Increased Melanoma Risk in Parkinson Disease

A Prospective Clinicopathological Study

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Objective: To evaluate the possible association of Parkinson disease (PD) and melanoma in North America.

Design, Setting, and Patients: Thirty-one centers enrolled patients with idiopathic PD. At visit 1, a neurologist obtained a medical history. At visit 2, a dermatologist recorded melanoma risk factors, performed a whole-body examination, and performed a biopsy of lesions suggestive of melanoma for evaluation by a central dermatopathology laboratory. We compared overall prevalence of melanoma with prevalence calculated from the US Surveillance Epidemiology and End Results (SEER) cancer database and the American Academy of Dermatology skin cancer screening programs.

Results: A total of 2106 patients (mean [SD] age, 68.6 [10.6] years; duration of PD, 7.1 [5.7] years) completed the study. Most (84.8%) had received levodopa. Dermatological examinations revealed 346 pigmented lesions; dermatopathological findings confirmed 20 in situ melanomas (0.9%) and 4 invasive melanomas (0.2%). In addition, histories revealed 68 prior melanomas (3.2%). Prevalence (5-year limited duration) of invasive malignant melanoma in the US cohort of patients with PD (n=1692) was 2.24-fold higher (95% confidence interval, 1.21-4.17) than expected in age- and sex-matched populations in the US SEER database. Age- or sex-adjusted relative risk of any melanoma for US patients was more than 7 times that expected from confirmed cases in American Academy of Dermatology skin cancer screening programs.

Conclusions: Melanoma prevalence appears to be higher in patients with PD than in the general population. Despite difficulties in comparing other databases with this study population, the study supports increased melanoma screening in patients with PD.

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An association between Parkinson disease (PD) and melanoma has long been suspected, but whether the association is with the dopaminergic treatments or with the disease itself remains a question. The introduction of levodopa therapy for PD in 1970 was followed 2 years later by a case report suggesting that the drug might precipitate recurrence of malignant melanoma. In the intervening years, no controlled study has assessed the possible relationship of levodopa and melanoma, and the strength of the association has been debated. As of 1999, the manufacturer had reported 50 drug safety reports of malignant melanoma possibly associated with carbidopa/levodopa therapy. More than 35 articles have been published, but the largest series presented only 11 new cases. The total number of cases is relatively small, considering that more than 200 000 cases of melanoma are identified in the United States within any given 5-year period, and more than 1 million Americans are taking levodopa.

Some hypothesize that PD itself might be associated with melanoma. A Danish retrospective medical record review of hospitalized patients revealed twice the risk of melanoma among patients with PD than in the age-matched general population. More recently, the incidence of PD was reported to be more than twice as high in patients with malignant melanoma than in age- and sex-matched control subjects. A retrospective analysis of the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial likewise found a higher than expected incidence of malignant melanoma.

The present 31-center study was designed to evaluate the possibility of an association between PD and melanoma in North America. The study prospectively screened patients with PD to establish the prevalence of melanoma, other skin cancers, and premalignant skin lesions.
The following 2 analyses evaluated melanoma prevalence: (1) histories and clinical screening data were compared with prevalence expected on the basis of patients' reports (Table 1), 414 in Canada and 1692 in the United States. Numbers of patients recruited per site varied from 8 to 131. The main reasons for early terminations (189 [8.2%]) were patient refusal to undergo the dermatologic examination and patient withdrawal of consent. The mean age of enrolled patients was 68.6 (range, 31-100) years. The mean duration of PD was 7.1 (range, 0-48) years. The Hoehn and Yahr stage ranged from 2.0 to 3.0 (mean, 2.2) (Table 1).

Nearly all of the patients (96.6%) were taking or had taken a dopaminergic agent (Table 1), most commonly levodopa (84.8% of the patients). The distribution of dopaminergic agents matched the clinical use of these agents at the time of this study (US data from the 2005 National Prescription Audit; IMS Health, Norwalk, Connecticut; http://www.imshealth.com/media/).

The mean (SD) number of melanoma risk factors per patient was 3.0 (2.3). Most patients (85.0%) had at least 1 risk factor, and 69.2% had at least 2, most commonly fair skin (56.9% of patients), blue eyes (42.0%), and se-vere or blistering sunburns in childhood (40.9%). Written documentation confirming the date and type of prior melanoma was obtained for 70% and 100% of cases in the SEER and AAD analyses, respectively. For both, the ratios of observed to expected cases were adjusted to the age and sex of the survey population.

## RESULTS

### PATIENT DEMOGRAPHICS AND DISEASE HISTORY

Of 2295 PD patients recruited by neurologists, 2106 completed the study according to the protocol (Table 1), 414 in Canada and 1692 in the United States. Numbers of patients recruited per site varied from 8 to 131. The main reasons for early terminations (189 [8.2%]) were patient refusal to undergo the dermatologic examination and patient withdrawal of consent. The mean age of enrolled patients was 68.6 (range, 31-100) years. The mean duration of PD was 7.1 (range, 0-48) years. The Hoehn and Yahr stage ranged from 2.0 to 3.0 (mean, 2.2) (Table 1).

