



Clinical and Epidemiological Aspects of Parkinson's Disease in the South of Western Siberia

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Background: The article is devoted to one of the most common neurodegenerative diseases in the world—Parkinson's disease (PD), the prevalence of which in Russia reaches 140–150 people per 100,000 people. The clinical and anamnestic profile of a patient with PD is presented, the prevalence of motor and non-motor symptoms is reflected, and a comparative characteristic of the neurological deficit in the Siberian population of patients with other cohorts of patients with Parkinson's disease in different countries and ethnic groups is presented.

Methods: We studied 140 patients with Parkinson's disease. A comprehensive assessment of neurological status was performed using the “Unified Parkinson's Disease Rating Scale (UPDRS).” In addition, we used the Beck Depression and MoCA scale test. Assessment of the presence and severity of olfactory dysfunction was performed using the Sniffin Stick odor identification test. The stage of PD was evaluated according to the classification of M. M. Hoehn and M. D. Yahr.

Results: The cohort of the study was dominated by overweight patients with a higher level of education, with concomitant arterial hypertension, coronary heart disease, and dyslipidemia. The severity of motor and most non-motor symptoms directly correlates with the duration of PD and the stage of the disease. The predominant form of the disease was a mixed form, which was also noted in research cohorts in Canada and the UK. The Siberian cohort tends to be more prevalent in hyposmia, daytime sleepiness, orthostatic hypotension, and depressive and REM disorders.

Conclusion: Our data show the importance of a comprehensive assessment of both motor and non-motor neurological deficits as well as the analysis of comorbid disorders and risk factors for the occurrence and progression of Parkinson's disease. They also show the prevalence of certain motor and non-motor symptoms in the Siberian cohort of patients with Parkinson's disease.

Keywords: Parkinson's disease, Siberia (Russia), hyposmia, cognitive impairment, depression

BACKGROUND

Parkinson's disease is a chronic progressive brain disease mainly associated with the degeneration of dopaminergic neurons of the substantia nigra with intraneuronal accumulation of the α -synuclein protein and the formation of intracellular inclusions (Lewy bodies). These are manifested by a combination of hypokinesia with rigidity, resting tremor, and postural instability, as well as a wide range of non-motor manifestations (mental, autonomic, sensory, etc.) (1–3).

Parkinson's disease is classified as a predominantly motor disorder, although clinical non-motor polymorphism in recent years has been the subject of extensive research (4–6). This is explained by a significant influence of non-motor symptoms on the quality of life, the progression of disability sometimes exceeding the negative effects of motor neurological deficit (7–9).

To date, there are no specific instrumental or laboratory markers of this disease that could be reliably used in everyday clinical practice. Despite the rapid scientific and technological advances in medicine, the diagnosis of PD in routine practice remains clinical and relies on the identification of cardinal motor signs of parkinsonism (hypokinesia, rigidity, rest tremor, and postural disorders) and the absence of atypical symptoms. In relation to this, a rigorous study of the clinical features and characteristics of the course of the disease is extremely important and is the key to success in a complex diagnostic process.

The study of the features of the course of various progressive diseases, including Parkinson's disease, is relevant in connection with the climatogeographic features of the Omsk Region, located in the south of the West Siberian Plain. The geographical location features open this territory for the interference of air masses: northern Arctic, warm southern Central Asian, dry western Central Asian, and cold eastern. The different nature of the air flow leads to sharp changes in temperature, making the whole weather of the region unstable. The climate of Omsk is continental temperate. According to <https://world-weather.ru>, obtained during long-term observations of air temperature, it is possible to present all the features of the climate in the Omsk region:

The lowest average temperature is -16.9°C (in January).

The highest average temperature is $+18.9^{\circ}\text{C}$ (in July).

Absolute minimum is -50°C .

Absolute maximum is $+40^{\circ}\text{C}$.

