerative processes characteristic of PD have begun, but clinical signs of the disease are not yet detectable.
2. Prodromal stage: Some signs of PD (mainly the non-motor) may appear, but these clinical signs are not yet sufficient to make a clinical diagnosis of PD.
3. Clinical Stage: The clinical diagnosis of PD can be made based on the motor symptoms characteristic of PD [3, 16, 31, 32].
   a. Early (non-complicated) PD
   b. Complicated PD
   c. Advanced PD [3, 28].

The symptoms of PD are varied. We can divide them into two main groups:

1. movement-related or motor symptoms including bradykinesia, rigidity, tremor and postural instability (stance and gait disorders) [22, 34, 35].
2. not related to movement (non-motor symptoms) including: hyposmia, sleep disorders, REM sleep behaviour disorders, insomnia, excessive daytime sleepiness, a wide range of autonomic dysfunctions (constipation, difficulty urinating, sexual dysfunctions and reduced cardiac chronotropic response during exercise), saliva production disorder, dysphagia, gastric emptying disorder, gastrointestinal symptoms (constipation, defecation disorders), urogenital disorders, sexual dysfunctions, thermoregulation disorders, visual function disorders, cardiovascular disorders (orthostatic hypotension, nocturnal hypertension, postprandial hypotension, blood pressure fluctuations), in advanced PD depression, anxiety, apathy, cognitive deficit and dementia, psychotic manifestations, impulse control disorders, dopamine dysregulation syndrome, pain in Parkinson's disease, fatigue (Figure 4). [17, 18, 22, 32, 35].

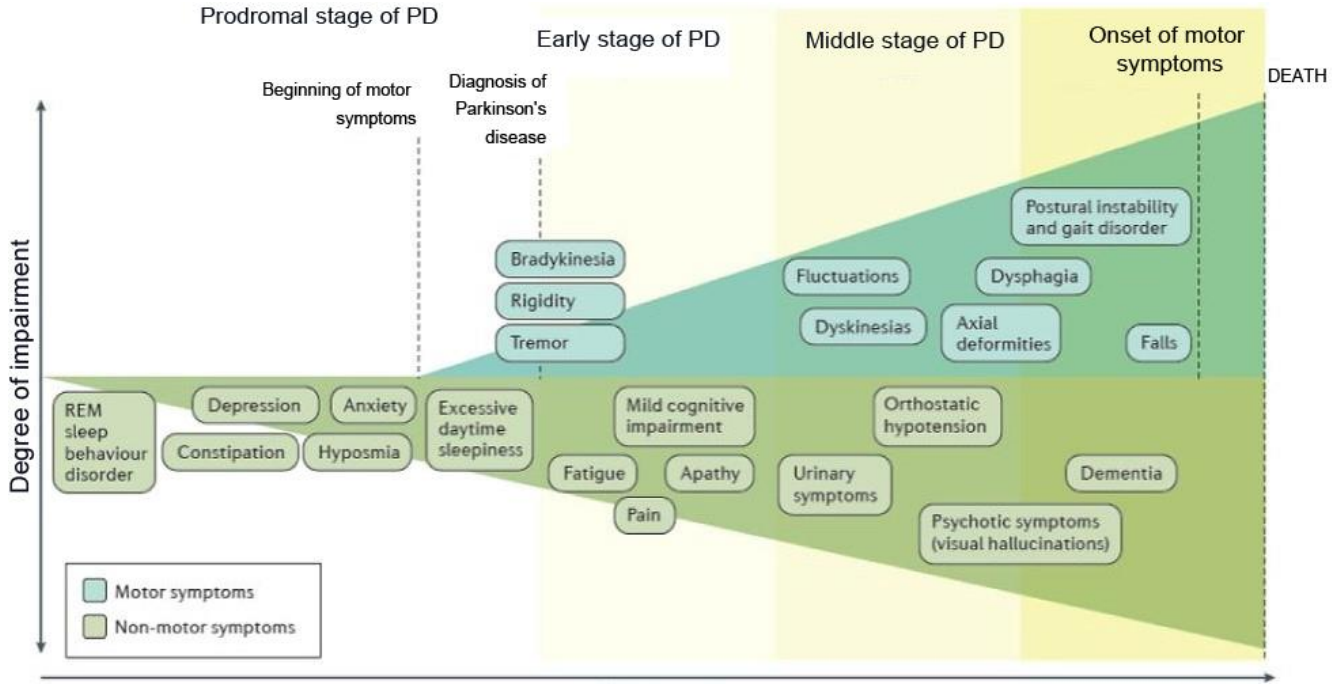


Figure 4. *Clinical symptoms during progression of Parkinson's disease.*

The diagnosis of Parkinson's disease begins with the onset of motor symptoms (early stage of Parkinson's disease) typically in the late fifties, but may be preceded by a prodromal phase of several years or even decades characterized by specific non-motor symptoms (prodromal stage of Parkinson's disease). Non-motor symptoms become more widespread and

distinct as the disease progresses, but may be present to varying degrees in all stages of PD. Progressive disability from Parkinson's disease is caused by the combination of these non-motor symptoms with increasing severity of basic motor manifestations, the development of motor complications induced by L-DOPA (moderate stage of PD) and the development of weakening of the effect of L-DOPA- on motor disorders such as postural instability, gait disorders (including freezing) and dysphagia (late stage of Parkinson's disease) [28].

After long preparatory works, the new clinical criteria system of the international Movement Disorders Society (MDS) was published in 2015 [3]. The central role of the motor syndrome dominates the diagnosis of MDS-PD, and the presence of the most common non-motor symptoms has also been incorporated into the new diagnostic system. The accuracy of the MDS-PD diagnostic criteria system is also confirmed by neuropathological examinations [39].

The presence of parkinsonian syndrome, which is defined as bradykinesia in combination with resting tremor or rigidity, is essential for the diagnosis of PD [32, 33, 37].

1. The diagnosis of clinically proven PD requires:
   1) Absence of absolute exclusion criteria,
   2) Presence of at least 2 supporting criteria,
   3) Absence of relative exclusion criteria („*red flags*“).
2. The diagnosis of clinically probable PD requires:
   1) Absence of absolute exclusion criteria.
   2) The presence of relative exclusion criteria ("red flags") balanced by supporting criteria:
      a. If one warning sign is present, at least one supporting criterion must be present.
      b. If two warning signs are present, then at least two supporting criteria must be present.
      c. No more than two warning signs may be present for this category.