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### DERMATOLOGIC EXAMINATION AND BIOPSY

From the dermatologic examinations, 519 patients were reported with lesions; 346 of these were pigmented lesions, of which 294 were biopsied per the dermatologist's recommendation. An additional 98 patients with nonpigmented lesions were also biopsied, for a biopsy rate of 18.6% of total study patients. Of patients undergoing biopsy, 24 (1.1% of the original cohort) were newly diagnosed as having invasive or in situ melanoma (Table 2).

### FURTHER ANALYSIS OF MELANOMA CASES

In this survey, 68 patients (3.2%) were diagnosed as having melanoma by history alone, 20 (0.9%) had newly diagnosed disease, and 4 (0.2%) had a history of melanoma and a newly diagnosed melanoma. The average age of the patients with melanoma was significantly older than the average age of the melanoma-free patients (Table 3).
For patients with melanoma, PD severity was significantly worse by Hoehn and Yahr scores, and the average number of risk factors was significantly higher. Sex, PD duration, and current levodopa use did not differ significantly for patients with or without melanoma (Table 3).

**HISTORICAL MELANOMA DATABASES**

The frequency of melanoma was compared with prevalence in 2 existing US databases using relative risk (RR; Poisson model) (Table 4). From the US centers, a total of 10 invasive melanoma cases were detected during the dermatologic examination or were documented as diagnosed during the 5 years before study enrollment. Based on the SEER 5-year limited-duration prevalence, 4.46 cases of invasive melanoma would be expected in a population of this size, age, and sex. Thus, the RR for invasive malignant melanoma in our US study population compared with SEER data was 2.24 (95% confidence interval [CI], 1.21-4.17). Regardless of whether the combined North American data or only the US data were used for comparison, the RR for melanoma appeared to be higher in PD patients than in surveys of the general population (Table 4). This difference was significant for the US data.

**COMMENT**

Malignant melanoma, although potentially fatal, is a curable disease if treated early. Establishing that PD is a ma-
major risk factor for malignant melanoma therefore has the potential for raising awareness and saving lives.

PREVALENCE OF MELANOMA IN PD PATIENTS COMPARED WITH THE GENERAL POPULATION

Apparent associations between PD and melanoma must be interpreted with caution. Our survey of PD patients offers evidence of a considerably higher melanoma prevalence than in the population at large. The results must be interpreted carefully because of the differences in the way our data were collected compared with the historical melanoma data recorded in the SEER database or from AAD screening. We screened more aggressively and completely than was done for the historical data. This careful screening might be expected to enhance diagnosis and better approximate the actual prevalence of melanoma in PD. The lack of a biopsy in 52 patients would be expected to cause an underestimation of melanoma frequency, strengthening the observation of an elevated melanoma frequency in the PD population. On the other hand, for the SEER comparison, written documentation substantiated the history of melanoma in 70% of cases, so misclassification is possible but unlikely.

Finding an appropriate population for comparison is difficult. The SEER registry data are from hospital records. One of their statistics is derived from a 5-year, limited-duration prevalence counting method, which determines the proportion of people alive on a certain day who had a diagnosis of melanoma within the past 5 years. The National Cancer Institute normalizes the data to the population within the catchment areas of each participating hospital. The hospital-based source minimizes early (in situ) melanoma, essentially reporting only invasive melanoma, which is much less prevalent than in situ melanoma. The risk-factor profiles of the patients are not well specified, and the methods of detection are not standardized. However, even if only invasive melanomas in the present study are considered, the incidence of malignant melanoma in our US patients is twice as high as that expected from the SEER data.

The question arises about whether the frequencies of major risk factors in our population of PD patients might differ in important ways from the frequencies in the referent populations. We adjusted for age and sex because older age and male sex are known risk factors for melanoma. For example, it may be that men are at higher risk because they tend to be employed in activities with more sun exposure. The SEER and AAD databases do not report frequencies of melanoma risk factors in a manner that allows for comparison, but a rough estimate of the frequency of such risk factors in the United States can be obtained from a combined database of 178,155 white North American health care professionals described by Cho and colleagues. A history of severe sunburn in childhood was reported by 40.9% of our patients compared with 77% in the combined database. In the combined database, 18% of the subjects had blond or red hair compared with 24.0% in ours; 4% had a family history of melanoma compared with 6.2% in ours; and 44% had more than 1 large mole compared with 19.6% with a pigmented lesion or congenital mole in ours. If such differences exist between our population of PD patients and the general North American population from which they are drawn, the frequency of melanoma may be skewed in complex ways.

A retrospective analysis of PD patients from the DATATOP trial likewise calculated that the incidence of melanoma in PD patients was 3-fold higher than that expected on the basis of demographically matched patients from the SEER database. As in our study, no relationship between levodopa therapy and melanoma onset was discerned.