From these data, it can be seen how large the temperature fluctuations during the year: 40° between average values and 90° between the minimum and maximum. This is one of the features of the continental climate. Omsk is characterized by the predominance of clear sunny days even in the autumn-winter period—from 223 to 300 during the year. The cloudiest month is December; in May, the number of such days is minimal. These climatogeographic features may probably influence the course of chronic progressive diseases, such as Parkinson's disease.

In accordance with the urgency of the problem, a retrospective clinical and epidemiological assessment of the clinical course of Parkinson's disease in the south of western Siberia was performed at Omsk State Medical University.

In accordance with the urgency of the problem presented at the Omsk State Medical University, a retrospective clinical and epidemiological assessment of the clinical course of Parkinson's disease in the south of western Siberia was carried out. The aim of our study is to assess the impact of climatic, geographical, and ethnic factors on the course of Parkinson's disease in the Siberian cohort of patients.

METHODS

Patients

All patients (Russians residing in the Siberian part of Russia) were diagnosed with PD at the Omsk State Medical University. All patients with PD were selected and studied according to the international Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr scores (10, 11). The diagnosis of PD was based on the UK PD Brain Bank Criteria (12). In addition, the Beck Depression Scale and Montreal Cognitive Assessment (MoCA) test was used (13). The severity of olfactory dysfunction was performed using the Sniffin Stick odor identification test.

In this work, we evaluated the clinical and epidemiological features of the course of the disease in 140 patients with Parkinson's disease. A retrospective analysis of medical documentation and an assessment of clinical parameters at the onset of the disease and at the time of the examination were carried out.

These were the criteria for inclusion of patients in the study:

- A reliable diagnosis of Parkinson's disease in accordance with the criteria of the European Federation of Neurological Societies (EFNS) in conjunction with the Movement Disorders Society 2013.
- Signed informed consent to participate in the study.
- The absence of other neurodegenerative diseases in the patient.

Criteria for exclusion of patients from the study:

- Secondary parkinsonism and parkinsonism—plus identified at the initial visit.
- The presence of severe concomitant somatic pathology in the stage of decompensation.
- The patient's refusal to participate in the study.
- Patient involvement in other clinical studies.
- The patient has other diseases that have a genetic component in the pathogenesis, due to the high risk of distorting the information received.

Statistical Analysis

Descriptive statistics for qualitative accounting features are presented in the form of absolute values, percentages, their standard errors (m), and standard deviations (σ). Data for variational series with non-parametric distribution are described as medians and quartiles (Me [25th; 75th percentile]). For comparison of non-parametric data, the Mann–Whitney U criteria were used. The critical level of significance of the tests is determined at $p \leq 0.05$. Statistical processing of the results was carried out using Statistica 10 licensed software packages (StatSoft, USA).

TABLE 1 | Risk/protective factors for patients with Parkinson's disease.

Risk/protective factors	Patients with PD (abs)	Patients with PD (%)
Industrial contact with pesticides	8	5.7
Household contact with pesticides	44	31.4
Smoking	31	22.1
Quit smoking after the onset	6	4.3
Never smoke	103	73.6
Drink at least 1 cup of coffee per day	78	55.7
Do not drink coffee	62	44.3
Mild traumatic brain injury	14	10

The study was approved by the Ethics Committee of the Omsk State Medical University.

RESULTS

According to inclusion/exclusion criteria, 140 patients with Parkinson's disease were included in the study, including 55 men and 85 women (the majority of patients had PD with the average duration of 3–10 years with the symptoms effectively managed by combination of adequate treatment options (dopamine agonists, levodopa, amantadine). The ratio of men and women in the group was 1:1.5, with a predominance of females. The age of patients ranged from 37 to 82 years (median [25th; 75th percentile], 67 years [61; 73]): women, 85 (66.3 ± 9.5; age, 68 years [61; 72]), and men, 55 years (66.5 ± 9.7; age, 68 years [61; 74]). The average age of all patients at the time of the examination was 66.4 ± 9.5 years. Treated patients with PD received different medications (dopamine receptor agonists: pramipexole in a dosage of 1.5 mg/day or piribedil in a dosage of 150 mg/day, L-dopa in a dosage of 150–200 mg/day, and amantadine in a dosage of 300 mg/day), either as monotherapy or in various combinations.