Table 1. *Supporting criteria for the diagnosis of PD.*

	Supporting criteria
1.	Clear and dramatic improvement after dopaminergic treatment
2.	The presence of levodopa-induced dyskinesias
3.	Resting limb tremor documented on clinical examination (past or current examination)
4.	Presence of loss of smell or cardiac sympathetic denervation on MIBG scintigraphy

Table 2. *Absolute exclusion criteria for the diagnosis of PD.*

	Absolute exclusion criteria: The presence of any of these manifestations excludes PD:
1.	Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities [(eg, gaze-evoked nystagmus, macro square-wave jerks (irregular involuntary eye movements that disrupt goal-directed gaze fixation., hypermetric saccades)]
2.	Vertical downward gaze palsy or selective slowing of downward vertical eye saccades
3.	Diagnosis of probable behavioural variant of frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 years of the disease
4.	Parkinsonism limited to the lower limbs for more than 3 years.
5.	Treatment with a dopamine receptor blocker or dopamine depletors at a dose and duration consistent with medication-induced parkinsonism
6.	Absence of observable improvement in mobility despite high doses of levodopa and at least moderate severity of the disease
7.	Unequivocal cortical sensory impairment (i.e., graphesthesia, stereoagnosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
8.	Normal functional neuroimaging of the presynaptic dopaminergic system
9.	The presence of another disease known to cause parkinsonism that is likely to be associated with the patient's symptoms, or based on a full diagnostic assessment, an evaluating expert believes that an alternative syndrome is more likely than PD.

Table 3. *Warning signs for the diagnosis of PD.*

	Warning signs – "red flags"
1.	Rapid progression of gait impairment requiring regular wheelchair use within 5 years of the onset of the disease
2.	Complete absence of progression of motor symptoms or manifestations after 5 years or more, unless stability is related to treatment
3.	Early bulbar dysfunction: severe dysphonia or dysarthria (unintelligible speech most of the time) or severe dysphagia (requiring soft food, NG tube or gastrostomy feeding) within the first 5 years of the disease
4.	Inspiratory respiratory dysfunction: either daytime or night-time inspiratory stridor or frequent inspiratory sighs
5.	Severe autonomic dysfunction within the first 5 years of the disease. This may include: a. orthostatic hypotension – orthostatic blood pressure reduction within 3 minutes of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic pressure, in the absence of dehydration, medications or other diseases that could plausibly explain autonomic dysfunction, or b. severe urinary retention or urinary incontinence within the first 5 years of the disease (except for prolonged or small amounts of stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be caused by prostate disease and must be associated with erectile dysfunction
6.	Recurrent (>1/yr) falls due to impaired balance within 3 years from the onset of the disease
7.	Disproportionate anterocollis (dystonic) or contractures of the arms or legs within the first 10 years of the disease
8.	Absence of any of the common non-motor manifestations of the disease despite the 5-year duration of the disease. These include sleep dysfunction (insomnia, excessive daytime sleepiness, REM sleep behaviour disorder), autonomic dysfunction (constipation, urinary urgency during the day, symptomatic orthostasis), hyposmia, or psychiatric manifestations (depression, anxiety, or hallucinations).
9.	Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (except mild reflex asymmetry and isolated Babinski sign)
10.	Bilateral symmetrical parkinsonism. The patient or their caregiver reports a symmetrical onset of symptoms and no side predominance is observed on objective examination [24, 32, 33, 37, 38, 40].

Within the differential diagnosis of parkinsonian syndromes, idiopathic PD accounts for approximately 80% of all causes of parkinsonism. The other 20% of cases are patients with so-called atypical parkinsonism, which is characterized by specific features (early falls, cerebellar symptoms, autonomic dysfunction, vertical gaze palsy, poor response to dopaminergic therapy, dementia) or secondary symptomatic parkinsonism [33, 40]. These include sporadic diseases of neurodegenerative aetiology such as progressive supranuclear palsy (PSP), multisystem atrophy (MSA), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB) [40]. and secondary parkinsonian syndromes such as [(vascular parkinsonism, drug-induced parkinsonism, parkinsonism in normal pressure hydrocephalus, posttraumatic parkinsonism, postencephalitic parkinsonism, intoxication parkinsonism (due to exogenous toxins such as carbon monoxide, manganese, methanol or endogenous toxins, for example copper in Wilson's disease or calcium in Fahr's disease), parkinsonism in brain tumours [33, 40].

Regarding the diagnosis of PD in the sense of neuroimaging methods, we find mostly non-specific, age-appropriate findings with MRI and CT. Rather, these tests serve to differentiate PD from other causes of parkinsonism. DaTSCAN shows reduced binding of ^{123}I-ioflupane in the presynaptic part of the nigrostriatal junction, which makes it possible to distinguish PD from other non-neurodegenerative causes of parkinsonism, such as drug-induced parkinsonism, or also from other tremor-dominant diseases, especially essential tremor [2, 8, 33, 41].

2.2. Method of Examination and Set of the Examined Patients

The aim of our retrospective study was to evaluate ^{123}I-Ioflupane brain SPECT examination using morphological and semiquantitative evaluation of scintigraphic findings in patients with suspected PD in the early stage of the disease and establishing a definitive diagnosis in the advanced stage of the disease.

The patient comes to the examination in the morning on an empty stomach. In the evening and in the morning before the examination, and in the evening after the examination, they take 2 tablets of Tyrozol (they are used to block the thyroid gland). Prior to that, we rule out iodine allergy in the patient through anamnesis. The radiopharmaceutical is administered parenterally into a vein at a dose of 185 MBq ^{123}I-Ioflupane. After application, the radiopharmaceutical spreads in the body through the bloodstream and accumulates in the striatum, where it binds to the structures of the carrier.

