

RURAL OR URBAN LIVING AND PARKINSON'S DISEASE

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ABSTRACT - Although the precise etiology of Parkinson's disease (PD) is as yet unknown, it appears that certain environmental factors are involved. Prior living in a rural area has been implicated as a possible risk factor for PD, particularly in the early onset type. We evaluated the role of previous living conditions in the clinical correlates and outcome characteristics of 118 PD patients. All of them were seen from January 1987 to October 1992. The Rural Group (RG) comprised 71 patients (60.2%) who had lived in the rural area for at least 10 years (mainly in early phase of life) and the Urban Group (UG) consisted of 47 patients (39.8%) who had lived their entire life in an urban environment. The average age at the beginning of the symptoms was 58.8 in the RG and 54.1 in the UG. The mixed form of the disease (tremor, rigidity and akinesia) was the most frequent in both groups. A minimum 6-month follow-up period was undertaken with 63 patients (average 20 months) and no difference in response to treatment or in progression of the illness was detected between the two groups. Our data show that the previous living environment does not appear to be a determining factor in either the clinical or outcome characteristics of PD.

KEY WORDS: Parkinson's disease epidemiology, Parkinson's disease etiology, environmental factors.

Antecedente de vida rural ou de vida urbana e doença de Parkinson

RESUMO - A etiologia da doença de Parkinson (DP) é ainda desconhecida mas parece que fatores ambientais podem estar envolvidos. A incidência da DP, particularmente a de início precoce, parece ser maior em indivíduos com antecedente de moradia na zona rural. Avaliamos as características clínicas e a progressão da DP em 118 pacientes segundo os antecedentes de área de moradia pregressa. Havia 71 pacientes (60,2%) com antecedente de no mínimo 10 anos na zona rural (especialmente nas fases iniciais da vida), o chamado Grupo Rural (GR), e 47 pacientes (39,8%) que tiveram antecedente de vida exclusivamente urbana, o chamado Grupo Urbano (GU). A média de idade de início dos sintomas foi 58,8 anos no GR e de 54,1 anos no GU. A forma mista da DP (com tremor, bradicinesia e rigidez) foi a mais frequente em ambos os grupos. Um período de acompanhamento de no mínimo 6 meses foi obtido em 63 pacientes (média de 20 meses de acompanhamento) e a progressão da sintomatologia foi semelhante nos dois grupos (GR e GU). Nossos dados indicam que o antecedente de moradia não parece ser determinante para o padrão de manifestação clínica e de evolução da DP.

PALAVRAS-CHAVE: doença de Parkinson, epidemiologia; doença de Parkinson, etiologia; fatores ambientais.

The cause of Parkinson's disease (PD) is not yet known, but there is evidence that points to environmental factors being responsible for its etiopathogenesis⁵. Parkinsonism occurred as a consequence of the encephalitis epidemic which swept the world between 1917 and 1926, although subsequent studies had shown no evidence whatsoever that the illness has an infectious ingredient⁶. At the end of the 70's, in the United States, certain cases of parkinsonism arose in young individuals

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who had been using a chemical substance similar to meperidine, subsequently discovered to be methyl-phenyl-tetrahydropyridine (MPTP)¹³. MPTP provokes lesions in neurons of the substantia nigra. In humans, it produces a clinical picture very similar to that of idiopathic PD and in primates and mice it induces the experimental model of parkinsonism¹⁷. After this discovery, researchers began to wonder if an exogenous neurotoxin, possibly environmental in origin, could be responsible for the development of the disease. In the last few years, a series of epidemiological studies have suggested that PD is more prevalent among individuals who live in rural areas^{10-12,15,18}. Among the possible causative factors associated with rural living, consumption of well water^{15,18} and exposure to pesticides^{2,8,16} have been frequently cited. In a previous study carried out by our group, signs of parkinsonism were detected in agricultural workers who had been exposed to the fungicide maneb⁷. Our initial impression was that the clinical picture was that of manganese poisoning, given that maneb is an organic compound containing this metal. However, since the clinical characteristics, the pattern of progression of the symptoms and the development of wearing-off and on-off fluctuation to levodopa in one particular patient, made us to suspect that the fungicide is associated, not with manganese poisoning but with idiopathic parkinsonism. Previous rural living also appears to be associated with the development of the illness in younger patients¹⁵. Moreover, this precocious form of the illness appears to have certain clinical characteristics which distinguish it from the later-developing form⁹. This polymorphous clinical behavior may suggest that more than one etiological factor may be involved in the origin of the process⁴. If we consider that previous rural or urban living may be responsible for producing different PD sub-types, it is reasonable to assume that the clinical characteristics and the natural history of the two sub-types should also be distinct.

The aim of the present study is to detect possible clinical and natural history differences between patients with previous rural and urban living.

PATIENTS AND METHODS

Our original sample consisted of 133 patients with idiopathic Parkinsonism first seen by us between January/87 and October/92. Of this total, 15 were excluded on the grounds of having lived in a rural environment for less than 10 years, leaving a total of 118 patients. Of these, 107 were attending the outpatient clinic of Movement Disorders Unit of the Department of Neurology and Neurosurgery of the Escola Paulista de Medicina and 11 were attending the outpatient clinic of the Hospital das Clínicas of FM-USP in Ribeirão Preto, SP. These two facilities belong to teaching hospitals and attend patients who both directly seek treatment and are referred by other sources. The majority of the patients live in an urban environment (Ribeirão Preto has a population of 500,000 and São Paulo, 10 million) but have had previous experience of rural living.

The diagnosis of idiopathic Parkinsonism was based on the presence of two or more of the cardinal signs (rest tremor, bradykinesia, rigidity, and postural instability), responsiveness to levodopa, no previous exposure to neuroleptic drugs, and absence of atypical features.