The studied group of patients consisted of 14 (10%) Mongoloids and 126 (90%) patients of the European race. By the level of education, the group was divided into the following categories: 13 (9%) people had secondary education, 25 (18%) patients received secondary special education, and 102 (73%) patients graduated from higher educational institutions.

The average weight in the main group was 76.0 ± 14.3 kg (73.5 [65; 86]). The average height in the study group was 165.4 ± 8.0 cm (164.0 [160; 170]). Thus, the average body mass index is 27.8 ± 4.7 (27.0 [24.7; 30.7]), which indicates the predominance of patients with overweight.

The study conducted an analysis of risk factors for the development of PD and protective factors. The data are presented in **Table 1**.

The analysis of anamnestic information about the presence of concomitant diseases showed that patients with PD are quite comorbid and usually have several nosological forms in the structure of the diagnosis. The data are presented in **Table 2**.

TABLE 2 | Comorbidity of patients with Parkinson's disease.

Diseases	Patients with PD (abs)	Patients with PD (%)
Ischemic stroke	4	2.9
Malignant neoplasms	3	2.1
Coronary heart disease	44	31.4
Arterial hypertension	55	39.3
Dyslipidemia	28	20
Diabetes	12	8.6
Hyperthyroidism	3	2.1

The presence of depressive symptoms was reported by 4 (2.9%) patients with PD, but depression of varying severity during the assessment of the Beck depression scale conducted in the framework of this study was detected in 46 (71%) of the 65 patients examined. The average level of depression in the group was 15.6 ± 9.1 points, which corresponds to mild depression.

MOTOR SYMPTOMS IN THE SIBERIAN COHORT

In the study group of patients, the stage was determined according to the classification of Hen-Yar (1967): in 31 patients, one stage of the disease was established, in 63 patients, two stages, in 45 patients, three stages, and in one patient, four stages of the disease.

The average disease duration in the observed group of patients was 6.9 ± 4.9 years. The debut of PD with motor symptoms was noted in 129 (92.1%) patients, the debut with non-motor symptoms was detected in 11 (7.9%) patients with PD. Of the motor symptoms of the debut, the obligate symptom was hypokinesia, which was anamnesticly established in all 140 (100%) patients. Other motor symptoms of PD debut in frequency were arranged in decreasing order as follows: resting tremor—76 (54.3%) patients, muscle rigidity—65 (46.4%) patients, and postural instability in PD debut was not noted.

In the analysis of the current clinical picture in patients with PD, hypokinesia was detected in 140 (100%) patients, resting tremor was diagnosed in 95 (67.9%) patients, rigidity in 97 (69.3%), and postural instability in 43 (30.7%) patients with PD.

Thus, the increase in the frequency of occurrence of the main motor symptoms of Parkinson's disease in the Siberian cohort over a 7-years period was 14% for resting tremor, 23% for muscle rigidity, and 31% for postural instability.

In our cohort of patients, 98 (70%) patients with a mixed form of the disease, 22 (16%) patients with a rigid-trembling form, and 20 (14%) patients with an akinetic-rigid form of Parkinson's disease were observed. We compared our data on motor deficiency with other cohorts of patients that were collected and systematized this year (14). The data are presented in **Table 3**.

Table 3 presents numerous studies of motor deficiency in Parkinson's disease in various ethnic groups (14–26).

TABLE 3 | Motor subtype in de novo PD cases by country.