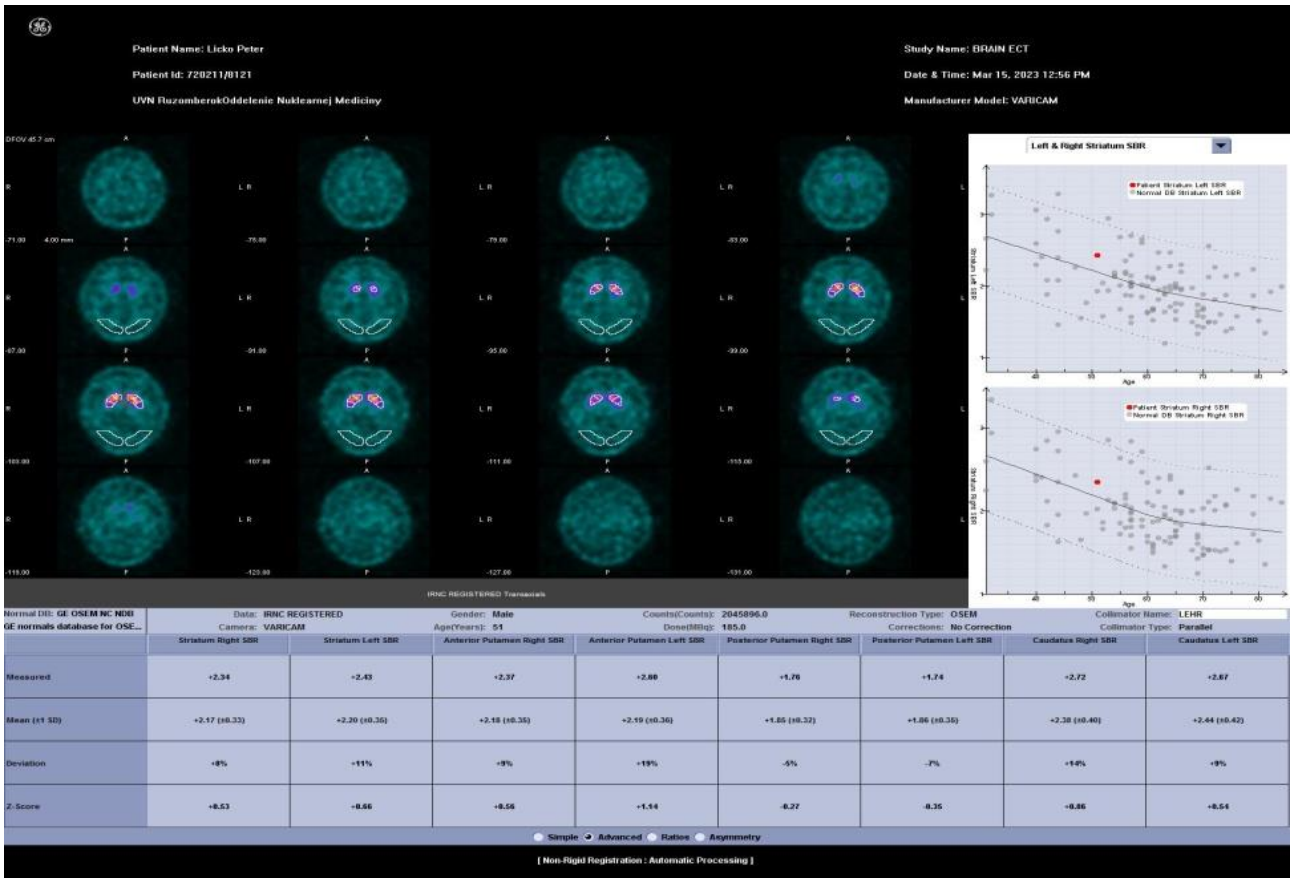


Figure 5. *Normal finding- morphological evaluation on the left, semiquantitative evaluation on the right in corpus striatum (BG).*

