

Does Cigarette Smoking Have a Protective Effect Against Parkinson's Disease?

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Objective: Previous studies reported that individuals with Parkinson's disease are less likely to have smoking history and it seems that nicotine has a neuroprotective effect. The authors have conducted a case-control retrospective study to determine if there is an association between cigarette smoking and Parkinson's disease.

Methods: In a matched case-control study, 92 individuals with Parkinson's disease (71 men, 21 women; mean age: 67.3±11 year) were compared to 184 people without such a diagnosis. (144 men, 40 women; mean age: 65.7±12.3 year).

Results: Nineteen patients in the group with a diagnosis of Parkinson's disease (20.6%) were smoker. In the control group, however, there were 103 smokers. Also, we found a dose-response correlation between amount of smoking and higher risk of having Parkinson's disease.

Conclusion: Consistent with the results of previous studies, we found that individuals with Parkinson's disease are significantly less likely to have smoked regularly than those without Parkinson's disease.

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Introduction

Studies reveal that there is a negative association between cigarette smoking and the risk of developing Parkinson's disease (PD). Although many of these studies have limitations, overall, they suggest that smoking may actually be a protective factor for Parkinson's disease. A recent meta-analysis of published studies concluded that individuals with PD are less likely to report having smoked cigarettes compared to those unaffected by PD (1). Thus, cigarette smoking may be considered, along with age and family history, as an established risk factor for PD. However, many observers have suggested that the effect of cigarette smoking may be a spurious result (2).

In laboratory experiments, the researchers demonstrated that nicotine inhibits activation of brain immune cells known as microglia. In the normal healthy brain microglia support and maintain neurons. They also help with the

metabolism of beta amyloid protein that accumulates in the ageing brain. Chronic microglial activation is a sign of brain inflammation that is a key step in nerve cell death. The researchers also identified the specific site, the alpha-7 acetylcholine receptor subtype, to which nicotine binds and blocks microglial activation (3).

The prevailing hypothesis among researchers is that nicotine helps to protect the brain by binding to nicotinic acetylcholine receptors that sit on the end of nerve terminals. This action by nicotine causes brain cells to increase the release of neurotransmitters depleted in diseases like PD and Alzheimer's dementia. Other studies support this view; especially animal based data indicate a dopaminergic effect of smoking on the brain (3).

Materials and Methods

Based on previously published diagnostic criteria for PD (4-6), we selected patients with PD referred to our clinics to take part in a case-control study. All affected participants were examined and diagnosed by a neurologist.

Affected individuals exhibited at least two out of three cardinal signs of PD (resting

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tremor, bradykinesia and rigidity) and had no atypical clinical features. Other causes of parkinsonism were ruled out. Those with a diagnostic uncertainty or atypical clinical features were excluded from the study. So were individuals with a history of encephalitis or neuroleptic therapy within the year prior to diagnosis. We also excluded those with a history of normal pressure hydrocephalus and secondary causes of parkinsonism.

Patients in control group were selected randomly from general population (hospital workers, blood donors, individuals who were referred to our clinics for routine check up and examinations). Control group did not have any family history of PD or other known neurodegenerative diseases, especially dementias. Control group were matched for age, sex and place of residence.

Regular smoking habit was assessed by two questions: 1) "Have you smoked at least 100 cigarettes in your lifetime?" and 2) "Did you ever smoke cigarettes at least once per week?" Those who answered "yes" to both questions were also asked about the following: the average number of cigarettes per day they smoked, the year they started smoking and whether they had quit smoking, and if so, when.

Individuals who smoked at least 100 cigarettes in their lifetime, smoked at least weekly or started smoking prior to the age of 40 were classified as "smokers". Those with a history of smoking more than a pack per day were regarded as heavy smokers.

To assess the association between cigarette smoking and risk of PD, we used t and the χ^2 tests.

Results

Out of 92 cases, 71 were men and 21 were women (mean age: 67.3 ± 11 years). In the control group, 144 were men and 40 were women (mean age: 65.7 ± 12.3 year).

Among the individuals with PD, 19 patients (20.6%) were smoker but in the control group there were 103 people (55.9%) with a positive history of cigarette smoking.

