ORIGINAL ARTICLE

A Case-Control Study of Parkinson's Disease in Urban Population of Southern Israel

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ABSTRACT: ***Background:*** In recent years, an increased prevalence of Parkinson's disease (PD) in southern Israel was observed. The aim of this study was to determine which exposures are associated with PD in the urban population of this region. ***Methods:*** Ninety-three PD patients living in towns were compared to 93 age and sex matched controls. A previously validated questionnaire, including demographic data, education, data on exposures, previous diseases, family history and habits, was administered. ***Results:*** In multivariate logistic regression analysis, it was found that history of work in construction sites was the strongest predictor of PD risk, followed by exposure to pesticides. In contrast, there was a negative association with smoking and history of mechanical factory employment. When the same statistical analysis was limited to association of PD with smoking, pesticides and construction work, the latter was found to be the strongest risk factor. ***Conclusion:*** The risk factors for PD in this population are work on a construction site and exposure to pesticides.

RÉSUMÉ: Étude cas-témoin sur la maladie de Parkinson dans une population urbaine du sud de l'état d'Israël. ***Introduction:*** Depuis quelques années, on a observé une prévalence accrue de la maladie de Parkinson (MP) dans le sud de l'état d'Israël. Le but de cette étude était de déterminer à quels agents les patients avaient été exposés et s'il existait une association avec la MP dans la population urbaine de cette région. ***Méthodes:*** Quatre-vingt-trois patients atteints de MPet vivant en région urbaine ont été comparés à 93 contrôles appariés pour l'âge et le sexe. Un questionnaire validé comprenant des données démographiques, la scolarité, des données sur l'exposition à différents agents, les maladies antérieures, l'histoire familiale et les habitudes de vie leur a été administré. ***Résultats:*** l'analyse de régression logistique multivariée a montré que le fait d'avoir déjà travaillé dans des chantiers de construction était le meilleur prédicteur du risque de MP, suivi de l'exposition aux pesticides. Par contre, il existait une association négative avec le tabagisme et le travail en usine. Quand l'analyse était limitée à l'association de MP avec le tabagisme, l'exposition à des pesticides et le travail dans un chantier de construction, ce dernier étant le plus grand facteur de risque. Les patients nés dans l'ancienne Union Soviétique étaient plus souvent atteints d'ulcère peptique. ***Conclusion:*** Les facteurs de risque de la MP dans cette population sont le travail dans un chantier de construction et l'exposition à des pesticides.

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The etiology of Parkinson's disease (PD) is unknown, but accumulating evidence supports the hypothesis that environmental factors have a major impact on pathogenesis. Parkinson's disease occurrence has been associated with rural residency and its lifestyle characteristics such as farming, well water use and exposure to pesticidal products. In 1989, we reported a cluster of PD patients in three adjacent kibbutzim (cooperative agricultural communities) in the Negev (southern Israel) and emphasized the possible role of well water consumption in the etiology of disease in these patients.[1] Since then, a prospective study on asymptomatic subjects over the age of 40 in this population revealed a high percentage of people with subtle extrapyramidal signs.[2] We found a very strong association between field crop work exposure and the presence of these signs. We also found an association with pesticide use.[2] Our assumption was that these people present signs of

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preparkinsonism and that some of them will progress to full blown Parkinson's disease.[3] Over the last 15 years the annual incidence of PD among persons over 40 in the "cluster" kibbutzim increased from 27.5/10,000 to 47.1/10,000.[2]

In recent years, an overall increase in prevalence of PD was also observed in the southern Israel region. This was a period of increased immigration (starting in 1989) from the former Soviet Union. The great majority of the new immigrants settled in the towns. It was the aim of this study to determine whether exposures associated with PD and preparkinsonism in rural communities of the Negev, play a similar role in PD among urban Negev residents.

Patients and methods

Ninety-three consecutive unselected urban patients diagnosed between 1989-1995 as suffering from PD and treated at the outpatient PD clinic of Soroka University Medical Center in Beer-Sheva (the only general hospital in the entire region serving approximately 600,000 inhabitants) were compared to 93 age- (± two years) and sex-matched controls. The latter were recruited from the outpatient dermatology, neurology and internal medicine clinics of this hospital. Inclusion criteria for PD were progressive disorder and presence of at least two of the cardinal signs of tremor, rigidity, bradykinesia, postural instability, and good response to l-dopa. Additional criteria were absence of significant cognitive impairment and lack of an alternative etiology known to cause secondary parkinsonism. Controls presenting extrapyramidal signs, or evidence of other neurodegenerative diseases, such as Alzheimer's disease or essential tremor, were excluded from this study. All subjects (patients and controls) resided in Beer-Sheva or in other towns of the Negev.

