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Review article:

Cigarette Smoking and Parkinson's Disease

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ABSTRACT

This is a review on cigarette smoking and Parkinson's disease (PD). The relationship between cigarette smoking and Parkinson's disease is very controversial. Cigarette smoking is an established risk factor for various diseases such as lung cancer, COPD and heart disease. However, beneficial effects have been debated over the years. It was in the late 1950's that studies reported a negative association between smoking and Parkinson's disease. More recently, several epidemiological studies have found a significant negative association between cigarette smoking and PD. That is, patients who smoke are 50% less likely to have PD when compared to their non-smoker counterparts. This suggests that cigarette smoking may have a "neuroprotective" effect on PD.

Keywords: Cigarette smoking, Parkinson's disease

PARKINSON'S DISEASE: PREVALENCE, ETIOLOGY AND THERAPY

Parkinson's disease (PD), is the second most common neurodegenerative disease in the U.S. (Bennett et al., 1996), it affects 1 million Americans with an incidence of 50,000cases/year (Kurkland, 1958). PD occurs in ~1% of the population over the age of 55. PD was first described as a "shaking palsy" of unknown origin by James Parkinson in 1917. PD is a movement disorder that is characterized by selective damage to dopaminergic nigrostriatal neurons that lead to motor deficits including rigidity, tremor, bradykinesia and possibly dementia (Bezard, 2001; Olanow and Tatton, 1999).

The primary pathology of PD is believed to involve the loss of dopaminergic neurons in the substantia nigra, with a resultant decline of dopamine in the striatum (Quik and Kulak, 2002). Studies have shown that PD patients often exhibit low levels of brain dopamine, which stems from the degeneration of the nigrostriatal dopaminergic pathway, which is made of dopaminergic neurons whose cell bodies are located in the substantia nigra pars compacta and whose projecting axons and nerve terminals are found in the striatum (Daur and Pzredborski., 2003). The most characteristic histological findings are loss of substantia nigra neurons, with Lewy bodies in the surviving neurons (Gibb and Lees, 1988).

The etiology of PD is unknown; however it is believed to be due to one or more of the following: age, genetics and/or environmental

factors such as pesticides. 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) is a chemical that is related to the opioid analgesic drugs. MPTP is oxidized by monoamine oxidase B (MAO-B) to form 1-methyl-4-phenyl-pyridinium ion (MPP+), which is taken up by dopaminergic neurons and leads to cell death. It has been reported (Langston et al., 1984) that injections of MPTP in squirrel monkeys resulted in parkinsonism. The symptoms and brain structures of MPTP-induced Parkinson's are fairly indistinguishable to the point that MPTP may be used to simulate the disease in order that scientists may study Parkinson's physiology and possible treatments within the laboratory.

The most common used treatment of PD is dopamine replacement therapy. Drugs used to treat PD include catechol-O-methyltransferase (COMT) inhibitors, dopamine receptor agonists, MAO-B inhibitors and most commonly the dopamine agonist, Levodopa.

IMPACT OF CIGARETTE SMOKING ON GENERAL HEALTH

Cigarette smoke is composed of more than 4700 chemical compounds including nicotine, the addictive substance of cigarettes, carbon monoxide, lead, cadmium and polycyclic aromatic hydrocarbons. According to the Centers for Disease Control and Prevention (CDC), in 2001 a reported 46.2 million Americans were smokers. This accounted for nearly 23% of all adults, meaning 1 in 4 adults smoke. Smoking kills more Americans than alcohol, car accidents, suicide, AIDS, homicide, and illegal drugs combined. Each year an average of 440,000 deaths are related to smoking. Tobacco use costs the United States ~$100 billion each year in direct medical expense and lost productivity (Morbidity and Mortality Weekly Report). Smoking during pregnancy accounts for low-birth weight, pre-mature birth and infant death (U.S. Dept. of Health and Human Services, 2001). It also increases neonatal health care costs (Adams et al., 2002). Cigarette smoking has been linked to common causes of death in the elderly and contributes to death and disability associated with chronic illnesses common in this age group (Bratzler et al., 2002).

Cigarette smoke contains carcinogens that alter biochemical defense systems that lead to deleterious effects on the respiratory tract, heart, pancreas, reproductive tract and other organs (Ostergaard, 1977). Smoking has been attributed to causing cancer, chronic obstructive lung disease (COPD) and cardiovascular disease. Smoking is believed to be the most preventable cause of death in the United States to date. However, the beneficial effects of cigarette smoke are rarely discussed. Smoking has been observed to reduce the incidence of various diseases including endometrial cancer, ulcerative colitis, hypertension during pregnancy, Alzheimer’s disease and PD (English et al., 1995; Graves et al., 1991; Van Duijin and Hofman, 1991).

IMPACT OF CIGARETTE SMOKING ON PARKINSON’S DISEASE

Cigarette smoking is the most preventable cause of death in the United States today. Cigarette smoking has been studied in relation to various neurological disorders, such as Alzheimer’s disease and Parkinson’s disease. However, the relationship between cigarette smoking and PD remains to be controversial. Several epidemiological studies have found a negative association between cigarette smoking and PD. It is reported that patients who smoke are 50% less likely to have PD when compared to their non-smoking counterparts. This suggests that cigarette smoking might exert a neuroprotective effect. The hypothesis is that cigarette smoking

protects against neurodegeneration thereby preventing PD. This is a review of cigarette smoking and PD.

