

Early Onset Parkinson's Disease in Saskatchewan - Environmental Considerations for Etiology

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ABSTRACT: The cause of idiopathic Parkinson's Disease (PD) is not known but it is believed to be related to some environmental agent(s). Given a long preclinical interval and onset of symptomatology around age 60 years, it becomes impossible to identify and analyze all prior environmental factors satisfactorily. To circumvent these difficulties we evaluated the childhood environment in those PD patients whose symptoms began at age 40 years or earlier. Twenty-one such cases were born and raised in the province of Saskatchewan. Nineteen of these 21 patients spent the first 15 years of life exclusively in rural Saskatchewan. Detailed population analysis indicates a strong predisposition to early onset idiopathic Parkinson's Disease (EPD) in those raised in rural areas ($p=0.0154$). All but one case utilized exclusively well water for the first 15 years of life — a trait significantly different from that expected in the provincial population. It is concluded that rural Saskatchewan environments contribute to EPD and that well water used in childhood should be considered as a potential vehicle for the etiological agent.

RÉSUMÉ: La maladie de Parkinson à début précoce en Saskatchewan - Considérations environnementales relatives à l'étiologie La cause de la maladie de Parkinson (MP) idiopathique n'est pas connue, mais on croit qu'elle est reliée à un (des) agent(s) environnemental(aux). A cause d'une longue phase préclinique et d'un début de la symptomatologie vers l'âge de 60 ans, une identification et une analyse satisfaisantes de tous les facteurs environnementaux antérieurs s'avèrent impossibles. Pour contourner ces difficultés, nous avons évalué l'environnement pendant la période de leur enfance chez les parkinsoniens dont les symptômes ont commencé à 40 ans ou avant. Vingt-et-un de ces patients sont nés et ont été élevés dans la province de la Saskatchewan. Dix-neuf de ces vingt-et-un patients ont passé les quinze premières années de leur vie exclusivement dans un milieu rural de la Saskatchewan. Une analyse détaillée de population indique une forte prédisposition pour la maladie de Parkinson idiopathique, à début précoce (MPP) chez les patients élevés en milieu rural ($p = 0.0154$). Tous les cas, sauf un, avaient utilisé exclusivement de l'eau de puits pendant les 15 premières années de leur vie — cette particularité différant de façon significative de ce qu'on est en droit de s'attendre dans la population en général. Nous concluons que l'environnement rural en Saskatchewan contribue à la MPP et que l'eau de puits utilisée dans l'enfance devrait être considérée comme un vecteur potentiel de l'agent étiologique.

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Parkinson's syndrome is a common neurological disorder with an annual incidence of 20.5/100,000 and the majority (85.5%) of these cases suffer from idiopathic Parkinson's Disease (PD).¹ The etiology of PD is not known but many leading authorities now believe that the cause is some environmental factor.² Although the pathological process is believed to exist for a long time prior to the onset of symptomatology,³ recognition of preclinical cases is not possible.⁴ Identification and analysis of all environmental factors up to the time of clinical onset at around age 60 years in the mobile North American society is virtually impossible.

One way to overcome these handicaps is to study a single factor at a time, e.g. the role of prior viral infection,^{1,5,6} the relationship of smoking and subsequent development of PD,^{7,8,9,10,11,12} etc. Another alternative is to study several

environmental factors in detail for a limited period of time. Since the latent interval between first contact with the offending agent and clinical onset is not known, it is impossible to identify the window of vulnerability.

Yet another choice is to study only those cases whose symptomatology began at an early age (EPD). The clinical features of PD usually present around age 60 and onset under age 40 years is rare.^{13,14,15,16} The proportion of PD cases where the symptomatology is evident by age 40 ranges between 1.0% and 10% in different reports.^{13,17,18} All other considerations being equal, EPD would presumably indicate an earlier and/or more intensive exposure to the causative agent as compared to typical late onset cases. In spite of the limited number of cases, we believe the EPD category could provide valuable clues to the etiology of EPD/PD.

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We were able to study environmental factors associated with all EPD cases born and raised in the province. A preliminary report concerning the University Hospital based parkinson clinic records indicated a strong predisposition to EPD in the rural population.^{19,20} The present study is an extension of that work and now includes all known EPD cases in the province.

