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The Relationship between Periodontal Disease and Motor Impairment in the Course of Parkinson's Disease

Związek pomiędzy chorobami przyzębia a upośledzeniem ruchowym w przebiegu choroby Parkinsona

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: The incidence of Parkinson's disease and the severity of accompanying motor impairment increase significantly with age. The etiopathogenesis and progression of Parkinson's disease at the molecular level is associated with the production of cytokines and acute phase proteins, which are also typical for inflammatory diseases, such as periodontitis and gingivitis.

Objectives: The aim of the study was to assess the correlation between neurological parameters, the indices of periodontal status and systemic parameters of inflammation, as well as their change after treatment.

Patients/Methods: The presented study is a retrospective analysis of data obtained from medical histories and patient charts. Charts of 93 patients diagnosed with Parkinson's disease and periodontal diseases over the period 2015–2017 were selected. Sixty-one of these patients received periodontal treatment: professional scaling, root planning – SRP and periodontal pockets rinsing with 3% H_2O_2 and constituted a study group. Additionally, the patients were instructed to use a 0.2% chlorhexidine mouthwash. The other 32 patients, who were not periodontally treated, formed a control group. Both groups continued their anti-parkinsonian treatment.

Results: The mean pocket depth at the baseline was 4.0 mm (SD 0.9 mm), mean bleeding index was 56.2%, and 63.9% of patients presented tooth mobility grade II or III. A significant correlation between periodontal and neurological parameters was observed at the baseline. After periodontal treatment, an improvement of both periodontal parameters and those related to the Parkinson's disease was observed in the study group. Those periodontally treated exhibited lower number of anti-parkinsonian medicines, lower number of falls, as well as better results in10-m walk test and timed-up-and-go test, as compared to the control group. The improvement was observed both 3 and 9 months after the end of treatment.

Keywords: **Parkinson's disease, periodontitis, motor impairment, CRP**

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INTRODUCTION

Neurodegenerative diseases constitute a significant health problem for the aging societies of Europe and the USA [8, 12]. Falls and difficulties in maintaining balance are related to the processes of base nuclei degeneration in the course of Parkinson's disease and progressive supranuclear palsy in Parkinsonian syndrome and dementia tauopathies [31]. Parkinson's disease, along with dementia of the Alzheimer's type, belong to the most common degenerative disorders in elderly people [27]. The incidence of Parkinson's disease and severity of accompanying cognitive impairment increases significantly with age. While in the age group of 55–65 years, a mean number of 0.3 new cases per 1000 of general population is observed, in the group above 65 years this index increases to 4.4 new cases per 1000 people. Parkinson's disease occurs in the population with an overall frequency of 0.15–0.3, and more frequently in men (1: 1, 5). Parkinson's disease risk factors include genetic predisposition. The description of the mutation in the gene encoding α-synuclein had a significant impact on understanding the etiopathogenesis of the disease. On the basis of prospective studies, it was found that about 10% of Parkinson's disease cases are genetically determined by triplications of nucleotides in PARK1-13 genes and by LRRK2 gene mutations [26]. The occurrence of clinical symptoms of parkinsonism is also influenced by the phenomenon of gene penetration, maternal imprinting and environmental factors, including the following: pesticides, heavy metal salts, and chronic inflammatory diseases of the central nervous system (CNS) [5].

The basic symptoms of parkinsonism are the following: bradykinesia, which consists in slowing down and reducing the number of arbitrary and precise movements, akinesia, and gait with small steps. Then there is plastic muscular stiffness and resting tremor. Due to the spectrum of degenerative processes, vegetative symptoms develop, such as excessive salivation and thermoregulation disorders. The postural instability, which is characteristic for patients with Parkinson's disease, results from a deficiency of dopamine in substantia nigra and striatum, and, consequently, from increased impulse of neurons that inhibit the thalamic nuclei. The absence of physiologic synkinesia and the presence of akinesia of upper limbs favor the manifestation of such a posture and such gait disorders as:

- propulsion and acceleration of gait with small steps, so-called „festinating gait", with a tendency to fall forward,
- falling backwards,
- oblique or side falling [19].