After giving written informal consent approved by the Institutional Ethics Committee, all the subjects filled a previously validated questionnaire,[2] administered in person by one of the authors (MM). The questionnaire was translated into Russian and administered in this language to the subjects who were not fluent in Hebrew. The questionnaire included demographic data on age, gender, place of birth, size of birth community, father's and mother's country of birth, date of immigration and a history of incarceration in a concentration or extermination camp, ghetto or prison. Data on education were also collected. Included were data for each type of former residence (e.g. rural community with less than 10,000 inhabitants and urban community with more than 10,000 inhabitants) for more than six months, type of drinking water source in every place of residence, and every employment for more than six months. The subjects were asked about any occupational or household use of pesticides, herbicides, fungicides, organic solvents, metals, CO, etc. There were questions on past medical history, hospital admissions, surgery, head trauma and chronic drug treatment as well as on family history of PD. Lifetime smoking histories were obtained, as well as data on alcohol consumption and recreational drug exposure.

Statistical analysis was performed on the SPSS statistical software package using chi-square tests with Yates correction, Fisher exact test (where appropriate), Spearman correlation and multivariate logistic regression analysis.

Results

Fifty PD patients (53.8%) lived in communities with less than 10,000 inhabitants (rural) before the emergence of the disease, as compared with 47 (50.5%) controls. Among PD patients, 37 (41.6%) completed less than eight grades (junior high school) as compared to 33 (36.3%) controls. Both groups reported similar number of school grades: 10.4 ± 4.5 and 10.6 ± 4.9 respectively. Fewer PD patients were born in former Soviet Union (36 versus 55) compared to other countries (57 versus 38) (p=0.008) (Table 1). Only one control subject was born in Israel. A higher proportion of PD patients lived in Israel more than 25 years.

More PD patients were builders and worked in offices (25/18 p=0.3); less did factory work (p=0.05) (Table 1).

PD patients showed higher frequency of pesticide exposure than controls (p=0.06, OR=6.34) (Table 1). For other chemical exposures (metals, fuel, glue, carbon monoxide and turpentine)

Table 1: Comparing PD patients and controls by variables* (treated by Chi-square test with odds ratio calculation)

Variables	PD (n)	Controls (n)	Significance	Odds Ratio	95% CI
Demographic					
Country of birth					
USSR	36	55			
			0.008	2.29	1.27-4.12
others	57	38			
Years since immigration					
<25	41	58			
			0.02	2.10	1.17-3.78
>25	52	35			
Occupation					
Construction	15	8	0.1	2.36	0.92-6.1
Mechan. factory	7	17	0.05	0.36	0.14-0.93
Exposure to pesticides	6	1	0.059^	6.34	0.75-53.8
Ever smoked	26	43	0.007	0.41	0.22-0.76

*Only for variables which were associated with PD (p<0.1)

^ Fisher exact test was used, for other variables Yates correction for Chi-square test

Table 2: Comparing PD patients and controls by chronic diseases* (analyzed by chi-square test, with odds ratio calculation).

Disease	PD (n)	Controls (n)	Significance	Odds Ratio	95% CI
Hypertension	28	44	0.02	0.48	0.26-0.88
Diabetes mellitus	11	26	0.01	0.35	0.15-0.75
Isch. heart disease	20	40	0.003	0.36	0.19-0.69

* Only for diseases which were associated with PD (p<0.05)

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Table 3: Estimated odds ratio for association between PD risk and different variables (treated by multivariate logistic regression)

Variables	Odds ratio	95% CI
Smoking	0.37**	0.19-0.72
Exposure to pesticides	6.81^	0.75-64.89
Work in construction	2.32	0.84-6.44
Work in mechanical factory	0.63*	0.22-1.83
Country of birth (other than USSR)	2.00	1.04-3.85
Peptic disease	1.83	0.42-4.36

* p=0.04, ** p=0.003, ^p<0.1. For other variables p>0.1

Table 4: Estimated odds ratio for association of Parkinson's disease with smoking, exposure to pesticides and work in construction (treated by multivariate logistic regression)

Variables	Odds ratio	95% CI
Smoking	0.36**	0.19-0.69
Exposure to pesticides	7.73^	0.86-69.6
Work in construction	2.94*	1.08-7.99

** p=0.002, * p=0.03, ^ p=0.07

the differences between groups did not reach statistical significance (p>0.1).

Sixteen PD patients were in a Nazi concentration camp in comparison with only nine controls (p=0.2). Eighteen PD patients versus 13 controls experienced head trauma (p=0.6).

Not all the subjects who were incarcerated in a concentration camp had a history of head trauma. Others were injured in road or work accidents or during World War II or in wars in Israel.

A negative association was found between PD and diabetes mellitus type II, arterial hypertension and ischemic heart disease (Table 2). Among these cases, there were more subjects with cholelithiasis (8 versus 4) (p=0.4). The proportion of subjects who suffered from peptic ulcer in both groups was similar, although PD patients born in the former Soviet Union suffered from peptic disease more frequently (10/36, 27.8%) compared to 5/56 (9.1%) among non Soviet Union born patients (p=0.04).