METHODS

In 1968 a special clinic to service parkinsonian patients was established at University Hospital, Saskatoon, and a large number of cases from across the province were registered. Data including age of onset of parkinsonism and type of parkinsonism were recorded in all cases.²¹

All neurologists (NL) and neurosurgeons (NS) practicing in the province were requested by letter, and subsequently in person, to identify all cases suspected of EPD. In addition, a newsletter was distributed in order that all physicians in the province would be aware of our search. All cases were evaluated by one of us (AHR) and only those suffering from PD with an onset by their 40th birthday were included in this study. Two EPD cases died and at autopsy were confirmed to have Lewy body disease.

Among the 557 PD patients seen during a 16 year period (December 1968-November 1985) in parkinson clinic, 27 (4.8%) had EPD. Five of these were born and raised outside the province, and childhood residence could not be established in one (a North American Indian). A total number of 21 patients were identified as having been raised in the province of Saskatchewan and form the basis of this report. We have received information on some other patients who reside outside of the province but who had been born and raised in rural Saskatchewan; these were excluded as all EPD cases now living elsewhere cannot be identified.

Birthplace and residence during the first 15 years of life were recorded in each case. Where families changed residence during the 15 year period under consideration, the new residential locations were identified. The population of each community at the time of the patient's residence there was noted from provincial census records. Communities were classified as urban (cities and towns) or rural (villages, hamlets, and farms) on the basis of provincial census criteria.

A detailed account of the family history of PD, ethnic background, eventual occupation, prior illnesses, and use of neuroleptic drugs was made in each case. The source of drinking water in every community where a patient resided during the first 15 years of life was established in each case.

The total number of person-years (population \times years) was estimated for all residents exposed to the provincial environments between 1904 and 1962 (corresponding to EPD cases' first 15 years of life). Similar information on the population exposure to rural and urban environments was tabulated for the same 59-year period. The probability of early life exposure to rural and urban environments in the general population was computed using a binomial distribution calculation.

RESULTS

All EPD cases were born between 1904 and 1947 (Table 1). The mean age at onset of symptomatology was 35 years (range = 25-40). Nineteen of the 21 patients were born and lived for

the first 15 years exclusively in a community with a population of 169 persons or less. A single patient was born and raised solely in an urban residence. One patient was born in an urban center and lived there until age 9 years, when her family moved to a small rural community (Figure 1). None of the communities where a patient was born or raised changed its status from rural to urban or vice versa during the 59 years studied.

From 1904 to 1962 the cumulative (rural and urban) population exposure was 43,458,168 person-years. Of that, 68.4% (29,739,477) represented rural and 31.6% (13,718,691) urban exposure (Table 1). For the 21 EPD patients, the first years of life exposure consisted of 291 (92.4%) rural and 24 (7.6%) urban person-years. Probability calculations are based on the census data shown in Table 1. The 291 rural/24 urban person-year distribution over the time period studied corresponds to a p-value of $<1.47 \times 10^{-23}$. This estimate considers only a portion of life in EPD cases but a larger segment of life in the remaining population. The data were also analyzed using the total provincial population figures for persons living in the province during the same period. The probability that 20 of 21 would have experienced exclusively rural exposure for the first 15 years of life is $p=0.0033$; the probability that 19 out of 21 would have experienced exclusively rural childhood exposure is $p=0.0154$. The first p-value (0.0033) is appropriate for the EPD cases if one classifies the individual who spent six of the first 15 years in a