Study	Year	Country	Total study participants (year)	Mean Age (year)	Sex M/F	TD (No.)	TD (%)	Rigid akinetetic or PIGD (No.)	Rigid akinetetic or PIGD (%)	Indeterminate or mixed (No.)	Indeterminate or mixed (%)	Method of subtyping
Reinoso	2014	Singapore	576	63.8	328/248	19	3.3	383	66.5	174	30.2	Lewis method and Rossi modifications
Rajput	2017	Canada	156	65.0	98/58	10	6.4	45	28.8	101	64.7	Novel method
Ramani	2016	UK	42	67.0	29/13	7	16.7	17	40.5	18	42.9	Novel method
Poletti	2011	Italy	42	65.0	28/14	10	23.8	24	57.1	8	19.0	Lewis method
Alves	2006	Norway	171	71.3	112/87	43	25.1	92	53.8	36	21.1	Jankovic
Auyeung	2012	Hong Kong	171	62.2	93/78	46	26.9	62	36.3	63	36.8	Novel method
Yuan	2013	China	51	61.9	24/24	20	39.2	19	37.3	12	23.5	Jankovic method with Korchovinov modifications
Moccia	2016	Italy	63	60.6	38/25	27	42.9	18	28.6	18	28.6	Jankovic
Konno	2018	USA	1,003	64.0	637/366	439	43.8	386	38.5	178	17.7	Most prominent symptom at diagnosis
Seong-Min Choi	2018	South Korea	192	66.2	94/98	87	45.3	82	4.1	23	12.0	Jankovic
Muller	2011	Norway	207	67.9	122/85	95	45.9	88	42.5	24	11.6	Jankovic
Hiorth	2013	Norway	207	67.9	122/85	95	45.9	89	43.0	23	11.1	Novel UPDRS ratio
Nicoletti	2016	Italy	485	65.6	292/193	311	64.1	104	21.4	70	14.4	Most prominent symptom at diagnosis
Rozhdestvensky	2020	Russia	140	66.4	55/85	22	16	20	14	98	70	Most prominent symptom at diagnosis

Lewis method with Rossi modifications, ratio of the mean tremor scores (TD) (items 20 and 21) and the mean akinetetic-rigid score (AR) (items 18, 19, 22, and 27-31); if the ratio TD/AR is >2.0, it was defined as TD and if AR/TD is more than 2.0, it was defined as AR. Mixed type was any indeterminate result. Jankovic: ratio of mean TD scores divided by mean of postural instability and gait items (falling, freezing, subjective gait difficulty, gait, and postural instability); if ratio is > 1.5 TD; PD; if ratio is < 1.0 PIGD, PD. Other subtyping methods are as described in the reference materials. TD, tremor dominant; PIGD, postural instability and gait disorder.