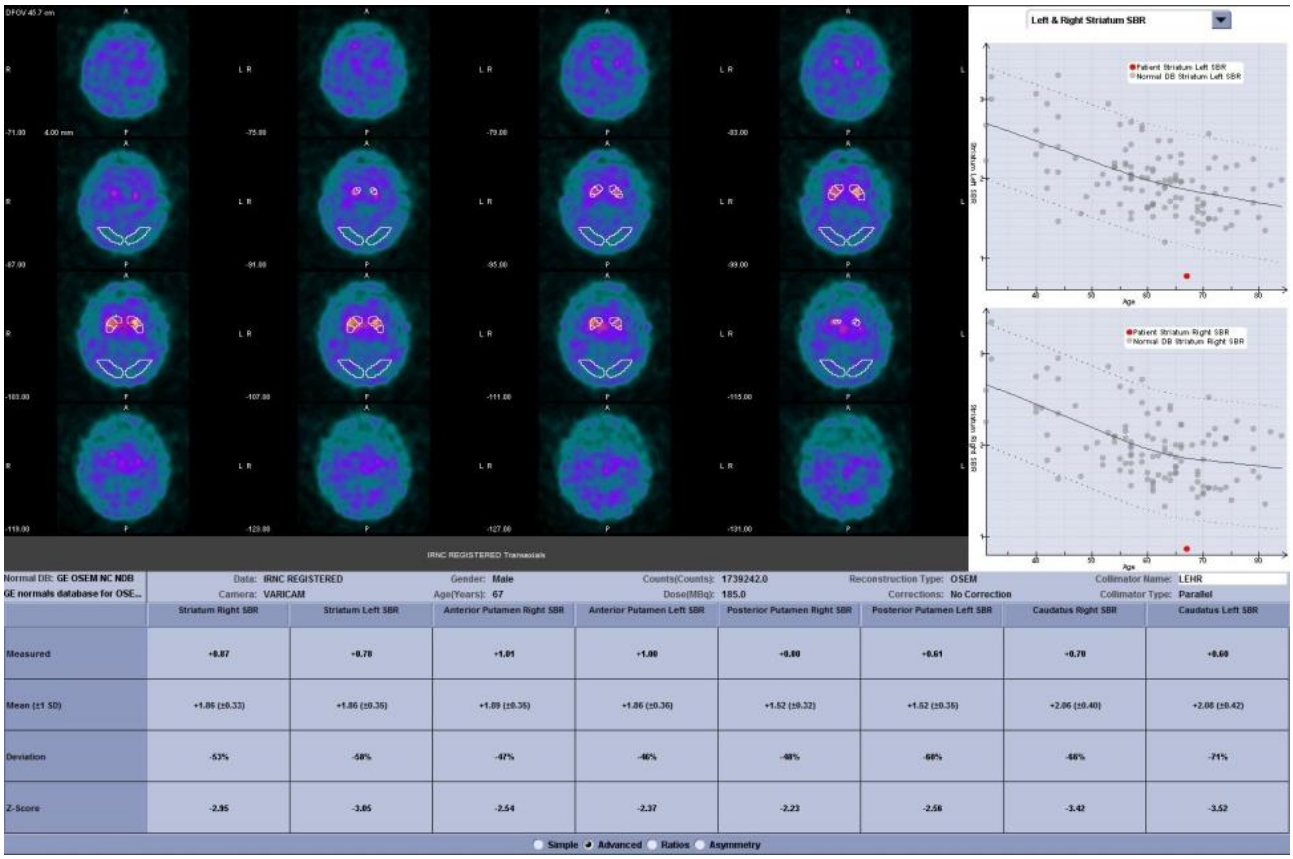


Figure 6. *Reduction of dopamine transport path during morphological and semiquantitative evaluation in corpus striatum (BG).*

SPECT examination of the brain is performed between 3 and 6 hours after its application. The radiopharmaceutical is quickly excreted from the blood, only 5% of the administered radioactivity remains in the bloodstream 5 minutes after application. Absorption of the radiopharmaceutical in the brain is fast, reaching 7% of the administered radioactivity 10 minutes after application. About 30% of radioactivity in the brain is absorbed in the striatum. During the examination, the patient lies on their back. We try to achieve the smallest possible radius of rotation of the gamma camera detector by bringing it closer to the patient's head and moving the table. The examination was performed with a gamma camera GE Millennium VG Hawkay option and evaluation software Xeleris (version 4.1) with recording parameters matrix 128 x 128, number of slides 64 (120) every 45 seconds. When the transport dopaminergic system is intact, the basal ganglia appear in the form of crescent-shaped formations. In primary parkinsonism, the basal ganglia appear atypically (reduced spherical formations). Indices during semi-quantitative evaluation are reduced (Figures 5, 6).

In the years 2006-2022, we examined 1050 patients with a presumed diagnosis of PD at the nuclear medicine clinic of the SNP Central Military Hospital in Ruzomberok. There were 469 (45%) men and 581 (55%) women in the examined group.

From the total group of 1050 (100%) individuals, in men there were normal findings in 129 individuals (12%), Parkinson's disease in 340 (33%), of which 50 (15%) male individuals had only incipient changes, detected during semi-quantitative evaluation indexes. In women, normal findings were found in 219 (21%) of those examined, Parkinson's disease was found in 362 (34%), of which incipient changes were found in 72 (20%) (Figure 7).

In the evaluation of a group of 469 (100%) men, in 129 (28%), the scintigraphic findings did not indicate the presence of PD, in 340 (72%) a pathological finding was found, indicative of PD. From the number of pathological findings, in 50 (15%) men deviations were found in the semi-quantitative evaluation of the findings, which we evaluated as changes of a timely nature, indicative of PD.

In the evaluation of a group of 581 (100%) women, scintigraphic findings were normal in 219 (38%), pathological findings indicating the presence of PD were found in 362 (62%) women. From the number of pathological findings in 72 (20%) women, deviations were found in the semi-quantitative evaluation of the findings, which we evaluated as an early stage of PD.

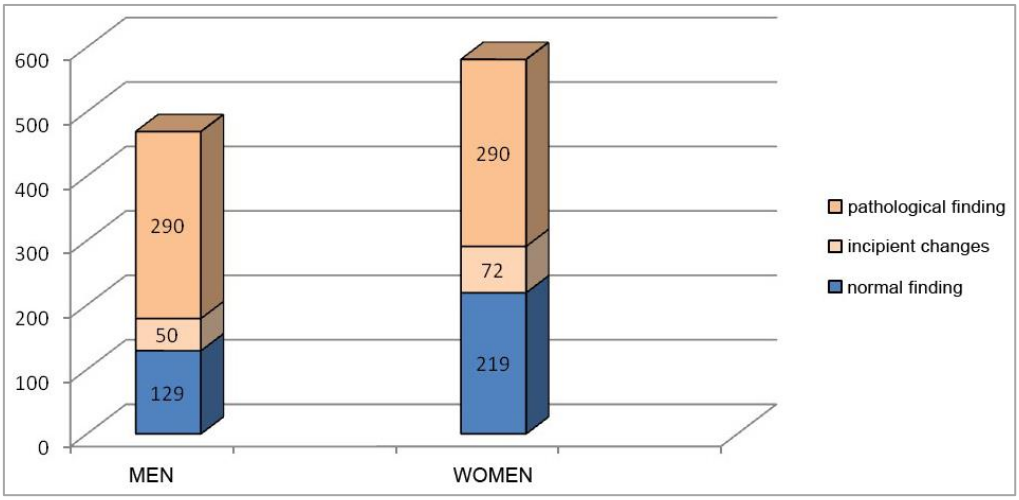


Figure 7. *Results of normal and impaired findings in ^{123}I-Ioflupane (DaTSCAN) examination. Normal results- no Parkinson's disease was found, pathological results- impaired transport system of dopamine was found. Incipient changes- deviations found during semiquantitative evaluation.*

When dividing the 1050-member group by age, the group under 55 years of age consisted of 285 individuals (27%), 55-75-year olds 492 individuals (47%) and over 75 years there were 273 individuals (26%).

In the group of patients younger than 55 years, there is a group of 33 individuals aged 35-40 (12%), namely 24 (8%) men and 9 (3%) women. In the men of this group, there were 6 (2%) individuals with normal findings and 18 (6%) individuals with pathological findings. In women, there were 7 (2%) individuals with normal findings and 2 (0.7%) women with pathological findings.

In the group of 285 individuals under the age of 55, we found pathological findings in 218 (76%) and normal findings in 67 (24%) individuals. In the group of 492 patients aged 55-75, we found pathological findings in 336 (68%) individuals, normal findings in 156 (32%) individuals. In the group of 273 patients older than 75 years, we found a pathological findings in 148 (54%) individuals, a normal findings in 125 (46%) individuals (Figure 8).