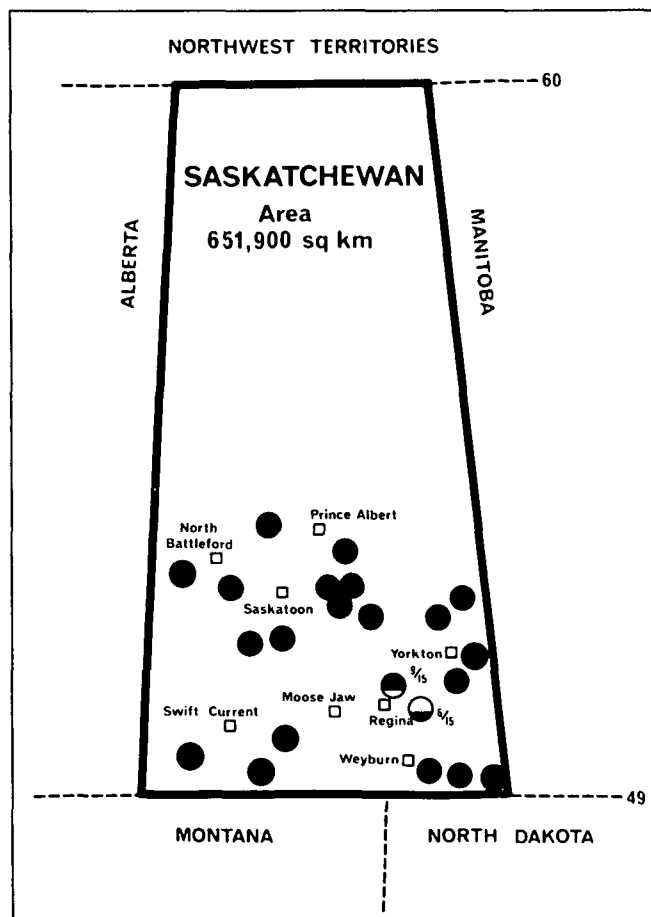


Figure 1 — Squares denote larger urban centers. Filled circles indicate location where each EPD case spent the majority of childhood. The partially filled circles represent patient #21 who spent part of childhood in a larger center and part in the country.

Table 1: Population Exposed to Provincial Environments During the 59-Year Period^a Expressed in Person-Years^b

Time Span	Total Provincial Person-Years	Rural %	Person-Years	Urban %	Person-Years
1904-05	182,556	84.4	154,077 (1)	15.6	28,479
1906-10	1,288,815	86.5	1,114,825	13.5	173,990
1911-15	2,462,160	79.9	1,966,525	20.1	495,635
1916-20	3,239,175	80.0	2,592,635 (4)	20.0	646,540
1921-25	3,787,550	79.0	2,993,680 (5)	21.0	793,870
1926-30	4,103,690	79.0	3,241,915 (4)	21.0	861,775
1931-35	4,608,925	76.8	3,539,655 (2*1)	23.2	1,069,270 (*1)
1936-40	4,657,735	77.8	3,621,855 (1)	22.2	1,035,880
1941-50	8,959,920	67.1	6,012,106 (3)	32.9	2,947,814 (1)
1951-60	8,317,280	44.6	3,706,810	55.4	4,610,470
1961-62	1,850,362	43.0	795,394	57.0	1,054,968
1904-62	43,458,168 (21) (100%)		29,739,477 (20*1) (68.4%)		13,718,691 (2*1) (31.6%)

() = number of early onset PD patients born into and raised in Saskatchewan population

(*) = case with both urban and rural exposure

a = time interval when each case lived first 15 years in the province

b = number of persons multiplied by years of residence

rural setting as having experienced exclusively rural early exposure. The second value ($p=0.0154$) is appropriate if one classifies the same individual as having had no rural exposure over the first 15 years. In any case, the p -value is less than 0.05, indicating a predisposition to EPD in those raised in rural communities.

Analysis of sex, ethnic background, and occupation in the 21 cases revealed no pattern of predisposition to EPD.

The source of drinking water was different in the two groups. Only one of the patients used a central water supply. This was the patient with exclusive urban exposure. One patient was born in a large urban center but her family lived in an isolated portion of the city where no central water supply was available. They fetched water from a nearby well. When the patient was 9 years old her family moved to a small rural community that had no central water supply.

In general, rural communities use well water and urban centers have central water supplies. Water supply information in all communities for the past eight decades cannot be as accurately established as population patterns. Assuming that all rural areas used well water and all urban areas had central water supplies, statistical analysis indicates that the probability of 20 out of 21 cases utilizing only well water is $p=0.003$, and therefore, highly significant.

DISCUSSION

Universal provincial tax supported government-run medical insurance in 1962 made health services equally and easily accessible to all Saskatchewan residents, and since 1975, drugs are also covered by the same insurance.²² The physician is required to identify the diagnosis for services rendered at each patient visit. All residents are expected to consult an in-province specialist for elective care, thereby assuring registration of all EPD cases with one or another neurological specialists in the province.

Since 1954 NL and NS services have been available in Saskatchewan. Most neurological problems and especially unusual ones (including EPD) are referred to one of the

specialists. The current practitioners also have access to patient records of previous specialists. This set-up, in conjunction with an active parkinson clinic at University Hospital, Saskatoon, made possible identification of all EPD cases seen over the past 23 years.