The risk factors of postural instability and falls include the following: the occurrence of falls and skeletal injuries in the past, vestibulo-cochlear disorders, sudden freezing of gait, emotional disorders, including depression and fear of falling [28].

Periodontitis is one of the most common chronic inflammatory diseases in the population. The clinical examination of periodontitis includes the assessment of the amount of bacterial biofilm (called plaque), bleeding of gums upon probing, presence of periodontal pockets, clinical attachment loss and tooth mobility. An important role in the pathogenesis of periodontitis play Gram(-) bacteria, such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonasgingivalis*, *Treponema denticola*, *Tannerella forsythia*. In the periodontal pocket, these bacteria stimulate a spectrum of proinflammatory cytokines such as IL-1β, Ll-6, TNF-α, IL-33. Inflammatory mediators affect periodontal tissues and act systemically through the circulatory system and hepatic synthesis of acute phase proteins [14].

The inflammatory reaction, both local and generalized, in the course of periodontitis, may affect CNS neurons through humoral and neuronal interactions [10, 16]. The humoral route is associated with crossing the blood-brain barrier by inflammatory factors. The barrier regulates the penetration of substances from the blood into the cerebrospinal fluid. Herrera et al. observed that infections may cause damage to the barrier, resulting in proinflammatory cytokines from blood vessels penetrating the cerebrospinal fluid [18]. This leads to the activation of CNS glial cells, leading to the induction of neurotoxic processes and release of cytotoxic compounds, such as free oxygen radicals (ROS), nitrous oxide, iNOS (inducible nitric oxide synthase) and pro-inflammatory cytokines: IL-1β, IL-6, IL-8, IL-12, IL-15, TNF-α. As a result, these reactions lead to neurodegenerative processes, damaging the midbrain dopaminergic cells [17].

The neuronal pathway is the second most important mechanism of inflammation propagation between the peripheral system and the CNS. In the course of systemic inflammatory response, autonomic ganglion neurons are activated, and peripheral and cranial nerve signals are propagated. This mechanism increases the expression of proinflammatory cytokines in the midbrain. The described phenomena were observed during Alzheimer's dementia and in Parkinson's disease [22]. Both Alzheimer's disease and other neurodegenerative diseases, including Parkinson's disease, belong to α-synucleinopathies. Given the similarities between the pathogenesis of Alzheimer's disease and Parkinson's disease, it seems plausible, that the general inflammatory processes, including those related to periodontal diseases, affects the course of Parkinson's disease. Some authors do indeed suggest

a correlation between generalized inflammation and the occurrence of neurodegenerative diseases [24], still the relationship between these two entities remains for the most part unknown.

The aim of the presented study was to assess the correlation between neurological parameters, the periodontal status and systemic parameters of inflammation, as well as their change after periodontal treatment.

PATIENTS AND METHODS

The Study Group

The presented study is a retrospective analysis of data obtained from medical histories and patient charts. They were under the care of Neurozentrum Wien Alte Donau, Wien, Kratochwjlestraße 12, Austria. If the anamnesis suggested the presence of periodontal disease (tooth mobility, bleeding gums), the patients were offered a dental examination, periodontal charting and treatment in a cooperating dental practice located in Wien (Zahnarztpraxis Wien Simmering, Wien, Sangerstrasse 10, Austria). Such a suggestion was noted in the medical record of the patients. Charts of 93 patients diagnosed with Parkinson's disease and suspected periodontal disease over the period 2015–2017 were selected for this study.

According to the analysis of dental records, 61 of these patients (27 females and 34 males), who received periodontal diagnosis and treatment, constituted the test group. The other 32 patients, who were not periodontally treated, formed a control group. Both groups continued their anti-parkinsonian treatment. The dental periodontal examination included the assessment of the following: number of teeth, approximal plaque index, bleeding index (in four points around each tooth) and pocket depth (six points around each tooth) as well as tooth mobility degree.

