

Melanoma, Parkinson's disease and levodopa: causal or spurious link? A review of the literature

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Since the early 1970s, a number of case reports have suggested that levodopa therapy for Parkinson's disease increases the risk of cutaneous malignant melanoma. As yet, no formal epidemiological study has been conducted to verify this hypothesis. To elucidate the relationship between levodopa and the risk of cutaneous malignant melanoma, a systematic literature search using computerized bibliographic databases was done. This review presents the case history evidence for and against the hypothesis of a causal association, and explores possible epidemiological, genetic, social, biochemical and toxicological factors that may increase the risk of melanoma in Parkinson's disease patients. All the case reports in the literature were considered. We concluded that (1) there is no epidemiological or experimental evidence of a causal role of levodopa in increasing the risk of melanoma incidence or progression; (2) there is good evidence of an excess risk of melanoma in patients with Parkinson's disease; (3) there is good evidence of a protective effect of tobacco smoking on the risk for Parkinson's disease; (4) there is good evidence of positive

correlation between social class and melanoma risk; (5) the relationship between the risk of Parkinson's disease and the risk of melanoma may be due to a common genetic profile or it can be attributed to a confounding role of social class, associated with both melanoma and Parkinson's disease possibly through an inverse relationship with tobacco smoking. *Melanoma Res* 16:201–206 © 2006 Lippincott Williams & Wilkins.

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Introduction

Levodopa treatment for Parkinson's disease (PD) was introduced at the end of the 1960s. In 1972, Skibba *et al.* [1] described a case of skin melanoma in a patient with PD. Since then, numerous case reports of a similar nature have appeared in the literature.

No formal epidemiological study of the hypothesis that levodopa therapy increases the risk of melanoma development has, however, been undertaken. A cohort study in Danish PD patients [2] found a consistent increase of melanomas. Common steps in the metabolic pathways of levodopa and melanin synthesis also suggest potential for interaction, although this has not been confirmed experimentally. Despite the paucity of data, the prescribing information of levodopa drug includes a warning of a possible increased risk of occurrence or progression of melanoma during treatment, and recommends a prudent approach to use in PD patients with a previous history of melanoma.

The present review examines what is relevant to the association between levodopa and melanoma: the case report studies on melanomas during levodopa treatment, the epidemiology and aetiology of cutaneous malignant melanoma (CMM), the aetiology of PD and the

association with melanoma risk, and the toxicology of levodopa with respect to melanocytic cells. In addition, the review presents possible explanations for the association between PD, levodopa and CMM, and questions whether this association is causal or produced by other factors.

Case reports describing an association between levodopa and cutaneous melanoma

As indicated above, the first case mentioned in the literature was reported by Skibba *et al.* [1] in 1972. The patient, a 50-year-old man already affected by PD, was diagnosed with melanoma in the left scapular area before levodopa treatment. This was treated with surgical removal and a skin transplant; there was no evidence of metastasis. In September 1971, the patient started levodopa treatment. In January of the following year, some pigmented nodules were removed from the transplant area, with a diagnosis of recurring melanoma. Levodopa treatment was interrupted at the end of January 1972.

Further cases were reported in the literature and summarized by Lieberman and Shupack [3]. The authors presented the highest dosages of levodopa but not the length of treatment, which varied from a few weeks to

several months. The data show that, in four of the five cases, melanoma actually preceded levodopa treatment by 2–88 months. One death occurred as a result of rapid clinical evolution (6 months between bleeding of a naevus and death from diffuse metastasis) and two cases in which melanoma had not recurred following treatment. In another case, recurrence is not documented.

Subsequently, another report linking the occurrence of superficial spreading melanoma without metastasis with levodopa in a PD patient is considered to be questionable because levodopa treatment was not actually started owing to the presence of the melanoma [4].

The final case report published in this period (1970s) was presented by Sober and Wick [5]. In this case, a 48-year-old man was diagnosed with melanoma 6 years after the onset of PD and the beginning of levodopa treatment. One year after the melanoma diagnosis, the patient had not had a recurrence or metastasis.

The state-of-the-art at this point is well summarized in the letters exchanged in *JAMA* in 1979 by Fermaglich and Delaney [4] on one side and Sober and Wick [5] on the other. Fermaglich and Delaney [4] stated that the available evidence suggests a risk of melanoma progression associated with the use of levodopa, and they recommend its proscription, suggesting bromocriptine as an alternative treatment. In contrast, Sober and Wick [5] regard the evidence (including experimental results) as insufficient. Nevertheless, they agree upon a cautious approach until there is clear epidemiological evidence on the matter.