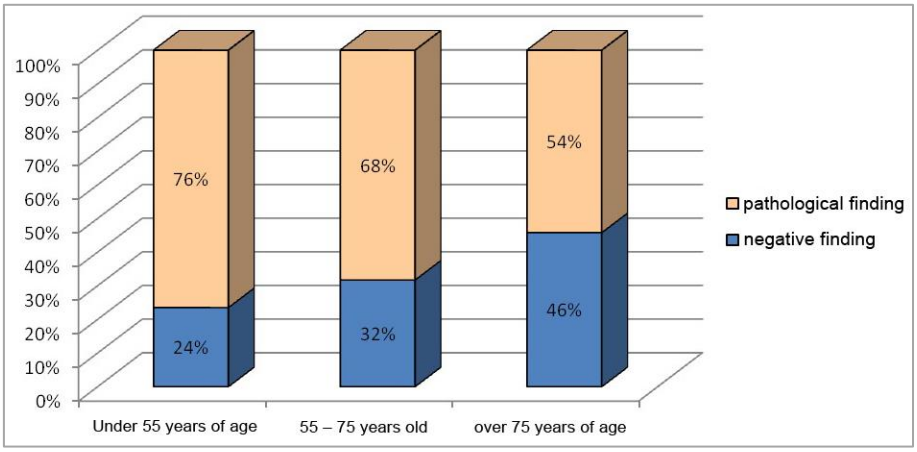


Figure 8. *Group of 1050 patients examined with ^{123}I-Ioflupane divided by age to groups with normal and pathological findings.*

From the total number of 702 pathological findings, a pathological finding in individuals under 55 years of age was found in 218 (31%), in 55-75 year olds in 336 (48%) individuals, in individuals older than 75 years in 148 (21%).

From the group of 1050 patients, in addition to the ^{123}I-Ioflupane examination, 180 patients also underwent a regional cerebral perfusion (rCP) examination using the SPECT radiopharmaceutical ^{99m}Tc-HMPAO (hexamethyl-propylene amino oxime). In this group, 150 individuals had a pathological finding indicative of PD, 30 individuals had a normal finding in the ^{123}I-Ioflupane examination. The age of the examined persons ranged from 65 years and above.

In patients with a positive finding indicating the presence of PD in the ^{123}I Ioflupan examination, changes in regional cerebral blood flow in the BG area were detected in various degrees in only 38 (25%) patients. In patients where perfusion disorders were found in different areas of the cerebral hemispheres, the clinical figure was not typical of multisystem atrophy, progressive supranuclear palsy, or corticobasal degeneration. Elderly people are often comorbid and there are many diseases that can affect not only the clinical findings, but also glucose metabolism in neurons and the blood flow, which is directly proportional to this. Examination of the regional blood flow of the brain shows the state of blood circulation, which depends on the state of metabolism at the intracellular level (Figure 9).

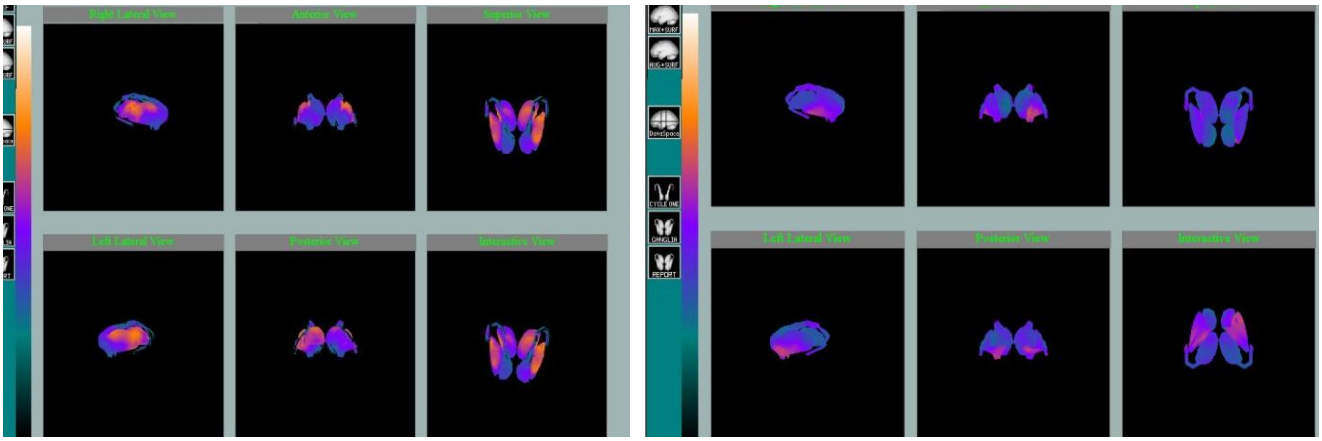


Figure 9. *Regional cerebral perfusion examination of BG and thalamus regions by ^{99m}Tc HMPAO. Normal perfusion findings on the left side, reduced perfusion on the right side.*

In patients with suspected Parkinson's disease, we also examined the ANS, on the one hand by examining the heart rate variability (HRV) of RR-intervals [15]. and on the other hand by examining the adrenergic innervation of the myocardium after the application of 100-185 MBq ^{123}I-Adreview intravenously [10, 12, 14, 22, 42]. Subsequently, planar projections of the chest were taken after 15 minutes, after 4 and after 24 hours after administration of the radiopharmaceutical. During the examination after 4 hours, the examination was also performed using the SPECT method, resulting in reconstructed SPECT sections and polar maps of the heart. The assessment of the regional distribution of the radiopharmaceutical is performed visually (scale of normal accumulation to lack of accumulation for 5 segments tip, septum, front, side and bottom wall of the left ventricle). As a

global indicator of ^{123}I-Adreview accumulation, the heart/mediastinum index (HM4) is determined after 4 hours and after 24 hours (HM24) after administration of the radiopharmaceutical and the rate of radiopharmaceutical washout from the myocardium (washout-relative change in the average activity before the heart in the time between the 15th minute and checks in 4 and 24 hours). All parameters measured in Parkinson's patients are lower than in healthy individuals. The examination was performed with a gamma camera GE Millennium VG Hawkeye option, evaluation software eNTEGRA (version 2.5302) with matrix recording parameters 128x128, number of slides 64 (120) every 45 seconds.