NON-MOTOR SYMPTOMS IN THE SIBERIAN COHORT

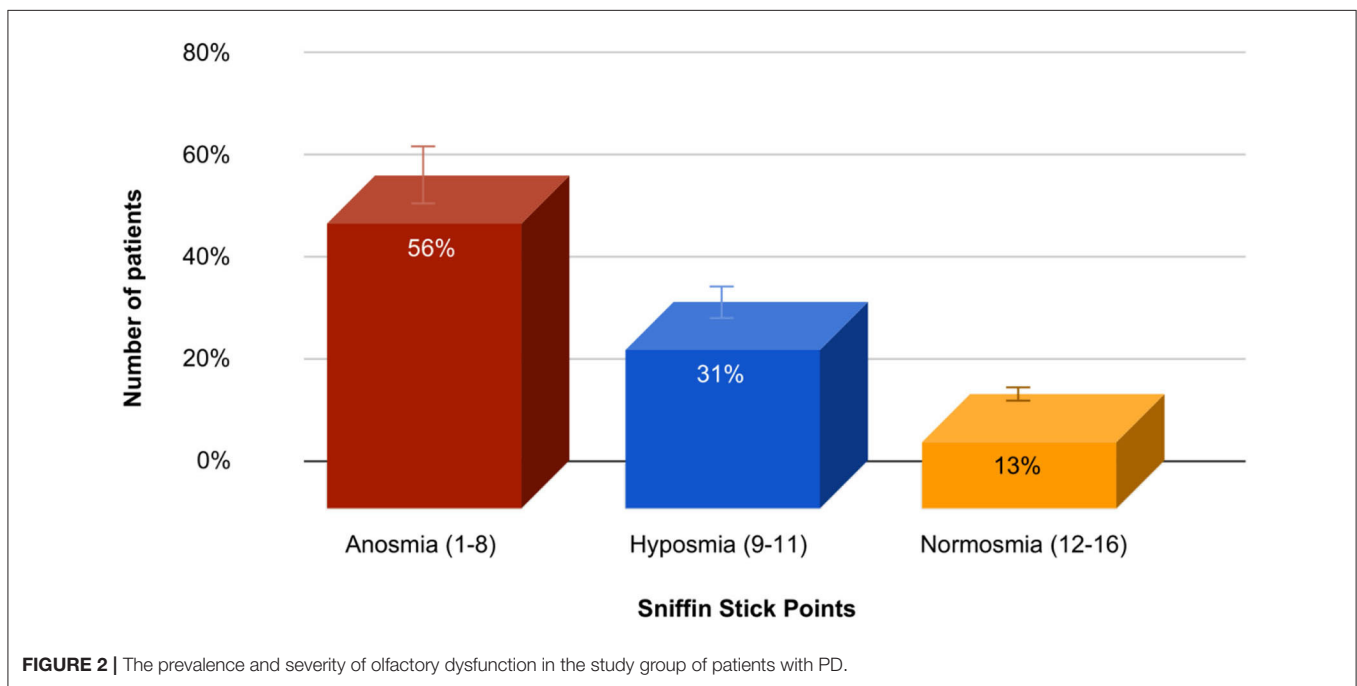
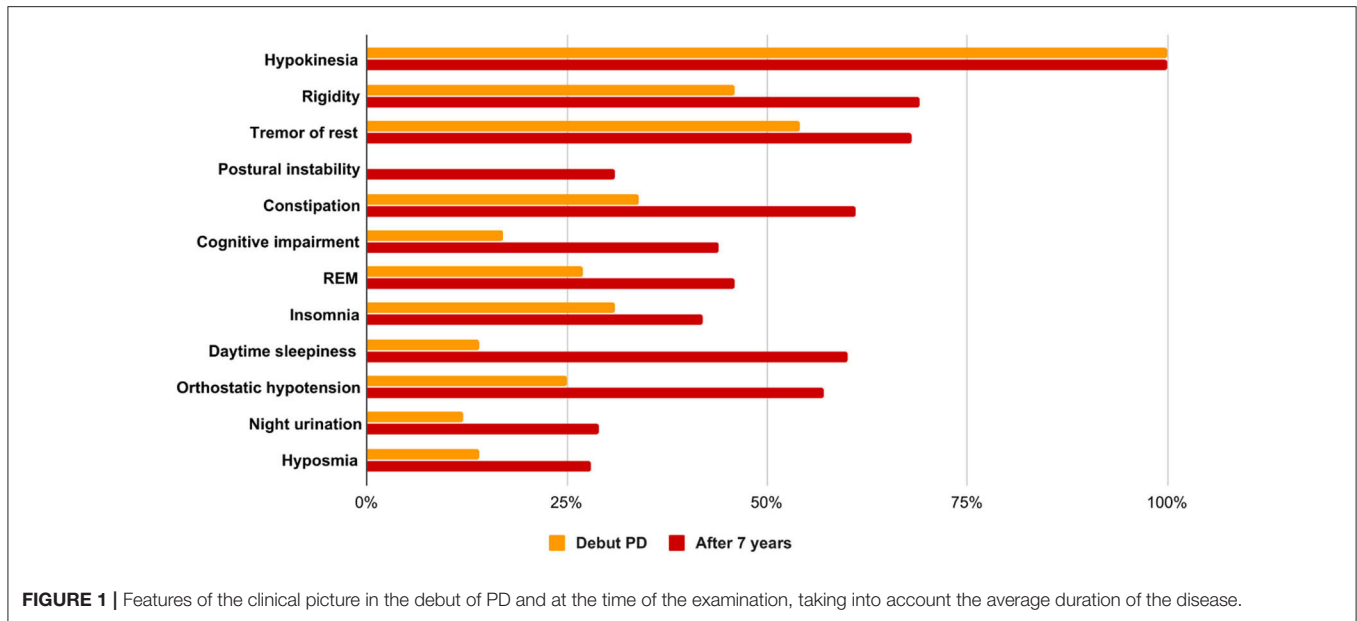
The most frequent non-motor symptoms of PD debut in the study group were constipation in 47 (33.6%) patients, cognitive impairment in 24 (17.1%) of 140 patients, behavioral disturbances in the REM phase of sleep in 24 (17.1%) of patients, insomnia diagnosed in various variations in 38 (27.1%) patients, daytime sleepiness in 43 (30.7%) patients, subjective olfactory sensation dysfunctions at the time of the motor debut of PD in 19 (13.6%) patients, unscheduled weight loss in 8 (5.7%) patients, anhidrosis of the skin in 7 (5%) patients, sweating already in the debut of PD in 21 (15%) patients, seborrhea (indicated as an additional non-motor symptom of the debut of PD) in 4 (2.9%) patients, orthostatic hypotension in 35 (25%) patients, dysphagia in 5 (3.6%) patients, and a dysfunction of the pelvic organs by the type of night urination and fecal incontinence in 17 (12.1%) patients.