Further case reports were published in the 1980s and 1990s and in more recent years. As in the first group of case reports, the melanoma sometimes followed and sometimes preceded levodopa treatment [6–19].

It must be noted that some of these case reports are 'negative' in terms of a link between levodopa and melanoma. For example, the paper by Weiner *et al.* [15] presented nine melanoma cases in levodopa-treated PD patients; in only one case did the melanoma recur. Woofter and Manyam [16] described the case of a man who died at the age of 97 years, after having taken 4.3 kg of levodopa in the 15 years following the melanoma diagnosis.

The case reports included above, with the exception of those of Wobbles and Bonenkamp [19], are also reported by Pfützner and Przybilla [18] in their 1997 review of the literature. In 2000, Siple *et al.* [20] found 34 case reports on Medline within 1999, and counted a total of 50 participants. The 34 published case reports were, however, not completely listed in the article's

bibliography and the 50 participants mentioned by the author come from an unpublished source (files of a levodopa manufacturer), thereby making a strict comparison impossible. We believe that, independently of their exhaustiveness, the case reports mentioned by Pfützner and Przybilla [18] and quoted in the present review represent the majority of this type of investigation.

Epidemiology and aetiology of melanoma

The incidence of melanoma is well documented by the world network of cancer registries. Since the early 1960s, the incidence has shown the fastest increase among tumours, matched only recently by prostate cancer. Data from the Surveillance, Epidemiology and End Results programme showed that the increase of CMM incidence in North America was particularly high in men, reaching a level of more than 40 cases per 100 000 in several areas in 1999 [21]. In European men (1993–1997), CMM incidence was as high as 17 cases per 100 000 in Switzerland, 10 in Denmark, nine in the Netherlands and more than seven in Finland, England and Scotland; rates were slightly lower in women. Rates in southern Europe were lower still, but with a consistent increase compared with earlier data: doubling in Spain from 2.2 in 1983–1987 to four cases per 100 000 in the period 1993–1997, for example, and increasing by about 30% in Italy in the same period, from five to seven cases per 100 000 [22]. In fact, mortality in developed countries showed increasing trends only till the end of the 1980s, when it stabilized or started to decline slightly. At present, mortality rates are 2.8 and 1.3 in men and women in North America, 1.6 and 1.2 in Europe, and five and 2.5 in Australia.

Knowledge of the aetiology of melanoma derives substantially from good case–control studies conducted from the 1980s onwards in America [23–27], Australia [28,29] and Europe [30–33]. These studies show that the aetiology consists of complex interactions between genetic characteristics (i.e. skin phenotype), social and environmental factors (e.g. exposure to sunlight).

All the indicators of pale complexion and sensitivity to sunlight are associated with a 2–4-fold increased risk of melanoma. Moreover, specific population subgroups with a collection of risk factors, such as people with red hair, blue eyes, a tendency to sunburn, and with a large number of freckles and naevi have observed relative risks up to 10 times that of the population average. Number of sunburns and age at first sunburn can be considered as intermediate indicators of skin sensibility and sun exposure [28].

Two robust aspects of the relationship between melanoma and sun exposure were observed early on in the research on this topic. First, there is a protective

effect of persistent tanning from chronic sun exposure, observed in cohorts of outdoor workers [31,32]. Second, there is an increasing risk of melanoma with higher social class. Factors such as opportunities for intermittent sun exposure on holidays, during seaside sojourns and water sports are (even more so in the past) positively related to an increase of melanoma risk and to social class.

Aetiological epidemiology of Parkinson's disease and association with melanoma risk

Notwithstanding the large number of analytical epidemiological studies, the aetiology of PD remains substantially unknown. Studies have focused on different factors and have been of varying size and quality [34–39].

Reviews have been conducted by Morens *et al.* [40], Tanner and Ben-Shlomo [41] and Fiala *et al.* [42].

Perhaps the most solid epidemiological evidence concerns the protective effect of tobacco smoking. Epidemiological evidence suggests a cause–effect relationship, and the hypothesis is supported by a credible biological mechanism. Consequently, the relationship between tobacco smoking and risk of PD is examined in depth in this review because, in our opinion, it also explains the apparent association between PD and melanoma.