In 97 patients with proven Parkinson's disease, we performed an examination of cardiac autonomic neuropathy with Ewing's tests and an examination of HRV with spectral analysis. At the same time, we performed resting myocardial perfusion scintigraphy with ^{99m}Tc tetrofosmin (Myoview) in these individuals. In 32 patients from this group, we also performed a ^{123}I-Adreview myocardial examination.

From a group of 97 patients with Parkinson's disease, during the examination of cardiac autonomic neuropathy with Ewing's tests and during the examination of HRV with spectral analysis, we found a pathological finding in 83 individuals.

During the scintigraphic examination of resting myocardial perfusion with ^{99m} Tc tetrofosmin, no more serious perfusion changes were detected. When examining the adrenergic innervation of the myocardium with ^{123}I-Adreview, we found changes in the distribution of ^{123}I-Adreview in the myocardium of different sizes. These were changes of minimal extent up to the state where the myocardium of the left ventricle did not appear at all (Figures 10, 11, 12).

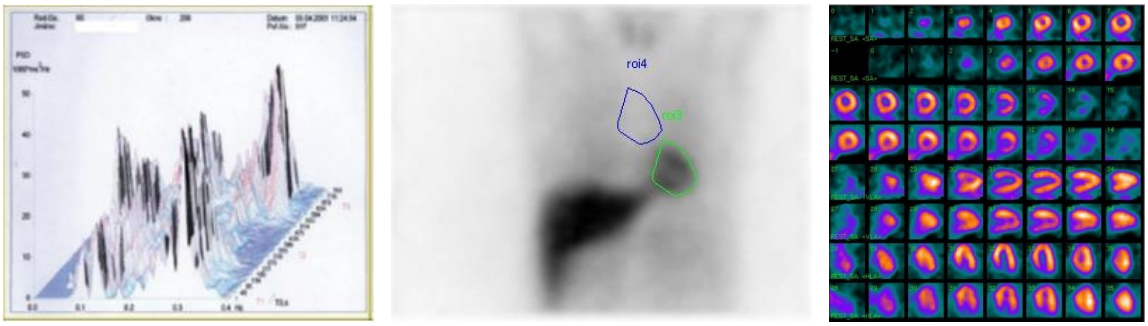


Figure 10. *Left part- Autonomous nervous system examination by the spectral analysis of the HRV (normal result). Middle part- Heart/mediastinum index - quantitative evaluation. Right part- Reconstructed SPECT slides: First line- ^{99m}Tc – tetrofosmin myocardial perfusion (Myoview), second line- adrenergic innervation of myocardium ^{123}I-Adreview. Both examinations with normal findings.*

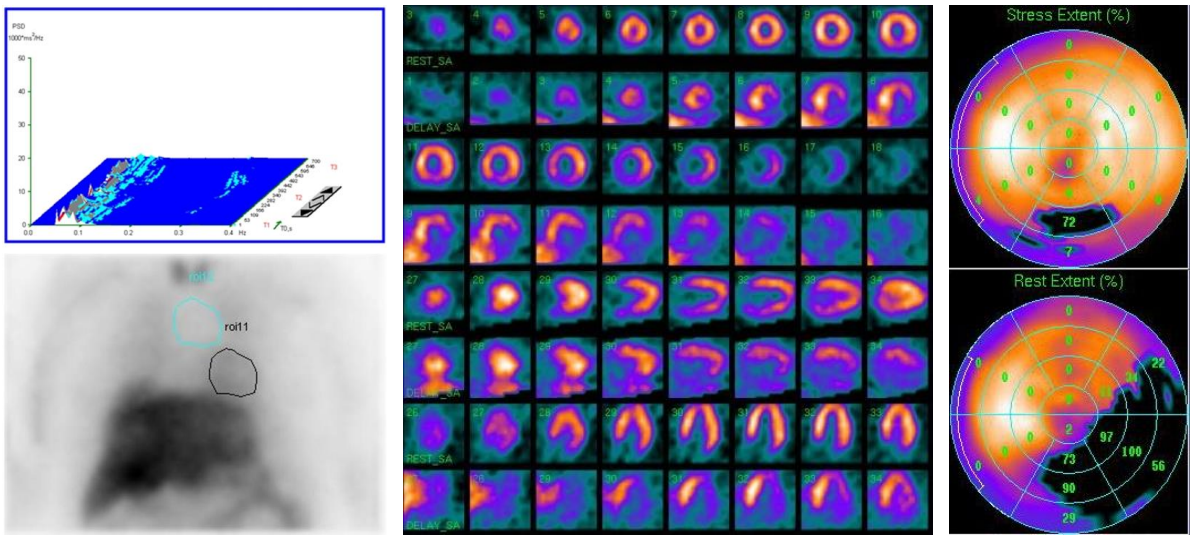
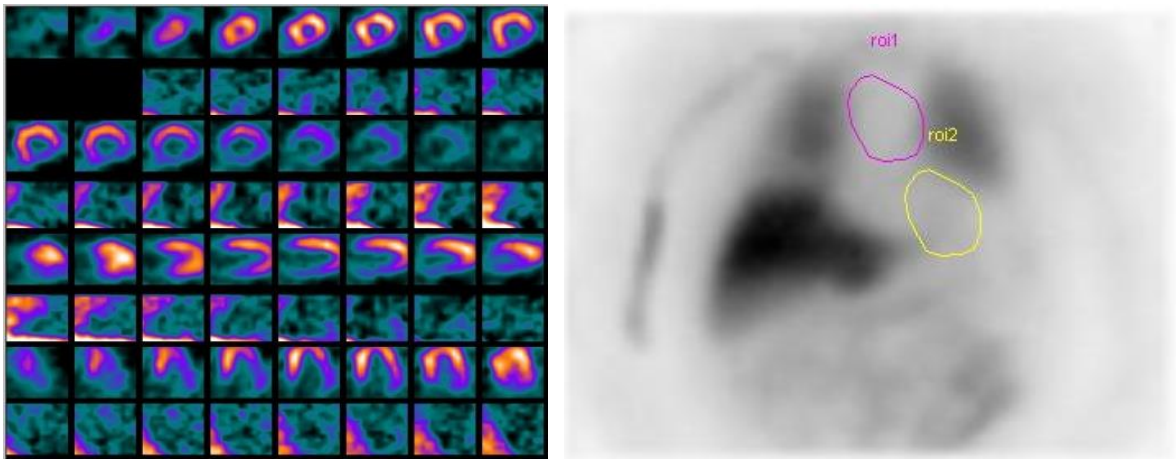


