Are men at greater risk for Parkinson’s disease than women?

G F Wooten, L J Currie, V E Bovbjerg, J K Lee, J Patrie

METHODS

The Medline database was searched for population based ascertainment studies of PD average annual incidence rates adjusted for sex and age. The studies included in our meta-analysis met six criteria: (1) The study must have been published after 1980. Inclusion of studies published before 1980 would lead to the inclusion of neurodegenerative disorders that would be recognised now as not being PD (for example, progressive supranuclear palsy, multiple system atrophy, etc). Also, older studies are more likely to be contaminated with cases of post-encephalitic parkinsonism than studies published after 1980: (2) studies must have excluded secondary and/or drug induced parkinsonism; (3) studies must have ascertained at least 50 cases of PD; (4) the reported data must have included the sex of the probands and been expressed as age adjusted data; (5) studies must have ascertained all age groups—that is, there must be no age criteria for inclusion; and (6) ascertained cases must have been based on general population counts rather than age stratified sampling. Seven studies met all inclusion criteria.4–10

Statistical analysis

Meta-analyses were performed to determine whether there was a difference in PD incidence between men and women. Two population parameters were statistically analysed: the population incidence of PD, and the population age adjusted incidence ratio. To determine whether the incidence of PD was similar among the men and women in the seven populations we used a Mantel-Haenszel test11 to test the null hypothesis that the ratio of the common odds for the incidence of PD among men and women was equal to 1. To determine whether the age adjusted incidence of PD was similar among men and women we used a non-parametric Wilcoxon rank sum test to test the null hypothesis that the median age adjusted incidence ratio (male/female) was equal to 1.12 A bootstrap re-sampling procedure13 was used to construct 95% confidence limits for the median age adjusted incidence ratio.

RESULTS

Table 1 shows the average annual incidence rates per 100 000 population adjusted for sex and age for the seven studies meeting our inclusion criteria. The weighted mean male to female ratio was 1.49.

Using the Mantel-Haenszel test within these study populations, the odds of a man being affected with PD, $\hat{c}_{M/F} = \text{common odds ratio (male/female)},$ was $1.17$ ($95\% \text{ CL (1.07 to 1.28)}, \chi^2_{\text{obs}} = 11.22; p = 0.0008$) times the odds of a woman being affected. Note that 1.17 is not an age adjusted ratio (that is, it is unweighted). Therefore, the relative incidence rate ratio of men to women of 1.49 more closely reflects the relative rates of PD occurrence between the sexes in the datasets that we have included in this meta-analysis.

Table 2 shows the data for the Wilcoxon rank sum test. Age adjusted incidence of PD using the Wilcoxon rank sum test was greater for men than women: the median of the age adjusted incidence ratios (men/women) was 1.49 ($95\% \text{ CL (1.24 to 1.95, } p = 0.031)$.

Based on these statistical tests a significantly higher incidence rate of PD was found among men with the relative risk being 1.5 times greater in men than women.
1995, an incidence study of PD as part of the Rotterdam parkinsonism, and other parkinson-plus syndromes. In 1984, Rajput et al in Olmstead County, Minnesota. Inclusion criteria. In 1984, Rajput et al reported sex specific incidence of parkinsonism from Olmstead County, Minnesota. Though the average age and sex specific incidence rates were higher for men in every decade of life, the authors explicitly included several types of parkinsonism including idiopathic PD, drug induced parkinsonism, and other parkinson-plus syndromes. In 1995, an incidence study of PD as part of the Rotterdam study was published in abstract form. These authors reported a similar age specific risk of PD for men and women, however, this study ascertained only subjects age 55 or older, thereby arbitrarily excluding a subpopulation of patients at risk for PD. Baldereschi et al recently reported PD incidence data from the Italian longitudinal study on aging (ILSA). The age adjusted average annual incidence rate was twice as high in men, but only 42 incident cases of PD were ascertained. The only study in our analysis reporting a male to female incidence ratio of less than 1 was that of Granieri et al, also from Ferrara in Italy. Baldereschi et al pointed out that their case finding methodology was superior to the record based strategy used by Granieri et al. The data reported by the ILSA group are particularly compelling because the investigators directly contacted the subjects in the general population and did not rely solely on medical records.