The first formal evidence of an inverse relationship between tobacco smoking and PD risk is derived from Dorn's study on American war veterans [43]. Smoking habits of a large cohort of American war veterans were established through a mailed questionnaire and revealed a net mortality deficit (mortality ratio 0.36) from PD in smokers compared with nonsmokers. When presenting this highly surprising result, the authors excluded two possible artefacts, namely that PD symptoms lead to cessation of smoking and that PD might be obscured as a cause of death in death certificates by other concurrent causes associated with tobacco. The same negative relationship was also noted in other large studies on tobacco consumption, specifically those by Doll and Peto [44] on British medical doctors and by Hammond [45] on one million Americans. Indeed, the final results of Doll and Peto [44] confirmed the protective effect of tobacco (SMR: 0.43).

A case–control study was later carried out by Nefzger *et al.* [46], with 198 cases and 198 controls being analysed. A protective effect was found for tobacco consumption [relative risk (RR) 0.33–0.44] and the data showed a good consistency for the different modalities and durations of exposure to tobacco. Of note, the patients' education levels and job titles were found to be higher than those of the controls.

Kessler and Diamond [47] published a second large-scale case–control study in 1971 analysing 468 cases (and as many controls) with a valid interview. Less strong protective effects of smoking than those in the study by Nefzger *et al.* [46] were found (RR: 0.66). The proportion of smokers in the control group was somewhat lower than that of the general population (contrary to that in the study by Nefzger *et al.* [46] in which it was slightly higher), and this can explain the differences between the two results.

Subsequently, several other studies were conducted, which differed in design, quality and scale. In general, however, investigators came to the conclusion that tobacco smoking or tobacco-related cancers were inversely related to PD. Morens *et al.* [40] provide a complete review of 34 studies published up to 1995.

More recent case–control studies in PD patients clearly confirmed the decreased risk in smokers [48,49].

The most important study with respect to melanoma risk is a cohort study conducted in Denmark between 1977 and 1999 in which data from 14 088 patients with a PD diagnosis were linked with the Danish Cancer Registry incidence files [2]. Apart from strongly confirming the deficit in tobacco-related cancers, this study found a clear excess of cutaneous melanoma risk (RR 1.95; confidence interval: 1.4–2.6). This excess of melanoma risk could be explained by the inverse relationship between tobacco smoking and social class, especially in men, whereas the risk of melanoma is positively correlated with this variable. If tobacco smoking protects against PD, PD patients would tend to belong to a higher social class and thus run a higher risk of melanoma.

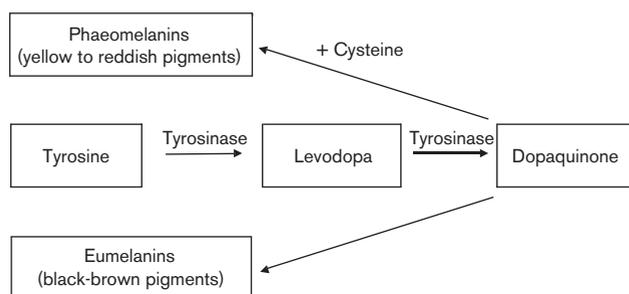
Biochemical relationship between levodopa and melanogenesis

It is well known that pigmented neurons, containing neuromelanin and high amounts of iron, are typically lost in PD. In contrast, neurons that survive are free of neuromelanin and contain low amounts of iron [50].

One of the important functions of cutaneous melanin is its role in the determination of phenotypic appearance. More than 80 genetic loci that regulate mammalian pigmentation are known, and a summary of the biochemical control of melanogenesis has been published [51].

The fact that levodopa is an intermediate in the biosynthesis of melanins necessitates investigation of the suggested link between levodopa and malignancies arising from melanocytic cells. The biochemical pathway responsible for the production of several pigments in mammalian melanocytes is quite well established [52] and is summarized in Fig. 1.

Fig. 1



Mechanism of formation of phaeomelanins and eumelanins. Common steps in the metabolic pathway of levodopa and melanins.

In-vitro studies

It has been shown that levodopa, an amino acid that is not normally found in cellular proteins, is incorporated into different cell lines and melanoma cells [53]. When the toxicity of levodopa on melanoma cells was discovered, it led to the consideration of its therapeutic potential. It has been shown that levodopa blocks cell proliferation in all phases of the cell cycle [54]. Clement *et al.* [55] advised caution when extrapolating results of culture assays to predict effects *in vivo*.

In-vivo studies

In animals

A few earlier studies investigate the effect of levodopa on experimental tumours. In one, levodopa at high dosage enhanced the survival time of animals bearing melanoma and mammary carcinoma but did not have any effect on leukaemia-transplanted mice [56].