Figure 11. *Left upper part- Autonomous nervous system examination by the spectral analysis of the heart rate variability (developed autonomous neuropathy).*

Left lower part- Heart/mediastinum index - quantitative evaluation
Middle part- Reconstructed SPECT slides with polar map (perfusion/viability examination in upper part, adrenergic innervation of myocardium ^{123}I-Adreview in lower part)
Right part- Reconstructed SPECT slides: First line- ^{99m}Tc – tetrofosmin myocardial perfusion (Myoview) with normal finding, second line- adrenergic innervation of myocardium ^{123}I-Adreview.



Right part- Heart/mediastinum index - quantitative evaluation

Figure 12. *Left part- Reconstructed SPECT slides: First line- ^{99m}Tc – tetrofosmin myocardial perfusion (Myoview) with normal finding, second line- adrenergic innervation of myocardium ^{123}I-Adreview. No image of the left ventricle present, severe impairment of the sympathetic innervation.*

2.3. Discussion

Parkinson's disease is a progressive neurodegenerative disease. Various other damages in the BG area are also manifested by similar PD symptomatology. These are drug-induced parkinsonism, parkinsonism in normotensive hydrocephalus, vascular parkinsonism, Fahr ś syndrome, progressive supranuclear palsy, multiple system atrophy, post-traumatic states, post-infectious states, etc.

In these disease states, treatment with classic antiparkinsonian drugs is ineffective or the effect of the treatment is minimal and short-lived. In clinical practice, to distinguish these conditions from PD, we use a specific diagnostic method, aimed at examining the state of dopamine transport proteins at presynaptic terminals in the BG area using the radiopharmaceutical ^{123}I- Ioflupane, SPECT examination of the brain [33, 40].

The exact distinction of PD from PS of other causes has several meanings:

1. Early diagnosis of PD allows us to start adequate treatment for the patient with all its medical and social aspects.
2. In case PD is excluded, but with existing parkinsonian symptomatology, we must look for another cause of these manifestations, which is of great importance from the point of view of treatment, prognosis and patient care.
3. In the case of the presence of PS, we do not expose the patient to long-term treatment with antiparkinsonian drugs, which often have serious side effects and little or no therapeutic effect.
4. We do not perform treatment on the patient that is financially demanding and the treatment effect is minimal.
5. For a patient with PS, we can provide appropriate treatment in time, especially rehabilitation and social support [43, 44].
6. The possibility of confirming and ruling out the comorbidity of psychosis and PD in the case of persistence of parkinsonian symptomatology during long-term antipsychotic treatment, by SPECT examination of the distribution and density of the dopamine transporter, we can correctly guide the patient's treatment with both antipsychotics and antiparkinsonian drugs [45].

During rCB SPECT ^{99m} TcHMPAO examination, changes may indicate:

1. Parkinson's disease (PD): normal perfusion.
2. Multisystem atrophy (MSA): reduced striatal and cortical perfusion.
3. Progressive supranuclear palsy (PSP): reduced frontal cortical perfusion.

Corticobasal degeneration (CBD): asymmetric cortical and BG hypoperfusion [2, 10, 14].

Parkinson-plus syndromes were not diagnosed in our group.

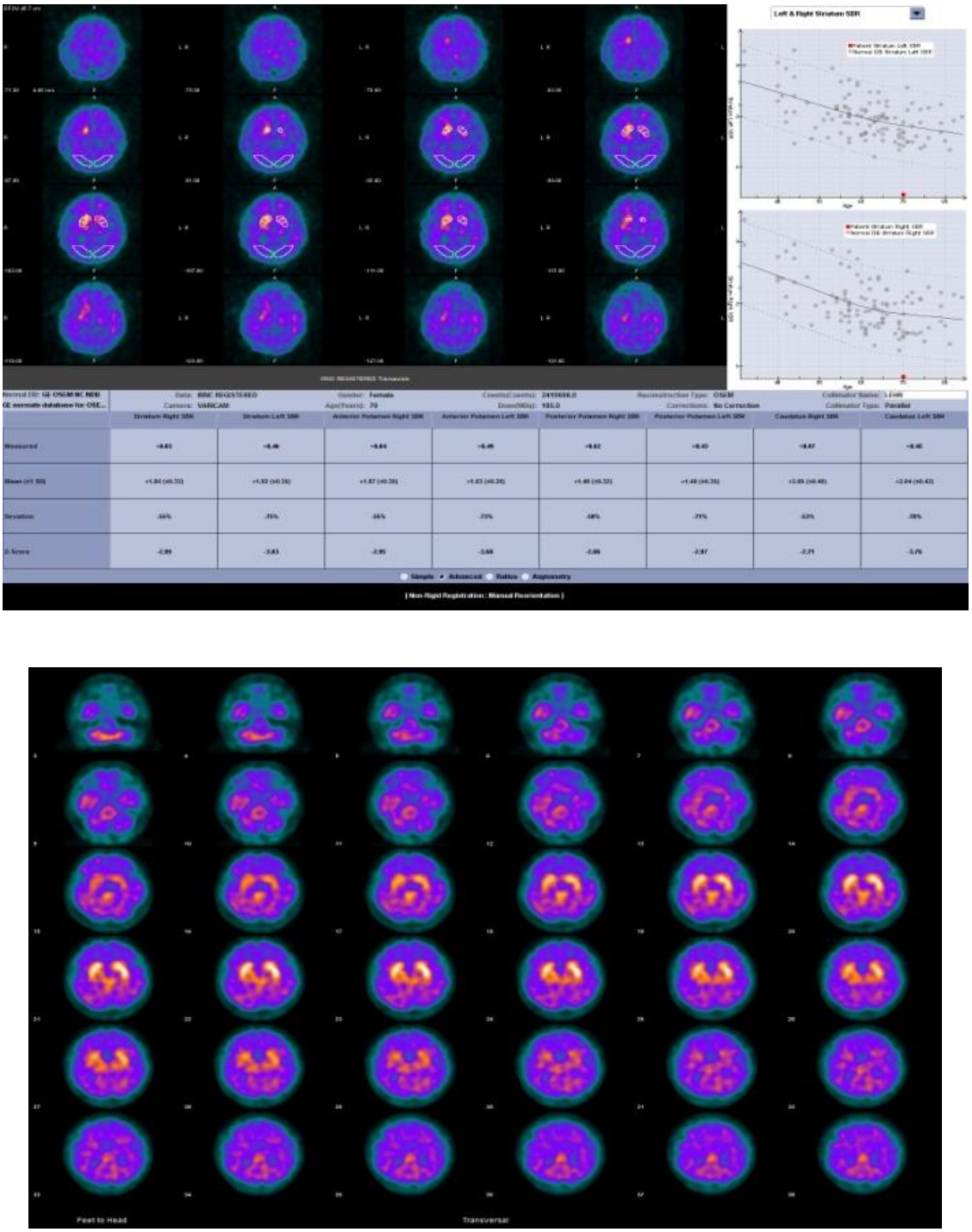
From a group of 97 patients with Parkinson's disease, during the examination of cardiac autonomic neuropathy with Ewing's tests and during the examination of HRV with spectral analysis, we found a pathological finding in 83 individuals.

