Height as a Potential Indicator of Early Life Events Predicting Parkinson’s Disease: A Case-Control Study

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Abstract: Aim of this study was to investigate the relationship between height in young adult age and Parkinson’s disease (PD) risk. We included 266 persons affected by idiopathic PD. Patients were matched by age and sex to 266 controls by a random selection from the municipality of residence. We collected information about height preceding PD from official documents where these characteristics referred to young adult age (nearly 30 years). We compared height in cases and controls by calculating differences in mean distribution and by χ² analyses. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated by logistic regression models. Mean height was significantly lower in persons affected by PD compared to controls (P = 0.03). Difference was significant only in men (P = 0.001). Logistic regression models showed an inverse association between height and PD (OR 0.35; CI 0.16, 0.79; P < 0.01 comparing individuals in the highest percentiles of height with those in the lowest). Our results indicate an association between height and PD in men. Considering that dopamine sensitivity in the hypothalamic-pituitary axis is related to adult height, our findings suggest a relationship between PD and factors modulating somatic growth early in life. © 2007 Movement Disorder Society

Key words: Parkinson’s disease; epidemiology; risk factors; height; anthropometric measures.

In medical literature, stature has been associated with diseases including cancer and cardiovascular disorders.1–3 The accumulating evidence that stature is an indicator of phenomena occurring during body growth linked to pathological processes implies that the search for risk factors associated with diseases occurring at a late age should be extended to the early phases of life.4 Growth hormone (GH) release after l-dopa stimulation is reduced in children with short stature.3 A functional relationship between striatal extracellular somatostatin and the GH and dopamine (DA) systems in the striatum of anesthetized rats has been reported.5 Also, dopamine receptor genes contribute to the inheritability of stature, and a possible haplotypic association between stature and the DRD2 gene has been reported as well.6,7 These data suggest an interaction between hypothalamic-pituitary axis activity and tissue sensitivity to dopaminergic stimulation. If this is true, people who later develop Parkinson’s disease (PD) may have characteristics related to a lower sensitivity to dopaminergic stimulation, preceding clinical symptoms.

We conducted a case-control study to investigate the possible association between PD and height in ages prior to the clinical onset of the disease.

PATIENTS AND METHODS

Cases and Controls

Patients with idiopathic PD were consecutively recruited among outpatients from the neurological clinics of Palermo and Messina, Italy, starting February 2001 to May 2005. The same diagnostic criteria used in a population-based survey on the prevalence of PD in Sicily were applied.8,9 Diagnoses of idiopathic PD were reached in two phases. In the first phase, parkinsonism was identified by the presence of at least two of four
cardinal signs in people who were not on anti-parkinsonian therapy: tremor at rest, rigidity, bradykinesia, and impaired postural reflexes; at least one of the above signs was required in individuals who were taking anti-parkinsonian therapy. In the second phase, diagnoses of idiopathic PD were supported by unilateral onset, progressive course, asymmetry of signs, and good responsiveness to anti-parkinsonian drugs (L-dopa or dopamine agonists). We considered as good responsiveness an improvement of at least 30% in the UPDRS motor scores compared to the score obtained before treatment. Vascular and other forms of parkinsonism were excluded through a screening for history of stroke, head trauma, encephalitis, and sudden onset or stepwise progression of symptoms. We also excluded individuals who consumed neuroleptic drugs during the 6 months before the onset of symptoms, or who showed the presence of cognitive impairment or of other neurological signs within the first year of the onset of symptoms. Brain CT, MRI, and SPECT, though not critical for inclusion, were also evaluated when available. PD onset was defined as the year in which one of the cardinal signs was first noted.

PD patients were matched (1:1) by sex and age (±2 years) to individuals free of neurological diseases randomly selected from the population records of the municipality of residence of the case. Diagnoses were reviewed by at least two neurologists. The same neurologists, through an extensive review of medical history and a careful neurological examination, ascertained the absence of neurological diseases in controls. We selected more than one control for each patient. Whenever it was not possible to trace a control through the information collected at the municipality records, or the control refused to participate in the study, we interviewed the next person in the randomization list.

**Risk Factor Assessment**

Height of cases and controls was abstracted from official documents (passport, identity cards, other kind of sources used in Italy such as association cards or railways cards where height is stated) where these characteristics referred to young adult age (30 years). Clinical records were also used when available. Trained personnel administered a face-to-face structured questionnaire to each case or control before any decision regarding diagnosis and inclusion was made. Clinical examination of cases and controls were made by expert neurologists trained in movement disorders.