In the control group, 9 females (22.5%) were smoker. In contrast, among individuals

with PD, only one female (4.7%) had a smoking history. This difference was statistically significant ($p < 0.05$).

Similarly smoking history was positive in 18 males in PD group (25.3%) in comparison to 94 males in the control group (65.2%).

Fifty three patients (28.8%) in the control group were heavy smokers (those who smoked more than a pack per day), while just 11 cases (11.95%) in PD group were classified as heavy smokers. We found a statistically significant inverse dose-response correlation between smoking and a diagnosis of PD ($p < 0.05$).

We could not find any difference in clinical presentation and course of disease between smoker and non smoker patients. In both groups, the most common presenting symptom was tremor (73.6% of smokers versus 75.4% of non smokers). The means age of onset of symptoms were not different between smokers and non-smokers (55.7 ± 8.7 years old versus 55.4 ± 12.9 years).

Discussion

Some previous epidemiological studies have suggested a negative association between cigarette smoking and the risk of PD. This observation was first made in a case-control study about 30 years ago (7). The results of our study are in accord with previous studies in showing an inverse relationship between smoking and a diagnosis of PD. Although previous studies have their own limitations, in general, they suggest that smoking may actually be a neuroprotective factor (3).

Hellenbrand et al. (8) in a study on 380 patients with PD and their 376 matched controls found a significant dose-response relationship between smoking and PD. They reported an odds ratio of 0.2 to 0.3 for a protective effect of smoking. Allam et al. (9) conducted a systematic review of prospective studies on smoking and PD. They found that there was an obvious protective effect of current smoking in the pooled estimate. Former smokers had a lower risk of developing PD compared to never smokers. Although their pooled estimates showed that smoking was inversely associated with the

risk of PD, the four prospective studies they included in their review had many limitations. They recommended that further studies are needed to evaluate the association of smoking and PD in women.

What might be the mechanism by which cigarette smoking could reduce the risk of PD? One or more substances in cigarette smoke may exert a direct or indirect neurochemical effect on neurons or glia to limit damage. Also, smoking may alter the metabolism of endogenous neurochemical compounds by brain or other organs to inactivate other neurotoxic substances (3,10,11).

Although cigarette smoke contains many substances, most researches have focused on neuroprotective effect of nicotine (11-13). Quik (11,13) showed that nicotine has been found to reduce MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) -induced dopaminergic toxicity in animal models of PD. One mechanism underlying the protective effect of nicotine may be its ability to increase the expression of neurotrophic factors that are known to promote survival of dopaminergic neurons. But tobacco contains numerous other chemical agents, whose influence on biological processes may play a part as well (3,12,14).

Smoking causes a reduction in activity of monoamine oxidase A and B, which might protect against neuronal damage by inhibiting the enzymatic oxidation of dopamine (DA) (12). Prasad et al. (14) evaluated the effect of chronic nicotine intake on the age-associated loss of nigrostriatal dopaminergic neurons. The striatal density of dopamine (D1 and D2) receptors and DA-uptake sites decreased with age. Concomitant with these changes was a pronounced loss of many behavioral functions associated with dopaminergic neurotransmission. Chronic oral intake of nicotine resulted in partial restoration of the loss of receptors as well as behavioral performances. Their results suggest that low doses of nicotine could have beneficial effects during aging.

Ishikawa et al. (15), in an interesting study in Japan, showed that smoking a cigarette could relieve symptoms in early-onset PD. In their study on 6 patients, smoking reduced tremor, rigidity, bradykinesia and gait

disturbances. These effects lasted for about 10-30 minutes, and relieved parkinsonian symptoms in the off-period. Nicotine chewing gum had a lesser effect. Nicotine is thought to activate the nigrostriatal dopaminergic pathway and increase the release of dopamine in the striatum, and this can explain the beneficial effects of smoking on PD symptoms.

Conclusion

One important goal in the treatment of PD is to be able to slow down or ideally stop the deterioration of symptoms. If, as the epidemiological evidence indicates, nicotine is a neuroprotective agent, some of the new pharmacological treatments such as adenosine A_{2A} receptor blockers might prove therapeutically beneficial in alleviating the symptoms of PD. Because nicotinic receptors are decreased in PD (13), nicotinic agonists might not only improve the symptoms but also slow down the relentless progression of the disease.

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