In the analysis of current non-motor symptoms, cognitive impairment was detected in 61 (43.6%) patients, psychotic disorders in the form of hallucinations in 7 (5%) patients, behavioral disturbances in the REM phase of sleep in 65 (46.4%) patients, olfactory dysfunction in 28 (20%), daytime sleepiness in 84 (60%), insomnia in various variations in 59 (42.1%) patients, unplanned weight loss in 12 (8.6%) patients, orthostatic hypotension in 80 (57.1%), dry skin in 6 (4.3%), hyperhidrosis in 29 (20.7%), dysphagia in 21 (15%), constipation in 85 (60.7%), and night urination in 41 (29.3%) patients.

Thus, the increase in the prevalence of non-motor symptoms of Parkinson's disease in the Siberian cohort for a 7-years period was constipation in 27%, cognitive impairment in 27%, REM disorders in 29%, hyposmia in 6%, orthostatic hypotension in 32%, insomnia in 15%, daytime sleepiness in 29%, and nocturia in 17%. BP progression over a 7-years period is shown in **Figure 1**.

Olfactory test (Sniffin Stick) or Sniffin Sticks odor identification test (Bürghard firm, Hamburg, Germany) was performed in 83 patients, and the average score was 7.6 ± 3.3 , which corresponds to anosmia. Identification test: the ability to detect odors from the proposed four names. The patient is given a pencil to inhale the smell and are offered four options, one of which he must choose. The result is the sum of the positive answers. A result of <8 points corresponds to anosmia, 9–11 points to hyposmia, and 12–16 points to normosmia. In this group of patients, olfactory dysfunction reaching the degree of anosmia was diagnosed in 47 (56.2%) patients, hyposmia in 26 (31.3%) patients, and normosmia in 11 (12.5%) patients. The data are presented in **Figure 2**.

A statistical analysis of a group of patients with Parkinson's disease at the onset of the disease and at the time of the study, taking into account the average duration of the disease course of 6.9 ± 4.9 years using the non-parametric Mann-Whitney *U*-test, showed significant differences in the severity of the main motor and non-motor symptoms. At the time of the study, patients had more pronounced resting tremor ($U = 1,021.5$; $p < 0.0000001$), general bradykinesia ($U = 1,854$; $p < 0.001$), and rigidity ($U =$



1,630.0; $p < 0.0007$). When comparing the severity of non-motor symptoms in the debut of BP and after 7 years, more pronounced constipation ($U = 1,387.5$; $p < 0.000001$), cognitive impairment ($U = 1,683.5$; $p < 0.0002$), behavioral disorders were noted in the REM phase of sleep ($U = 1,775.5$; $p < 0.0004$), insomnia ($U = 1,082.5$; $p < 0.0000001$), daytime sleepiness ($U = 1,534.0$; $p < 0.000008$), orthostatic hypotension ($U = 1,826.0$; $p < 0.000008$), and hyposmia ($U = 836.0$; $p < 0.00004$). There is also a tendency to increase the severity of night urination ($U = 1,814.5$; $p < 0.02$).