The cause of Parkinson's disease has been thought to be either genetic or environmental. Twin studies in Parkinson's disease represent the strongest argument against genetic etiology.^{23,24} The search for an environmental cause has included prior viral infections,^{1,5,6,25} association with smoking,⁷⁻¹² and the role of a variety of organic compounds.²

Irreversible degenerative changes in the substantia nigra in man^{26,27} and in monkey²⁸ have been demonstrated on exposure to a synthetic narcotic compound, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). However, Lewy body inclusions, the hallmark of PD, are not seen in MPTP-induced parkinsonism cases²⁹ and they remain biochemically distinct from naturally occurring disease.³⁰

The literature to date provides no convincing lead into the etiology of PD, though the most likely cause is believed to be some environmental agent(s).²

Some leading authorities believe the preclinical interval for PD is two to three decades.³ Since the diagnosis is generally not possible until around age 60 years, numerous environmental factors deserve consideration as potential etiologic agents — a difficult, if not impossible, task in a mobile North American society. The disease occurs in all races and all geographic areas, more attention should therefore be given to commonplace, universally operative environmental factors.

In order to limit the number of variables to be considered, we chose to evaluate only those patients whose clinical symptomatology was evident by the 40th birthday. Early onset parkinsonism is frequently a manifestation of multiple system atrophy, inherited disorders, rare basal ganglia diseases, carbon monoxide poisoning, manganese poisoning, cyanide poisoning, or neuroleptic drug therapy.³¹⁻³⁶ The pathological changes in these disorders are distinct from PD. While some of the drug induced cases have preclinical PD,³³ histological changes of PD are not attributable to neuroleptic agents. Our study was limited to PD

cases. Two cases were autopsied and showed Lewy body disease. The percentage of EPD cases found in our PD population (4.8%) is comparable to that reported in other studies.^{13,17,18}

We concentrated on environmental factors operative during the first 15 years of life to limit the number of agents to be considered. Another reason for choosing this time period was the well known fact that environmental factors during early life are crucial for the development of multiple sclerosis later in life.

Although it was nearly impossible to reduce our data to any single point which would permit simple analysis, there emerged one significant common denominator: the variable of rural and urban environments in the EPD cases and in the general population of the province. We observed that those exposed to rural environments were much more liable to develop EPD than those who lived in larger communities ($p=0.0154$). Neurological specialists are located in two larger centers. Although such specialist distribution would favor case ascertainment in the urban population, nearly all our cases came from rural areas. This further authenticates the reliability of our observations.

We have identified differences existing between provincial rural and urban environments. Persons living in the rural areas are more likely to be involved occupationally with farming and therefore may be exposed to a wide range of pesticides and herbicides. In the urban centers, government, university, and trade are predominant. No major industries operate in either setting. Racial distribution is essentially homogeneous between the two environments. Air quality is similar in urban and rural areas alike. Rural areas use fresh farm products as food sources more often than their urban counterparts, however, long winters limit the availability of many fresh farm products to only 3-4 months. Finally, urban centers use running water while all rural areas (populations less than 250) use well water.

An analysis of occupations revealed no peculiarities with respect to EPD patients, when compared with persons living in rural Saskatchewan. There was no racial or ethnic predisposition to EPD and family history was positive in only two patients; in each case the patient's mother developed PD at a later age.

The source of childhood drinking water was carefully documented in all cases. Twenty of the 21 households used well water at the time when the patients were growing up. Relying almost solely on well water, some augmented that with water stored in large barrels or dugouts. The exact source of water consumed by all residents of Saskatchewan during the 59-year interval under study cannot be established. In general, urban centers had a central water supply whereas rural Saskatchewan communities did not, instead using well water. The exception to this generality is evident in the single case who lived in a city and yet used well water. Because of this uncertainty, unequivocal statistical analysis of the source of drinking water is not possible. On the basis of urban and rural population distribution (Table 1), we estimate that the probability of 20 out of 21 patients using well water exclusively during the first 15 years of life, on the basis of chance alone, is approximately $p=0.003$, and thus significant.

We believe that EPD cases were exposed to some factor(s) that was dominantly operative in rural communities and that childhood drinking water is a potential vehicle for such an agent. Higher prevalence rates for Parkinson's disease have been identified in rural areas of Quebec specializing in market-gardening and wood-mills.³⁷ As well, recently others have reported finding a similar association between well water con-

sumption and Parkinson's disease.^{38,39} Since water is a universal commodity used by all human beings, water-related factor(s) could affect all nationalities. Insidious and chronic contamination of well water, with herbicides and pesticides for example, might produce harmful chemical agents leading to the development of Parkinson's disease. It is also conceivable that drinking water from a central water supply, where some processing occurs — chemical or otherwise, may provide a degree of protection from development of EPD.

We recognize our inability to analyze all the possible premorbid factors operative in EPD cases. Nevertheless, we believe that the identification of a high risk population base in rural Saskatchewan is a valuable clue that could prove crucial in determining the cause of PD.

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