Table 1. Characteristics of the two groups.

	Rural Group (RG)	Urban Group (UG)	Total
No. of patients	71 (60.2%)	47 (39.8%)	118 (100%)
Gender	41M/30F	31M/16F	72M/46F
Age of onset Mean \pm SD (in years)	58.8 \pm 12.6	54.1 \pm 13.3	56.9 \pm 12.9
More than 6 mo. follow-up	37 patients	26 patients	63 patients
Mean time of follow-up (N=63)	23 mo.	16 mo.	20 mo.

Age of onset RG vs. UG.

Mann-Whitney test: Not significant.

Table 2. Clinical pattern of PD.

	Rural Group	Urban Group	Total
Mixed form	51 (71.8%)	33 (70.2%)	84 (71.1%)
Rigid-akinetic form	7 (9.9%)	5 (10.6%)	12 (10.2%)
Predominant tremor	13 (18.3%)	9 (19.1%)	22 (18.6%)
Total	71 (100%)	47 (100%)	118 (100%)

Chi-square test: Not significant.

Table 3. Symptomatology based on Hoehn-Yahr staging in 63 patients with a more than 6 months of follow-up (N=63).

	Rural Group	Urban Group	Total
Better	7 (18.9%)	8 (30.8%)	15 (23.8%)
Not modified	16 (43.2%)	14 (53.8%)	30 (47.6%)
Worse	14 (37.8%)	4 (15.4%)	18 (28.6%)
Total	37 (100%)	26 (100%)	63 (100%)

Chi-square test: Not significant.

We divided the patients into two groups: the Rural Group (RG), with 10 years or more of rural living (at least the first 10 years of life), comprising 71 patients, and the Urban Group (UG), whose members had lived exclusively within an urban environment, comprising 47 patients. Rural living was considered present only in those who had lived in farms or in small villages near farms.

The patients were evaluated according to gender, age of onset of the symptoms of parkinsonism, clinical form of the illness (predominantly rigid-akinetic, tremor or mixed) and of the stage of Hoehn-Yahr in the first and most recent consultation. The Hoehn-Yahr stage in which the patient remained for the largest part of the day was used as the reference.

All patients received conventional PD treatment (i.e., generally anticholinergics or amantadine in stages I and II and levodopa+carbidopa or levodopa+benserazide, separately or in combination with the anticholinergic drugs or amantadine, for the remainder). Selegeline was not administered to any of the patients in this study.

Those patients who were seen by the same medical group for 6 months or more were assessed as to their stage of Hoehn-Yahr in their first and last consultations. Those whose stage had decreased were considered to have improved and those whose stage had increased were considered to have deteriorated.

In order to compare the results of the two groups (RG and UG), we used the chi-square test or Fisher's exact test. The Mann-Whitney test was utilized in the comparison of the ages at which symptoms began.

RESULTS

Table 1 shows the characteristics of the two groups. Symptoms of parkinsonism first appeared before the age of 40 in 4 RG (5.6%) and 6 UG patients (12.8%), a statistically not significant difference ($p > 0.05$).

The initial symptomatology was similar in both groups, as can be seen from Table 2. The mixed form of onset (tremor + rigidity + akinesia) was the most frequent and occurred in similar proportions in the two groups.

We were able to carry out a follow-up of more than 6 months in 63 (53.4%) of the 118 patients. Table 3 shows the progression of symptomatology throughout the follow-up period. The

majority of the patients (62.2% of the RG and 84.6% of the UG) either remained stable or showed an improvement in their stage of Hoehn-Yahr. The difference between the two groups was also statistically not significant.

DISCUSSION

The way in which the patients reached us and their socioeconomic situation were essentially the same. In these respects, the sample was thus considered to be homogeneous.

The predominance of those patients who had previously lived in a rural environment, although both treatment centers were located in large cities, appears to reflect the migratory nature of the Brazilian urban population. The majority of the RG patients in this study are currently living in the cities concerned, but had, of course, previously resided in rural areas for a considerable period of time, mainly in early phase of life. We arbitrarily stipulated that this period should be a minimum of 10 years because we considered this to be a sufficiently lengthy period for the individuals concerned to be exposed to putative neurotoxins which could give rise to Parkinson's disease.

Our results showed that there was no significant statistical difference between the two groups by any of the parameters assessed. These results are open to criticism on the grounds that the two groups were not controlled regarding the age of onset of symptoms. However, the average age of the beginning of the disease in the two groups showed no significant difference from a statistical point of view, which leads us to believe that the comparison is a valid one. As regarding follow-up, the ideal situation would have been to subdivide the patients by the age of onset of PD and the use or not of levodopa. However, such subgroups would have been exceedingly small and would not have permitted statistically valid comparisons. Moreover, the follow-up period was not very lengthy (an average of 20 months for the two groups).

In spite of these possible sources of error, our results suggest that living in an urban or rural environment by itself does not constitute a sufficiently strong factor to modify the clinical expression of PD. To confirm our findings we think that an epidemiological study shall be done comparing parkinsonian patients with exclusive rural living and exclusive urban living.

Thus, the existence of different clinical subtypes of the disease is possibly due to individual predisposition, perhaps genetic, and not to exogenous factors. It is known that PD does not generally show hereditary characteristics but some cases have shown clear autosomic dominant transmission with reduced penetrance¹⁴. Identical twin studies have shown low PD concordance¹⁹, although PET scan studies on twins using fluorodopa demonstrated that the non-parkinsonian twins have a greater tendency towards nigral dysfunction³. Barbeau et al.¹ were the first to call attention to the possibility that a combination of genetic and environmental factors may be responsible for the origin of the disease. In this hypothesis, known as the ecogenetic theory, environmental neurotoxins act on an individual already genetically predisposed to their effects¹.

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