Thus, the best epidemiological datasets currently available consistently suggest that men are at greater risk for developing PD than are women. The reasons for the increased risk in men are not known. Is male sex in itself a risk factor for PD or is it a surrogate for some other primary risk factor to which men have greater exposure? For example, some case-control studies have suggested that toxicant exposure and head trauma may be risk factors for PD. Thus, the “male lifestyle” and certain sex roles that men assume such as farm work could account for some of the excess incidence in men. Alternatively, there is increasing evidence from in vitro as well as clinical studies in humans that oestrogen may be neuroprotective. The mechanisms whereby oestrogen may be neuroprotective may include activation of the mitogen activated protein kinase pathway, modulation of Bcl-x(L) expression, and/or synergy with the free radical scavenger, glutathione. It may be relevant that the excess of PD in men, where mitochondrial dysfunction has been reported, is similar to the high ratio of affected men to women in Leber’s hereditary optic neuropathy. Leber’s hereditary optic neuropathy results from homoplasmic mutation of mitochondrial DNA encoding a portion of complex I of the mitochondrial electron transport chain; but, the mechanism for the increased risk of Leber’s hereditary optic neuropathy in men is not known. Finally, several recent genetic linkage studies have localised a PD susceptibility gene to the X chromosome, a finding that could, potentially, explain the higher incidence of PD among men. Whatever the cause of increased risk of PD among men, a search for its basis may yield new clues to the pathogenesis of this enigmatic disease.

**DISCUSSION**

Our meta-analysis of seven studies of PD incidence meeting stringent criteria suggests that men are at greater risk for PD than women. Incidence rates adjusted for sex and age control for confounding factors in both prevalence and death rate studies. In particular, incidence studies minimise both the effects of sex differences in the populations from which the subjects are ascertained, a problem with prevalence studies, and the inaccuracy of death certificates, a problem with death rates. Technically, one of the least biased ascertainment methods would be a door to door survey. Only one of the studies included in our analysis used door to door ascertainment methods. Thus, potential bias in ascertainment methods and case identification must be considered for the other six studies. In none of the seven studies included in our meta-analysis were all subjects directly contacted by the investigators. Finally, we used the age adjusted rates provided by each of the studies. While it is probable that the various authors used standard methods for adjusting, it is also probable that several adjustment methods were used, and the differences in these methods may have resulted in different study specific rates than if unadjusted data from each study had been age adjusted by a uniform method.

Several recent incidence studies failed to meet our inclusion criteria. In 1984, Rajput et al reported sex specific incidence of parkinsonism from Olmstead County, Minnesota. Though the average age and sex specific incidence rates were higher for men in every decade of life, the authors explicitly included several types of parkinsonism including idiopathic PD, drug induced parkinsonism, and other parkinson-plus syndromes. In 1995, an incidence study of PD as part of the Rotterdam study was published in abstract form. These authors reported a similar age specific risk of PD for men and women, however, this study ascertained only subjects age 55 or older, thereby arbitrarily excluding a subpopulation of patients at risk for PD. Baldereschi et al recently reported PD incidence data from the Italian longitudinal study on aging (ILSA). The age adjusted average annual incidence rate was twice as high in men, but only 42 incident cases of PD were ascertained. The only study in our analysis reporting a male to female incidence ratio of less than 1 was that of Granieri et al, also from Ferrara in Italy. Baldereschi et al pointed out that their case finding methodology was superior to the record based strategy used by Granieri et al. The data reported by the ILSA group are particularly compelling because the investigators directly contacted the subjects in the general population and did not rely solely on medical records.