The first report of the negative association between cigarette smoke and PD is that of Dorn, 1959 who reported decreased PD occurrence among smokers after conducting mortality studies. In the 1970's more studies, both case-control and longitudinal, were published and confirmed a negative association of smoking with PD. In 1992, a comprehensive study was conducted to test the hypothesis that cigarette smoke protects against the development of PD. A group of 14,436 twins from the National Academy of Sciences-National Research Council World War II Veteran Twins Registry were interviewed as part of the study. This study investigated the association of cigarette smoking behaviors and PD. The study showed that the risk of PD is inversely correlated to the dose or pack-years smoked. These results suggested that there is a biologic protective effect of cigarette smoking on PD and that this is not just an epidemiological theory.

Several epidemiological studies have been published on the negative association between smoking and PD. Numerous studies have concluded that there was no significant difference between patients with PD and controls exposed to smoke (Rajput, 1984; Wang et al., 1993; McCann et al., 1998). Rajput identified 118 cases of idiopathic PD and 236 controls and determined that there was no significant risk for ever-smoked and PD from non-smokers. Although these studies failed to detect a significant association between smoking and PD, others confirmed a negative association. Mayeux et al. (1994) examined smoking in relation to PD in Manhattan, NY and concluded that PD reduces smoking. Godwin-Austen et al. (1982) also demonstrated a negative association between smoking habits and PD. Furthermore, a population-based case-control study conducted by the Henry Ford Health System database demonstrated a strong negative association between smoking and PD (Gorell et al., 1999). Several other epidemiological studies have also found a beneficial effect of smoking in PD (Fratiglioni and Wang, 2000; Hernan et al., 2001; Checkoway et al., 2002).

Morens and his group (1995) reviewed several epidemiological reports associating cigarette smoking and PD. They found various biases in the 46 articles they reviewed including selective mortality, cause-and-effect, and smoking-associated symptoms. Moreover, the authors underlined that the negative association was due to a direct chemical protective effect of smoking; and found that smoking protects against toxic neuronal damage, and that smoking is associated with the inhibition of free radical damage to cells within the substantia nigra. This critical review provided strong evidence for the hypothesis on the negative association with PD and revealed the need for direct animal studies.

Since it has been suggested that there is a negative association of cigarette smoking with PD, in vitro studies have tested the effect of cigarette smoke exposure on MPTP-induced neuronal changes. Parain et al. (2003) examined the neuroprotective effect of cigarette smoke and nicotine on a MPTP-induced mouse model of PD. Chronic nicotine treatment resulted in a significant reduction in the loss of dopaminergic neurons in the substantia nigra. These authors found that nicotine and low exposure to cigarette smoke may have a neuroprotective effect on the dopaminergic nigrostriatal system. Furthermore, Quik et al. (2006) investigated the effect of long-term nicotine treatment against nigrostriatal damage in non-human primates. Results showed that levels of striatal tyrosine hydroxylase, dopamine transporter, vesicular monoamine transporter, dopamine

and nicotinic receptors were greater in nicotine-treated MPTP-lesioned primates when compared to lesioned primates not receiving nicotine. This suggests that nicotine may contribute to the lower incidence of PD among smokers.

Cigarette smoke has also been shown to inhibit monoamine oxidase (MAO) activity, and MAO is known to breakdown dopamine (Fowler et al., 2000). Several studies also suggest that nicotine stimulates dopamine release (Janson et al., 1992; Westfall et al., 1967; Clarke et al., 1985); thereby conceivably suppressing early signs of PD. Numerous studies have also shown that cigarette smoke contains more than 10^{14} free radicals per puff (Church and Pryor, 1985; Bluhn et al., 1971; Forbes et al., 1967; Pryor, 1992; Pryor and Ston., 1993; Pryor et al., 1990). However, although cigarette smoke contains several free radicals, it also contains carbon monoxide (CO), and CO seems to be protective against hydrogen peroxide ($H_2 O_2$) induced membrane damage (McKenney et al., 1990; Metz et al., 1974; Sagone et al., 1975). CO also inhibits neural MAO-B-associated metabolism of dopamine to produce $H_2 O_2$ and possibly creates a protective nigral "reducing environment" (Baron, 1986), therefore suppression of free radical generation in early life could possibly lead to reduced risk of PD by preserving
dopamine producing cells.

CONCLUSIONS

A review of a portion of the existing literature revealed that there is a definite link between cigarette smoking and PD. Secondly, there is a negative association between smoking and PD. Furthermore, direct animal studies predict a possible protective effect of smoking on the development of PD and parkinsonian symptoms, but the mechanism by which this occurs is un-clear. Therefore the mechanism by which smoking may impart a neuroprotective effect remains to be elucidated in an animal model. Determining the underlining mechanism by which smoke imparts its effects may aid in defining the etiology and pathogenesis of PD. Furthermore, it may be utilized in the development of targeted drug therapies for PD.

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