**Data Analysis**

Differences between means of height in cases and controls were compared by the $t$-test. Frequency distribution of height was compared in cases and controls by $\chi^2$ analysis. We estimated the association between height and PD by the calculation of the odds ratio (OR). OR with 95% confidence intervals (CI) and two-tailed $P$ values ($\alpha = 0.05$), adjusted for age, sex, education level, type of work, smoking habits, and coffee consumption, were calculated by logistic regression analyses. Logistic models are ordinary models; for this reason a noncomplete correspondence may exist between the number of cases and controls stratified by sex reported in the tables. Height was categorized according to the percentiles of distribution in the whole sample (25th, 50th, and 75th percentiles) and independently for men and women. Subjects were classified also as nonsmokers (less than an average of a pack of cigarettes per month during adult life) and smokers (at least an average of a pack of cigarettes per month during adult life). Coffee consumption was classified as nondrinkers (less than an average of a cup of coffee per week during adult life) versus drinkers (at least an average of a cup of coffee per week during adult life). To calculate these habits, people were also asked at what age they started smoking, or drinking coffee, their age at cessation, and any possible discontinuation. Education level, taken as completed years of school, was stratified in 4 groups: 0 years, 1 to 8 years, 9 to 13 years, more than 13 years. The type of work was divided in the following categories: intellectual, manual workers, housewives, all others. Apart from the type of work, other variables including age of cases and controls were included in multivariate models as continuous ordinal variables. The local ethical committee revised and approved the study.

**RESULTS**

Two hundred sixty-six cases and an equal number of controls were included. Response rates were high both in cases (90%) and in controls (86%), whose characteristics are shown in Table 1. The distribution of the occupation was not significantly different among cases and controls, although intellectual jobs were more represented in men (both cases and controls). As previously reported in other studies smokers were more common in controls compared to cases but difference was not significantly different. Coffee drinking was significantly more frequent among controls compared to cases. We observed no differences in age distribution between cases and controls. Mean age at PD onset and duration of PD symptoms at the date of interview were similar in men and women. As shown in the table, mean difference of height between cases and controls was about 1.4 cm, the median difference being 1 cm ($P = 0.026$). Mean height difference between cases and controls in men was 2.55 cm, the
median difference being 2 cm ($P = 0.004$). Both of the observed extremes of height ranges were higher in healthy men than in PD patients. Mean difference of height between cases and controls in women was not significantly different (0.32 cm; $P = 0.58$).

Table 2 illustrates calculations stratified by sex according to the percentiles of height distribution. PD was inversely associated with height (Table 2). This association was significant in men in the highest percentile, with a significant trend ($P < 0.01$). We did not observe any significant association between PD and height among women. Table 3 shows the results of multivariate regression model where height of PD patients is compared to the height of controls by stratifying for the percentile of distribution of height within gender. The lowest percentile for each gender represent the referent category (lower than 165 cm in men and lower than 156 cm in women), the second category is between 165 and 173 in men and between 156 and 163 in women. Finally, the highest percentile is higher than 173 cm in men and higher than 163 cm in women. We also introduced a term for interaction by gender and height. The interaction approximated only the statistical significance for the highest percentile. This may be due to a sample not large enough to discriminate the effect of gender, but it would anyway suggest that the association between PD and height may be different in men and women.

**DISCUSSION**

The results of the current study are consistent with an inverse association between PD and height. The association was extremely significant among people in the highest quartiles of height and in men. We did not find, on the contrary, an association between PD and height among women.

**Consideration on Methods**

Our study has its strengths and its limits. The sample size was large enough to allow a power of more than
80% with CI of 95% and two-sided $P$ values. Power calculation was made considering a height difference of at least 1 cm to detect an OR of 2. Power was estimated for the whole sample; the differences observed in height among women do not allow enough power to be sure that the observed negative results are not due to chance alone. This is demonstrated by the height gender interaction, which approximates the statistical significance. Diagnoses were made independently of risk factor collection. The diagnosis of idiopathic PD, based on validated criteria suitable for epidemiological purposes, was reached by at least two neurologists trained in movement disorders who were not the same as those who administered the questionnaire. The demographic characteristics of cases and controls were similar. Strata by gender also showed similar distributions. To reduce the risk of confounding and cohort effects, we performed analyses adjusted by sex, age, education, and type of work. We also made adjustments for smoking and coffee consumption because these risk factors have been reported to be associated either with both PD and somatic growth in many studies and they could therefore represent potential confounders. This study has also its limits. The most evident limit is the effort to retrospectively collect information about height at ages many years before the onset of disease symptoms. Information was collected from individuals and its accuracy was tested by reviewing official documents such as identity cards, passports, or other sources reporting such information, and by clinical records when available. All people included in the study were able to provide at least the identity card to collect information on height. Potential errors caused by the documents’ lack of accuracy would, however, be randomly distributed throughout the whole sample.