We compared the results of evaluating some non-motor symptoms in our cohort of patients with Parkinson's disease with

symptoms in other cohorts of patients around the world; data for which were systematized this year (27). The data are presented in **Table 4**.

Table 4 shows the prevalence of major non-motor symptoms identified during studies in different corners of the globe (8, 28–37).

The average score during neuropsychological testing of the cognitive sphere using the Montreal scale for assessing cognitive functions was 23.4 ± 3.9 , which corresponds to moderate cognitive impairment. A score of 20 and lower was scored by 13 (15.1%) patients, and in the range of 21–25 points, 43 (51.8%)

TABLE 4 | Some non-motor symptoms in patients with PD by country.

Study	Year	Country	Total study participants	Mean years since diagnosis	Anosmia (%)	Dysphagia (%)	Constipation (%)	Nocturia (%)	Weight change (%)	Memory problems (%)	Hallucinations (%)	Depression (%)	OH (%)	EDS (%)	Insomnia (%)	RBD (%)	Hyperhidrosis (%)
Duncan	2014	UK	158	0.5	44	20	42	25	23	54	22	37	32	25	18	35	10
Romenets	2012	USA	70	3.8	21	16	30	68	21	42	12	38	38	14	41	38	19
Hui-juan Li	2015	China	82	5.1	45	33	67	87	29	95	15	67	38	73	78	52	65
Cosentino	2013	Peru	300	5.8	36	22	56	77	53	61	20	81	48	33	48	36	43
Khedr	2013	Egypt	112	6.2	10	24	52	60	33	30	13	47	54	39	46	15	21
Cheon	2008	S Korea	74	6.4	28	31	66	68	35	61	18	65	64	26	56	35	60
Rodriguez-Violante	2011	Mexico	232	6.6	34	33	58	62	28	47	19	67	46	28	47	33	39
Martinez-martin	2007	International	545	7	29	28	53	62	18	45	23	50	28	31	46	36	30
Tanveer	2018	Pakistan	97	7	26	28	60	77	38	59	30	52	53	41	53	36	37
Bostantjopoulou	2013	Greece	166	7.1	26	14	46	52	7	31	2	42	28	9	26	27	21
Chaudhuri	2010	UK, Germany, Spain	242	8	43	27	48	65	23	51	17	49	39	35	47	39	31
Rozhdestvensky	2020	Russia	140	6.9	56	15	61	41	9	44	5	75	57	60	42	46	21

Any data that was not available is replaced with a dash. OH, orthostatic hypotension; EDS, excessive daytime sleepiness; RBD, REM sleep behavior disorder.

patients were observed; the normal values of this test [i.e., 26–30 were noted in 28 (33.1%) patients with PD].

CONCLUSION

Of course, factors such as ethnicity (38), geographical location of the region of residence (39), diet (40), overall life expectancy (41), genetic characteristics of the population (42, 43), and presence of concomitant diseases (44) affect the development and nature of the course of both neurodegenerative and other chronic progressive neurological diseases. A comparative assessment of the clinical parameters of Parkinson's disease in populations is to some extent difficult due to the variability of approaches for obtaining clinical data and their interpretation. In addition, the UK PD Brain Bank Criteria used in most studies provide a diagnostic accuracy of only 82.7% for the diagnosis of Parkinson's disease (45). This indicator, of course, affects the statistical reliability of clinical and epidemiological studies of Parkinson's disease and can lead to some distortion, especially in the early stages, when the clinical picture is usually incomplete, the response to dopaminergic drugs is uncertain, or signs of atypical parkinsonism have not yet appeared. Despite significant advances in understanding the pathogenetic aspects of this disease, we still lack clear imaging or biochemical markers to accurately diagnose Parkinson's disease.