No formal periodontal diagnosis was made at this stage, as the main aim of the dental and periodontal treatment was to relieve the symptoms and to eliminate the inflammatory state that is known to aggravate the course of many systemic conditions, including neurodegenerative disorders. No research project was planned by the medical and dental staff at this stage. Still, the periodontal examination confirmed the presence of periodontal inflammation, as defined by bleeding index ≥ 10%, in all the patients. Moreover, the retrospective analysis of the periodontal charts revealed the presence of pocket depths exceeding 4 mm in all the patients.

The treatment protocol included non-surgical periodontal procedures: professional scaling and root planing (SRP), periodontal pocket rinsing with 3% H_2O_2. Mechanical plaque control techniques were extended for chemical agents; therefore, the patients were instructed to use 0.2% chlorhexidine mouthwash, since it is the gold standard in antiplaque protocols.

The inclusion criteria were the following: Parkinson's disease (PD) diagnosed at least three years before the periodontal treatment, receiving at least one antiparkinsonian drug from the following groups: dopamine agonists, anticholinergics, COMT inhibitors, dopaminergic receptor agonists, MAO-B inhibitors and NMDA receptor antagonists. The patients were subjected to physiotherapeutic treatment, twice a week for 45 min (Bobath rehabilitation method). The study included patients with at least one fall during the 3 months preceding the initiation of periodontal treatment or denial to undergo such the treatment. All patients qualifying for the study suffered from gingivitis and/or chronic generalized periodontitis: mild, moderate or severe.

Patients were excluded from the study if they presented at least one of the following: diagnosed Parkinsonian syndrome secondary to cerebrovascular diseases, posttraumatic complications, senile dementia, secondary polyneuropathy (toxic damage to axonal fibers), presence of cardiovascular diseases, including arrhythmias, atrial fibrillation, atrioventricular block Mobitz II and III, acute and chronic inflammation of the airways and urinary tract, and dental treatment within one month preceding the study.

Ethical statement

The project was approved by the Bioethics Committee of Warsaw Medical University (project identification code no. AKBE 91/2019). All the patients agreed to participate in the study by signing the informed consent form, which has been independently revised and approved by the Ethical Board.

Data collection

All the necessary data was extracted from the medical records of patients. The parameters describing the severity of Parkinson's disease included the following: number of medicines taken daily, number of falls in the last 3 months, 10-meter walk test, time-up-and-go test, UPDR III score and CRP level, as a measure of systemic inflammation. The periodontal parameters included bleeding index and pocket depth. The bleeding index was measured as bleeding on probing (BOP) at four sites of each tooth according to the Ainamo and Bay scale. Pocket depth (PD) was the distance from the free gingival margin to the bottom of periodontal pocket. The number of present teeth, tooth mobility and approximal plaque index (API) were assessed as well. The BOP and PD are part of the routine assessment of patients treated for Parkinson's disease and periodontal disease, respectively, recorded on a regular basis in the medical records.

Statistical analysis

The statistical analysis was carried out using the PQStat v. 1.4.4. software. A $\chi 2$ test and Mann-Whitney U test were used to compare the categorical and quantitative

Table 1. Characteristics of the test group and the control group

	Test group	Control group	Comparison
Number of individuals	61	*32*	–
Age (mean ±SD) *	range: 49–89 years 70.8 ±8.4	range: 54–83 years 69.8 ±8.0	p = 0.5875
Gender ** Female Male	27 (44.3%) 34 (55.7%)	11 (34.4%) 21 (65.6%)	p = 0.4843

Table 2. Periodontal status of patients at the study baseline

Test group		
Number of teeth [median (Q1–Q3)]		*9 (5–13)*
API [mean ±SD]		82.9% ±20.0 p.p.
Bleeding index [mean ±SD]		46.2% ±22.9 p.p.
Mean PD [mm] [mean ±SD]		4.0 ±0.9
Tooth mobility – percentage of patients	In total	60 patients (98.4%)
	grade II or III°	39 patients (63.9%)
	grade III°	12 patients (19.7%)

variables between the study and control group at the baseline as well as 3 and 9 months after periodontal treatment (or denial to undergo such the treatment). The correlation between the neurological parameters, the indices of periodontal status and systemic parameters of inflammation at the baseline was assessed by means of a multiple regression analysis, including correction for age. Finally, the correlation between the changes of neurological and periodontal parameters after treatment was assessed by means of Spearman's rank test.