During the scintigraphic examination of resting myocardial perfusion with ^{99m} Tc tetrofosmin, no serious perfusion changes were detected. When examining the adrenergic innervation of the myocardium with ^{123}I-MIBG, we found changes in the distribution of ^{123}I-MIBG in the myocardium of different extent. These were changes of minimal extent up to the state where the myocardium of the left ventricle did not appear at all (Figures 10, 11, 12).

In the diagnosis of PD, a pathological finding can be detected during an examination with ^{123}I Ioflupane, and it does not have to be Parkinson's disease, but diseases that, in terms of the differential diagnosis of parkinsonism, are classified as

atypical parkinsonism, the so-called Parkinson-plus syndromes. Atypical Parkinsonian syndromes include multisystem atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Clinically, they may resemble the symptoms of Parkinson's disease, but the response to dopaminergic treatment is poor.

An additional examination in these patients can be imaging of the postsynaptic dopaminergic system using ^{123}I-IBZM (iodobenzamide) SPECT. In atypical parkinsonism, there is a reduction in the accumulation of the radiopharmaceutical at postsynaptic receptors, in Parkinson's disease this finding is normal (Figure 13). [18, 36].



Right part- ^{123}I-IBZM examination- normal finding on basal ganglia.

Figure 13. *Left part- ^{123}I Ioflupane examination - pathological finding on basal ganglia.*

As part of the differential diagnosis between Parkinson's disease and MSA, an examination of the peripheral state of

the ANS can sometimes help, by examining HRV with Ewing's tests or spectral analysis, followed by adrenergic innervation of the myocardium with ^{123}I -Adreview. In patients with advanced Parkinson's disease, signs of degeneration of the peripheral ANS are typical. In patients with MSA, the autonomic disorder is of a central type, the peripheral autonomic innervation is intact [10, 14].

3. Conclusion

PD and PS often have similar clinical symptoms, but they form separate clinical entities that often respond differently to antiparkinsonian treatment. While the response of PD patients to this treatment is usually good, in PS the response to antiparkinsonian drugs is short-lived or non-existent. Distinguishing PD from PS is therefore of great clinical, therapeutic, prognostic and socioeconomic importance.

As it follows from our file, in the case of 1050 individuals with certain clinical manifestations of parkinsonism, when examined with ^{123}I Ioflupane, in 348 (33%) individuals, the findings were normal, i.e. it was not PD. In these patients, a significant and long-term effect cannot be expected from treatment with antiparkinsonian drugs. On the other hand, in patients with unclear clinical symptoms, morphological and semi-quantitative evaluation of scintigraphic findings that confirmed the presence of PD is of great benefit, which was the case in 702 (67%) patients in our group. Furthermore, in 122 (12%) patients with atypical clinical symptoms, with early parkinsonian symptomatology, even during the examination with ^{123}I-Ioflupane, changes were detected only during semi-quantitative evaluation, which enabled the early initiation of adequate treatment. From the above results, it follows that for the confirmation of the definitive diagnosis and for the initiation of adequate treatment of PD, examination using ^{123}I Ioflupane (DaTSCAN) is of irreplaceable importance. Examination of cardiac autonomic neuropathy in patients with Parkinson's disease is also of great clinical importance in differential diagnosis, but also for the prognosis of Parkinson's disease.

Abbreviations

ANS	Autonomic Nervous System
BG	Basal Ganglia
CBD	Corticobasal Degeneration
CERETEC	Radiopharmaceutical 99mTc-HMPAO (Hexamethylpropylenaminooxim)
CT	Computed Tomography
DaTSCAN	Radiopharmaceutical 123I-Ioflupane
LBD	Dementia with Lewy Bodies
fMRI	Functional Magnetic Resonance
IBZM	Radiopharmaceutical 123I-Iodobenzamid
LB	Lewy Bodies
MDS	Movement Disorders Society
MIBG	Radiopharmaceutical 123I-Metaiodobenzylguanidine
MRI	Magnetic Resonance
MSA	Multisystem Atrophy
NMS	Non Motor Symptoms
PET	Positron Emission Tomography
PD	Parkinson's Disease
PSP	Progressive Supranuclear Palsy
rCP	Regional Cerebral Perfusio
SNS	Sympathetic Nervous System
SPECT	Single Photon Emission Computed Tomography
HRV	Heart Rate Variability

Author Contributions

Anton Lacko: Methodology, Validation

Stefan Madarasz: Data curation, Methodology, Supervision

Kamil Kolejak: Conceptualization, Methodology, Supervision

Jozef Babecka: Conceptualization, Methodology, Visualization

Lucia Lackova: Conceptualization, Formal Analysis, Supervision, Visualization, Writing – original draft

Conflicts of Interest

The authors declare no conflict of interest.

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