Another limit derives from the inclusion of prevalent cases. The large sample size, the disparity of results between men and women, and particularly the increasing significant trend with increasing height reduce the risk of prevalence–incidence bias but do not rule out this possibility altogether. The possibility exists in fact, that if taller persons are at higher risk for other disease and with a worst prognosis, then shorter individuals could be over represented among PD patients. Finally, misdiagnoses especially between idiopathic PD and vascular PD have a very low chance to modify our results because of the diagnostic criteria adopted. Moreover, in almost all the patients enrolled in the study at least an imaging study was performed.

Consideration on Results

This is to our knowledge the first study exploring the association between PD and height. The difference in heights was significant only for men. Interestingly, our results did not reveal any association between PD and height in women. If we look for a possible biological explanation, the effect of estrogens has to be considered. Many reports indicate that estrogen treatment tends to reduce the final adult height of tall girls. Other reports have suggested an association between PD and the estrogen stimulation during a woman’s life. The interaction between sex steroid exposure and PD may partly account for the lack of association we observed between PD and height in women.

Many studies have been conducted investigating the association between PD and other somatic characteristics such as the body mass index (BMI) preceding disease onset, but the results have been inconsistent. There are several reasons for the discordant findings. Recall and classification bias presumably affected retrospective studies in which the information was based only on self-reported data. This is not anyway the case of the study we refer to. Also, in diseases like PD, the degenerative process starts many years before the onset of symptoms and it is hard even in prospective studies to discriminate the temporal relationship between continuous phenomenon related to the exposure and the disease.

An ever increasing amount of data indicate the need to explore factors occurring early in life, related to body growth and tissue differentiation, which predetermine the risk for chronic and degenerative diseases. For these reasons we investigated the association between PD and stature. There are several indications that corroborate our findings. First, height is determined in the very early phases of life and is only in part modified by other factors possibly associated with PD. Second, it is possible to collect information about height with sufficient reliability by retrieving clinical records or official documents where such data are recorded before any disease has occurred. Third, the temporal relationship between final adult height and the disease is clear and distinguishable. Fourth, body growth expresses phenomena which are clearly and closely linked to brain development. Recent studies hypothesize that the pathological mechanisms underlying PD follow steps that may be in some way related to central nervous system development.

Other interesting speculations increase the interest of a possible relationship between PD and stature. Physical symptoms, indicating a growth hormone deficiency, include reduced vitality, premature fatigue, reduced strength, and a low tolerance to exercise. Individuals also experience decreased psychological well-being, socially inhibited behavior, low self-esteem, and emotional distress. Moreover, growth retardation seems to be associated with altered behavior and fear of novelty.
Many studies have suggested that a pre-morbid personality may explain the inverse relationship observed between PD risk and some habits such as cigarette smoking, coffee consumption, or alcohol drinking. According to this hypothesis, people who later develop PD tend to avoid novelty seeking because of a personality trait preexisting to PD. These results, considered altogether, indicate that personality traits may simply reflect an altered response to physiological and psychological stressors because of mechanisms associated with growth retardation.

Previous studies have reported an inverse association between stature and diseases like cardiovascular pathologies while a direct association has been reported between cancer and greater height. These studies provide no reason for believing that a selective morbidity or mortality cohort effect may have generated our results. A recent study also indicated an inverse association between dementia and height, and it is increasingly thought that certain events—apart from genetic considerations—occurring in the initial phases of life make a substantial contribution to what will finally happen with ageing.

Height in adult life is influenced by many factors operating early in life. The Intrauterine environment is ageing. The relationship between a degenerative disease like PD and events occurring early in life strikes us as being an interesting issue worth investigating through other epidemiological and biological studies.

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REFERENCES

5. Crespi F. Functional in vivo interaction between growth hormone and dopamine systems are correlated to changes in striatal somatostatin levels as detected by voltammetry. Exp Brain Res 1993; 94:363–370.