RESULTS

The study included a total of 93 subjects, 61 of whom underwent periodontal treatment and 32 comprised the control group. The characteristics and comparison of these groups is presented in Table 1.

There were no significant differences between the study and control groups in terms of age, gender, or severity of Parkinson's disease at baseline (summary data on parameters describing Parkinson's disease is included in Table 4).

Table 2 presents the periodontal status of the test group. On average, the patients had 9 preserved teeth (interquartile range from 5 to 13). In the majority of the patients, a high level of plaque index, bleeding index and tooth mobility were observed. The average depth of periodontal pockets was 4.0 mm (SD 0.9 mm).

Due to a strong correlation of both periodontal and neurological parameters with age, the age of patients was also taken into account when assessing the correlation between the two groups of variables (Table 3).

After taking into account this common risk factor, a statistically significant yet weak correlation was observed between the motor functions of patients and the level of oral hygiene (API).

Further analysis included comparison of the values of parameters describing the severity of Parkinson's disease at the study baseline and after 3 and 9 months between the test and control group (Table 4).

Baseline values did not differ between the groups. After periodontal treatment, an improvement of four parameters was observed in the study group: the number of medicines, number of falls, 10-m walk test and timed-up-and-go test. The improvement was observed both 3 and 9 months after the end of treatment. As for the UPDRS III score and mean CRP level, improvement in these parameters was also observed after periodontal treatment; however, the differences between the study group and the control group were not statistically significant. Finally, the correlation between the improvement of parameters describing the severity of Parkinson's disease and the improvement of periodontal parameters after treatment was analysed (Table 5).

The analysis included all the evaluated indices with the exception of the number of teeth, which did not change during the study. Despite an improvement in most parameters describing the severity of Parkinson's disease after periodontal treatment, their change did not always correlate with improvement of periodontal status, and if such relationship existed – as for plaque, bleeding and tooth mobility indices – it was rather weak ($r \leq 0.3$). A significant correlation was also found between the improvement of the majority of neurological parameters and a decrease in CRP levels. Still, it has to be noted that the CRP level reflects general inflammation in the body and is not specific to periodontal diseases.

DISCUSSION

In the presented study, positive changes in both the state of periodontal tissues and some selected parameters of Parkinson's disease activity were observed after periodontal treatment. The reduction of bacteria in periodontal pockets, including the Gram(-) bacteria, which release i.a. lipopolysaccharides (LPS), could be one of the

Table 3. Correlation between periodontal and neurological status at the baseline, corrected for age (Multiple Regression Analysis – Standardized b-factor and p value for periodontal parameters)

	No. of medicines taken daily	No. of falls in the last 3 months	10-meter walk test [s]	Time up and go	UPDRS III score	CRP
No. of teeth	b = –0.23	*b = –0.14*	b = 0	b = –0.17	b = –0.17	b = 0.19
	p = 0.1650	p = 0.31	p = 0.9793	p = 0.1531	p = 0.1816	p = 0.2554
API	b = 0.28	b = 0.26	b = 0.23	b = 0.23	b = 0.23	b = –0.07
	p = 0.0585	p = 0.0352	p = 0.0129	p = 0.0341	p = 0.0386	p = 0.6219
Bleeding index	b = 0.04	b = 0.11	b = 0.12	b = 0.10	b = 0.07	b = –0.05
	p = 0.7896	p = 0.4465	p = 0.2577	p = 0.4088	p = 0.5554	p = 0.7573
Bleeding index	b = –0.06	b = –0.06	b = 0.06	b = 0.10	b = 0.10	b = –0.12
	p = 0.7057	p = 0.6535	p = 0.4966	p = 0.3750	p = 0.3700	p = 0.4120
Tooth mobility (grade II or III°)	b = 0.19	b = 0.26	b = 0.15	b = 0.18	b = 0.16	b = 0.03
	p = 0.2166	p = 0.0439	p = 0.1284	p = 0.1166	p = 0.1686	p = 0.8576
CRP	b = –0.03	b = 0.04	b = 0.13	b = 0.03	b = 0.06	–
	p = 0.7638	p = 0.6644	p = 0.0513	p = 0.7221	p = 0.5042	