Seven PD patients have at least one first degree relative suffering from PD as compared with only three in control group (p=0.3).

Only 26 PD patients ever smoked as compared to 45 controls (p=0.007, OR=-2.42) (Table 1). The PD patients did not differ from the controls by age at which they started smoking (24.6± 15.7 and 23.8 ± 14), length of time smoking (28.8± 16.2 and 31.3 ± 17.8 years respectively), and age when they stopped smoking (53.7 ± 17.3 and 55.3 ± 14.3 years respectively).

In multivariate logistic regression analysis we included factors presented in Table 1 (except number of years living in Israel because of its strong correlation with the country of birth, r=0.79) and peptic ulcer, and we found that history of work in construction was the strongest predictor of PD risk, followed by exposure to pesticides. Parkinson's disease was inversely associated with ever smoking and with factory employment (Table 3). By using a same statistical analysis, limited to association of PD and smoking, exposure to pesticides and history of work in a construction site, the strongest risk factor was construction work history followed by exposure to pesticides (Table 4). Again, smoking was found to be a strong protective factor against PD development.

Discussion

The etiology of Parkinson's disease is unknown, but there is a significant bulk of evidence that environmental factors may play a role. The increase in the prevalence of PD in the urban population of southern Israel is not related to the recent immigration from former Soviet Union and it seems to be a result of a long-term (more than 25 years) exposure to environmental factors present in the region.

Our study revealed an association of borderline significance between urban cases of PD and past pesticide use. In the literature there are still conflicting reports regarding the plausible connection between pesticide/herbicide exposure and the risk for PD. Hubble et al[4] conducted a case control study at a rural and an urban site in Kansas and also found that pesticide use can be considered a risk factor, distinct from rural living, for the development of PD. Semchuk et al[5,6] also found a threefold chance to develop the disease in association with herbicide use. One of these studies included patients followed-up in the city of Calgary.[6] Butterfield et al[7] conducted a case-control study on subjects presently living in towns or in communities with less than 10,000 inhabitants, and found that PD was positively associated with insecticide exposure, with past residence in a fumigated house and with herbicide exposure. Seidler et al,[8] in a large scale case-control study, including rural and urban residents in Germany, also reported a significant association of PD with pesticides, in particular organochlorines and alkylated phosphates and with wood preservatives. Case-control studies conducted elsewhere, reported an increased prevalence of PD among residents of rural communities which is possibly linked to well water use.[9,10] Another case-control study found that long duration of residence in rural areas, long-term farming, the use of herbicides and pesticides and the consumption of raw vegetables were all interrelated and increased the risk for PD.[11] Recently, Marder et al,[12] in a study on an urban multiethnic community found an association between PD and rural living, area farming and well water only in African-Americans whereas in Hispanics, farming was protective and drinking unfiltered water was a risk factor for the disease.

Barbeau and his collaborators[13] found a very high correlation between the incidence of the disease in the province of Quebec and the level of pesticide use. Tanner et al,[14] in a study done in China, reported a high exposure rate to chemical, pharmaceutical, herbicide or pesticide industries before the onset of the disease. However, Morano et al[15] in a mixed rural and urban population of Spain, found only a marginal significance of the association between PD and exposure to pesticides. Likewise, Wechsler et al[16] did not find a strong association of PD with pesticides, herbicides or fungicides exposure but they found that

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several home pesticides or herbicides were more frequently reported to be used by cases than by controls.

In this study, a negative association was found between PD and arterial hypertension, non-insulin dependent diabetes mellitus and chronic ischemic heart disease. A lower frequency of arterial hypertension in PD patients was already reported[17] but other studies failed to confirm this finding.[14] Ischemic heart disease, however, was also previously reported to be less frequent in PD patients.[18,19]

Our study, like many others,[7,14,19-21] showed again a very strong negative association between PD and smoking.

Another finding of the present study was that of an association between PD and peptic disease in the group of patients born in former Soviet Union. Such an association was reported by some researchers[22] but refuted by others.[14] We assume that this association is related to previous therapies for peptic disease, such as bismuth salts, which were used in Soviet Union for many years while abandoned in the western countries.

By using multivariate logistic regression analysis, history of work in construction was the strongest predictor of PD risk, followed by exposure to pesticides. Parkinson's disease was inversely associated with ever smoking and mechanical factory work. By using the same statistical analysis, for association of PD and smoking, exposure to pesticides and history of work in construction, the strongest risk factor was history of work in construction followed by exposure to pesticides. Again, smoking was found to be a strong protective factor for PD development.

This case-control study on urban PD patients of the Negev found an association between PD and environmental exposures e.g. pesticides, work in construction. More studies on urban PD patients are needed to confirm these associations.

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