Thus, the best epidemiological datasets currently available consistently suggest that men are at greater risk for developing PD than are women. The reasons for the increased risk in men are not known. Is male sex in itself a risk factor for PD or is it a surrogate for some other primary risk factor to which men have greater exposure? For example, some case-control studies have suggested that toxicant exposure and head trauma may be risk factors for PD. Thus, the “male lifestyle” and certain sex roles that men assume such as farm work could account for some of the excess incidence in men. Alternatively, there is increasing evidence from in vitro as well as clinical studies in humans that oestrogen may be neuroprotective. The mechanisms whereby oestrogen may be neuroprotective may include activation of the mitogen activated protein kinase pathway, modulation of Bcl-x(L) expression, and/or synergy with the free radical scavenger, glutathione. It may be relevant that the excess of PD in men, where mitochondrial dysfunction has been reported, is similar to the high ratio of affected men to women in Leber’s hereditary optic neuropathy. Leber’s hereditary optic neuropathy results from homoplasmic mutation of mitochondrial DNA encoding a portion of complex I of the mitochondrial electron transport chain; but, the mechanism for the increased risk of Leber’s hereditary optic neuropathy in men is not known. Finally, several recent genetic linkage studies have localised a PD susceptibility gene to the X chromosome, a finding that could, potentially, explain the higher incidence of PD among men. Whatever the cause of increased risk of PD among men, a search for its basis may yield new clues to the pathogenesis of this enigmatic disease.

**Table 1** Average annual incidence rates per 100 000 population adjusted for sex and age

<table>
<thead>
<tr>
<th>Author(ref)</th>
<th>Site</th>
<th>Year</th>
<th>Number of cases ascertained</th>
<th>Number of M/F</th>
<th>Population sampled M/F</th>
<th>Age adjusted incidence per 100000 population/y (M/F)</th>
<th>M/F ratio (weighted mean ± 1.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender (4)</td>
<td>Poznan, Poland</td>
<td>1989</td>
<td>159</td>
<td>78/81</td>
<td>625506/672629</td>
<td>13/10</td>
<td>1.30</td>
</tr>
<tr>
<td>Wang (5)*</td>
<td>China, 29 provinces</td>
<td>1991</td>
<td>566</td>
<td>327/239</td>
<td>1936717/1932445</td>
<td>2.1/1.7</td>
<td>1.24</td>
</tr>
<tr>
<td>Granieri (6)</td>
<td>Ferrara, Italy</td>
<td>1991</td>
<td>394</td>
<td>175/219</td>
<td>89429/97952</td>
<td>9.32/10.65</td>
<td>0.88</td>
</tr>
<tr>
<td>Kuoppio (7)</td>
<td>Southwestern Finland</td>
<td>1999</td>
<td>385</td>
<td>187/198</td>
<td>92250/104614</td>
<td>21.5/11.0</td>
<td>1.95</td>
</tr>
<tr>
<td>Vines (8)</td>
<td>Navarre, Spain</td>
<td>1999</td>
<td>96</td>
<td>63/33</td>
<td>259870/263693</td>
<td>10/1.49</td>
<td>2.06</td>
</tr>
<tr>
<td>Bower (9)</td>
<td>Olmsted County, MN</td>
<td>1999</td>
<td>154</td>
<td>89/65</td>
<td>682764/741710</td>
<td>13/0.88</td>
<td>1.48</td>
</tr>
<tr>
<td>Mayeux (10)</td>
<td>Northern Manhattan, NY</td>
<td>1991</td>
<td>83</td>
<td>36/47</td>
<td>72807/110127</td>
<td>17.1/11.3</td>
<td>1.51</td>
</tr>
</tbody>
</table>

*Door to door survey.

**Table 2** Age adjusted incidence ratio (men/women)

<table>
<thead>
<tr>
<th>Site</th>
<th>Age adjusted incidence ratio (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>1.30</td>
</tr>
<tr>
<td>China</td>
<td>1.24</td>
</tr>
<tr>
<td>Italy</td>
<td>0.88</td>
</tr>
<tr>
<td>Finland</td>
<td>1.95</td>
</tr>
<tr>
<td>Spain</td>
<td>2.06</td>
</tr>
<tr>
<td>US (MN)</td>
<td>1.48</td>
</tr>
<tr>
<td>US (NY)</td>
<td>1.51</td>
</tr>
<tr>
<td>median ratio</td>
<td>1.49 (95% CI (1.24, 1.95))*</td>
</tr>
<tr>
<td>p(Fmedian &lt; 1)</td>
<td>0.0312</td>
</tr>
</tbody>
</table>

*Confidence limits based on non-parametric bootstrap.

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REFERENCES