Table 4. Assessment of changes in parameters describing the severity of Parkinson's disease after treatment

		Test group	Control group	Comparison of groups (Mann-Whitney U test)
No. of medicines taken daily [median, (Q1; Q3)]	Baseline status	2 (2; 3)	2 (2; 3)	p = 0.3882
	After 3 months	2 (1; 2)	2 (2; 3)	p = 0.0034
	After 9 months	2 (1; 2)	2 (2; 3)	p < 0.0001
No. of falls in the last 3 months [median, (Q1; Q3)]	Baseline status	1 (1; 2)	2 (1; 2)	p = 0.3053
	After 3 months	0 (0; 1)	2 (1; 2)	p < 0.0001
	After 9 months	1 (0; 1)	2 (2; 3)	p < 0.0001
Time up and go [mean ±SD]	Baseline status	7.4 ±0.8	7.4 ±0.7	p = 0.6416
	After 3 months	7.0 ±0.7	7.5 ±0.7	p = 0.0028
	After 9 months	7.1 ±1.0	7.6 ±0.7	p = 0.0007
UPDRS III score [median, (Q1; Q3)]	Baseline status	8.0 ±0.9	7.9 ±0.6	p = 0.7065
	After 3 months	7.6 ±0.8	8.0 ±0.7	p = 0.0026
	After 9 months	7.5 ±1.0	8.1 ±0.7	p = 0.0003
CRP [mean ±SD]	Baseline status	21 (19; 26)	20 (17; 24)	p = 0.1351
	After 3 months	19 (17; 24)	20 (18; 24)	p = 0.3821
	After 9 months	18 (16; 23)	20 (18; 24)	p = 0.1030
	Baseline status	0.9 ±1.0	0.6 ±0.6	p = 0.1803
	After 3 months	0.7 ±1.0	0.7 ±0.5	p = 0.3896
	After 9 months	0.8 ±0.9	0.7 ±0.6	p = 0.3047

Table 5. Assessment of a correlation between improvement of parameters describing the severity of Parkinson's disease and improvement of periodontal parameters (Spearman's rank correlation test)

Refers to change of listed parameters (m0-m3)	No. of medicines taken daily	No. of falls in the last 3 months	10-meter walk test [s]	Time up and go	UPDRS III score	CRP
API	r = 0	*r = 0.28*	r = 0.04	r = 0.24	r = 0.12	r = 0.04
	p = 0.9782	p = 0.0286	p = 0.7551	p = 0.0677	p = 0.3440	p = 0.7658
Bleeding index	r = –0.22	r = 0.04	r = 0.16	r = 0.30	r = 0.12	r = –0.06
	p = 0.0923	p = 0.7354	p = 0.2175	p = 0.0205	p = 0.3509	p = 0.6695
Mean PD	r = –0.21	r = –0.22	r = 0.02	r = 0.13	r = –0.03	r = –0.04
	p = 0.0990	p = 0.0871	p = 0.9002	p = 0.3285	p = 0.8388	p = 0.7420
Tooth mobility (grade II or III°)	r = –0.18	r = –0.09	r = 0.19	r = 0.27	r = 0.06	r = 0.10
	p = 0.1701	p = 0.4799	p = 0.1378	p = 0.0369	p = 0.6675	p = 0.4390
CRP	r = 0.27	r = 0.28	r = 0.27	r = 0.19	r = 0.26	–
	p = 0.0078	p = 0.0064	p = 0.0093	p = 0.0735	p = 0.0107	