Other antitumour assays demonstrate that levodopa and dopamine, the principal levodopa catabolite, are capable of prolonging the survival of mice [57].

In humans

Melanocytes have a 'nonvital' role in adult humans, so potential toxicity to normal melanocytes is not a serious problem. The possibility of using these agents to act selectively on cells with mature phenotypes (like melanoma cells), in combination with other neoplastic drugs, appears interesting. More details can be found in a review by Wick [58]. In 1991, Gurney *et al.* [59] attempted to treat malignant melanoma with high concentrations of levodopa but, in the 17 metastatic melanoma patients given oral levodopa/carbidopa, no clinical response was shown. Nevertheless, no patient in this study experienced an increase in tumour growth following treatment. According to the authors, while levodopa/carbidopa may be regarded as an ineffective treatment for metastatic melanoma, a previous history of

melanoma should not be regarded as a contraindication to antiparkinsonian therapy.

Discussion

By definition, case reports are descriptive and not demonstrative or conclusive. When they signal a possible association that implies a risk, this should lead to the design and performance of adequate formal studies to test the hypothesis. In the case of levodopa and melanoma, this has not happened and, over the last 30 years, even more case reports have monotonously appeared. Even assuming, however, that there is no increased melanoma risk following levodopa treatment, the real number of cases of random association between levodopa and melanoma would have been enormously higher than the few dozens identified by case reports, given the growing incidence of melanoma in the general population and the growing PD prevalence that is treated with levodopa. This argument has already been expressed by Sober and Wick [60] in their letter in 1979, and repeated by Rampen [61] in his letter in 1998.

Moreover, some case reports are spurious and even contradictory. This is the case with those publications reporting melanoma before the beginning of levodopa treatment and those in which melanoma did not progress over the course of treatment. Nevertheless, the false impression of an association persists and a further case report in a similar vein was published in 2002 [19].

While the evidence for a role of levodopa in increasing the risk of melanoma or its progression is completely inconsistent, as also discussed by Fiala *et al.* [42] in their review of a long series of published case reports, there is good evidence of a positive association between melanoma incidence and PD. This evidence is mainly based on the results of the Danish PD cohort study [2], in which the association between PD and melanoma is very high (standardized incidence ratio: 2.35) within the first year after PD diagnosis and decreases in subsequent periods, implying that the association is not due to PD treatment, but to some pre-existing causal or confounding factor. A causal relationship would mean that a common factor could cause both the destruction of substantia nigra neurons and the neoplastic transformation of cutaneous melanocytes, rather than that PD could directly cause CMM or vice versa. A common genetic pattern could be responsible for both diseases and so explain their association. Or, alternatively, the association may be due to a third external factor associated with both PD and CMM. At least one such factor exists, and that is social class. Indeed, there is good evidence that this is positively associated with melanoma, probably through a greater recreational sun exposure habit among the wealthier participants. Similarly, there are direct elements (in the study by Nefzger *et al.* [46] for instance) of

a positive association between social class and PD. Above all, however, there is the weight of the following combination: an inverse association between tobacco and PD, an inverse association between tobacco and social class, and thus a direct positive association between PD and social class. The magnitude of each of these associations (with OR between 1.5 and 2.5 each) adequately explains the PD-melanoma association observed in the Danish cohort [2]. It must be highlighted that this sequence of reasoning about causality remains true, independently of whether each factor is a causal or a confounding one. Some of them are more likely to be confounding factors (e.g. social class); others are more likely to be truly causal factors (recreational sun exposure as a risk factor for melanoma, and nicotine as a protective factor for PD).

Conclusions

No evidence exists of a causal role of levodopa in increasing the risk of melanoma or accelerating its growth. The early association observed can be interpreted as casual, and subsequent associations published are no more than anecdotal, and even then less frequent than would be expected on the ground of no additional risk.

No evidence exists of a carcinogenic effect of levodopa in experimental models: results are negative in culture cells, in rodents and in humans. Levodopa has been tested as an antineoplastic drug, without showing any appreciable effect either in slowing or spreading and accelerating tumour growth.

Good evidence, mainly based on the statistically powerful Danish cohort study, suggests that the incidence of melanoma is doubled in people affected by PD. Strong evidence exists of a protective effect of tobacco smoking against the risk of PD; the effect is attributable to a role of nicotine in the substantia nigra. As a consequence, the association between melanoma and PD can be interpreted as noncausal, if a common genetic pattern increases the risk of both, or confused by social class, which is positively related to both (in the case of PD, via inverse association with tobacco).

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