In our work, we estimated the prevalence of motor and non-motor neurological deficits, as well as some risk factors and concomitant diseases in the Siberian cohort of patients with Parkinson's disease. The predominant debut of BP is the motor debut. The progression of the disease is characterized by an increase in the frequency of both motor and non-motor symptoms. When comparing the prevalence of motor symptoms with other cohorts of patients (Table 3), we found the greatest similarity with Canadian (24) and, to a lesser extent, UK (15) cohorts of patients, in which mixed forms of Parkinson's disease also prevailed. This similarity may be due to the close climatic and geographical features of western Siberia and Canada with a sharply continental climate, and the predominance of patients of the European race in our cohort. The analysis also noted the predominance of tremor in the structure of the clinical picture of Parkinson's disease in the Italian (14, 23), Norwegian (18, 26), and South Korean (16) cohorts. Against this background, a study of Reinoso et al., conducted in 2014, which shows the predominance of an akinetic-rigid form or postural instability with gait disorders of up to 66.5% in a cohort of patients with Parkinson's disease (21), looks quite interesting. The ratio of disease forms in the US (22) and China (19) cohorts was approximately equal.

In this article, we compared the prevalence of non-motor symptoms of Parkinson's disease in Siberian and other cohorts around the world. Based on these data, the Siberian cohort demonstrates a greater prevalence of olfactory disturbances, daytime sleepiness, orthostatic hypotension, depressive disorders, and behavioral disorders in the REM phase of sleep compared with cohorts similar in terms of the duration of Parkinson's disease (29–33, 35, 36). However, the prevalence of

dysphagia, nocturia, weight changes, and hallucinations turned out to be lower than in the cohorts of patients similar in terms of sample size and duration of the disease. It is possible to consider these parameters only tentatively, since they have differences in the methodology for assessing non-motor symptoms, cohorts have ethnic differences, which probably affect the final result.

In the study group of patients, mild depressive symptoms, mild cognitive impairment, and severe olfactory impairment (anosmia) were noted.

The severity of motor and most non-motor symptoms directly correlates with the duration of PD and the stage of the disease, which is confirmed by most clinical trials of this disease (46–48).

The comorbidity of patients with Parkinson's disease is an urgent public health problem. A study by Mollenhauer et al. reflected the negative dynamics of the rapid progression of Parkinson's disease in patients with cardiovascular risk factors, impaired regulation of blood glucose levels, impaired uric acid metabolism, and inflammation (49). According to Huang Y.F. in patients with PD, the risk of stroke is higher than in the population (50). In the Siberian cohort of patients with Parkinson's disease, women with higher education, overweight, concomitant arterial hypertension, coronary heart disease, and dyslipidemia predominated. The predominance of females in the analyzed cohort of patients with Parkinson's disease is probably associated with regional features of a higher medical demand for females. The data obtained during the study are consistent with the results of other studies in various cohorts and in different parts of the world (51–53).

Smoking as a protective risk factor in Parkinson's disease is confirmed by a large number of scientific studies (54–57). Our data indirectly confirm and are consistent with previously published studies. The analysis found that 75% of respondents never smoke. The study found that household contact with various pesticides is relevant for 30% of respondents.

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The Siberian cohort of patients with Parkinson's disease has its own peculiarities in the clinical picture of the disease, in questions of comorbidity, which necessitates further studies of various clinical, epidemiological, and genetic aspects of the disease using unified protocols to better understand the nature of the disease. The results presented in the article indicate the main directions of further deeper study of this pathology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access the datasets should be directed to Roman Andreevich Delov, delov_roman@mail.ru.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Omsk State Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR: study conception and design. IG, EK, EM, and RD: acquisition of data. RD: analysis and interpretation of data, drafting of manuscript, and critical revision.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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