mechanisms that impact progression of Parkinson's disease. The inflammation of periodontal tissues facilitates the passage of bacteria into the blood and leads to the systemic inflammatory reaction. According to other studies on neurodegenerative disorders, mainly Alzheimer's disease, this kind of systemic inflammatory reaction can damage the blood-brain barrier, leading to activation of microglial cells and damage of dopaminergic cells of substantia nigra [22, 24]. Some early studies indicate a similar pathogenesis of Parkinson's disease [11]. Therefore, prophylaxis and treatment of co-existing periodontal disease could not only improve oral health, but also slow down the progression of neurodegenerative processes.

The spectrum of disorders characteristic of parkinsonian syndromes includes increased muscle tone (hypertonia), tremor at rest, slowness of movements (bradykinesia) and disorders in postural muscles coordination. The first symptoms, by their mutual modulation, cause postural instability and their forward-flexed posture, by which they compensate the loss of balance, transferring at the same time the centre of gravity beyond the contour of their body axis and increasing the risk of falls [3].

Falls represent the most common cause of injuries in patients over 65 years age, not only in the group of patients suffering from Parkinson's disease [15, 20, 29]. One out of every three people over the age of 65 falls on average once a year [23]. In the course of parkinsonian syndromes, falls happen much more frequently [1]. Most patients diagnosed with Parkinson's disease fall once a month, 38% of them fall once a week and 13% even more frequently [25]. Wood et al. stated that 68% of patients affected by this disease fall at least once a year, and 46% of all the patients at least once every three months [2, 32]. According to Renteln-Kruse, 25% of patients require hospitalization after the fall [30]. Most of the patients present with femoral neck fracture and fracture of splanchnocranium, requiring life-saving osteosynthesis procedures [4]. The highest mortality is observed in the case of hip fractures and pericerebral hematomas [9]. In addition, it was proved that femoral neck fractures, compared to fractures of other skeletal parts, result in the deterioration of motor functions, reducing quality of life and leading to loss of social competencies [6, 13]. Falls and their consequences lead to a heavy burden on the national healthcare systems [21].

A study conducted by Block [6] showed that falls alone in the group of older people over 80 years of age cause a significant increase in the cost of living and are a major socio-economic burden for society. The studies carried out in the Netherlands proved that in the age group above 85 years, the falls were the third most frequent reason for hospitalization and accounted for 5.9% of all the costs of healthcare [7]. As a result of demographic changes and increasing life expectancy, we should take into account the increasing number of falls and higher costs of their treatment.

The etiopathogenesis of Parkinson's disease is based on the dysfunction of neurons in the midbrain substantia nigra. Degeneration of dopaminergic neurons results in a compensatory increase of glutaminergic neurons and increased inhibitory impulsation of thalamic nuclei and mesocortical pathway.

The post-mortem examinations indicate a deficiency of the neurotransmitter – dopamine in the area of base of the brain nuclei. These structures participate in motor system activation. The above regulation consists in the modulation of the flow of information between associative cortex and thalamic nuclei. The neurodegenerative process affects also the noradrenergic and cholinergic

systems, including the nuclei of the basal ganglia. Their task is to coordinate motor and mental activities, and together with the prefrontal cortex, impact the decision-making process, the selection of motor activities and memory related phenomena.

LIMITATIONS

It is assumed that chronically elevated levels of cytokines and inflammatory mediators affect the course of systemic diseases, including those of inflammatory etiology, such as heart and brain diseases of a vascular origin, diabetes, kidney diseases, as well as Alzheimer's and Parkinson's diseases. A general inflammatory response occurs in the advanced stages of periodontitis and is manifested by elevated levels of fibrinogen and C-reactive protein (CRP) in the peripheral blood.

CONCLUSIONS

The evidence collected so far does not warrant any definitive statements concerning the need to include periodontal screening and treatment in patients with Parkinson's disease. However, the immunological phenomena in both diseases as well as promising results of the presented study point to the need for further studies on the correlation between Parkinson's disease and the prevalence and treatment of periodontal diseases.

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