The AAD conducted screening at voluntary, free skin examinations, resulting in subjects who were self-selected and possibly motivated by concern about a skin lesion. On the other hand, people with diagnosed melanoma may be under a physician’s care and unlikely to come for community screenings. The AAD population was skewed toward women (61%), higher educational levels (55% college or graduate school), and white race (94.9%) and tended to be younger (41.6% who were younger than 51 years) than PD patients. The net effect on melanoma prevalence is hard to predict given the much younger age, which would reduce melanoma risk, and the self-selection, which would increase melanoma risk. The rates at which history of melanoma (known to be an important risk factor) were reported were similar for the AAD population and the PD patients in our sample.

RELATIONSHIP OF LEVODOPA USE OR PD TO MELANOMA

Our finding of increased melanoma prevalence in PD patients might be confounded if levodopa increased the risk of melanoma. However, a recent Danish case-control study of patients with malignant melanoma revealed no evidence that levodopa affected melanoma risk despite a 4-

| Table 4. Comparison of Melanoma Risk in Current Survey vs Expecteda |
|-------------------|-------------------|-------------------|-------------------|
|                    | Invasive Melanoma  | Any Melanoma       |                    |
|                    | Age-/Sex-Adjusted  |                    |                    |
|                    | SEER Data          |                    |                    |
| No. of            | Expected No. of    | RR (95% CI)        | No. of            | Age-Adjusted | Sex Adjusted | RR (95% CI), |
| Cases Observed    | Cases |                      |                    | Sex Adjusted  |                | AAD Data     |
| United States only (n=1992) 10 | 4.46 | 2.24 (1.21-4.17) | 22 | 3.08 | 3.11 | 7.13 (4.65-10.95) | 7.08 (4.62-10.87) |
| United States and Canada (N=2106) 10 | 5.47 | 1.83 (0.98-3.40) | 24 | 3.82 | 3.86 | 6.28 (4.16-9.47) | 6.21 (4.12-9.37) |

Abbreviations: AAD, American Academy of Dermatology; CI, confidence interval; RR, relative risk; SEER, Surveillance Epidemiology and End Results database.

aData are from the National Cancer Institute and Geller et al.10,11
to 5-fold increase in risk for malignant melanoma in PD patients. Our study likewise provides no evidence that levodopa use increases the incidence of melanoma.

Uncertainty about the role of medications as risk factors for melanoma in PD has led to changing guidelines. Contraindications in the prescribing information of carbidopa/levodopa, ropinirole hydrochloride, rotigotine, and pramipexole dihydrochloride note that epidemiologic studies have shown that PD patients have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than does the general population, but whether the risk can be attributed to PD or to drugs used to treat PD is unclear. They therefore recommend periodic dermatologic screening by a qualified dermatologist. Similar statements appear in selegiline hydrochloride and rasagline prescribing information. As suggested by the wording in the prescribing information, published evidence suggesting a link between specific PD medications and melanoma is weak. During the 34 years since the association was first suggested, approximately 40 articles have described cases and editorialized about the association. However, no controlled studies substantiate that the melanomas are drug related. Our study does not support the idea that dopaminergic medications increase the risk of melanoma beyond that expected in PD patients.

STUDIES OF THE PREVALENCE OF MELANOMA IN PD

Several systematic surveys suggest a relationship between PD and melanoma or skin cancer. A survey of 7046 PD patients in Denmark found a positive association of PD with melanoma (odds ratios, 1.44 and 1.26, respectively). This group also found an elevated incidence of malignant melanoma and skin carcinoma in PD patients (odds ratios, 1.44 and 1.26, respectively). A retrospective case-control study of 202 PD patients in Minnesota reported an RR of 1.76 (95% CI, 1.07-2.89) for nonmelanoma skin cancer. These data all suggest that the increased incidence of melanoma in PD patients is related to the disease rather than to treatments. Recently, a large-scale, controlled prospective study in the United States demonstrated a 6-fold increased risk of melanoma in PD patients.

Looking at the relationship from the opposite perspective, a review of PD patients from the SEER database noted that melanoma was the only cancer associated with significantly increased mortality risk.

This is, to our knowledge, one of the few large studies of the possible association of PD and melanoma or the only study that includes prospective dermatologic examinations. The data suggest that risk of melanoma may be higher in PD patients than in comparable populations. Our findings support earlier studies suggesting that melanoma prevalence is higher in PD patients than in the general population.

This study provides the best estimate to date of the current prevalence of melanoma in PD patients in North America (24 of 2106 [1.1%]). Comparisons with the population at large are not definitive because no similar dermatologic screening program has been performed on a matched cohort without PD. Existing epidemiologic data on melanoma prevalence are not optimal for comparison because of likely biases.

Our study cannot provide an estimate of the incidence of melanoma in PD patients because it is based on a single dermatologic examination. Regardless of the exact prevalence of melanoma in the general population, a prevalence of greater than 1% warrants increased vigilance and regular screening for melanoma in PD patients.

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