Short report

Levodopa and melanoma: three cases and review of literature

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SUMMARY Three patients are reported who developed a melanoma while taking levodopa for Parkinson's disease. There were two cutaneous melanomas and one metastatic melanoma with occult primary. The literature on the association of Parkinson's disease, levodopa therapy and melanoma is reviewed. The capacity of levodopa to induce melanomas and its alleged adverse effect on the clinical course of the disease are questioned.

Levodopa has been used extensively in the treatment of Parkinson's disease since the early 1970s. Soon after its introduction Skibba *et al* reported a patient with Parkinson's disease who, whilst receiving levodopa, developed locally recurrent disease from a melanoma that had been excised 4 years previously.¹ This patient also developed additional "primary melanomas". Since then several more reports have appeared on the relationship between melanoma, Parkinson's disease and levodopa therapy.²⁻¹¹ Most authors have been concerned about a possible enhancement of melanoma growth activity caused by an increased substrate availability of levodopa. We wish to present three further cases where melanoma has developed in patients receiving levodopa and would like to take issue on the alleged deleterious effect of levodopa on the biologic behaviour of melanoma.

Case reports

Case 1

A 67-year-old male patient started attending for Parkinson's disease in September 1981 and received treatment with levodopa and benserazide. Eighteen months later a pigmented lesion on the right shoulder was excised. This lesion had been growing for a short period and proved histologically to be melanoma (superficial spreading type; level III; Breslow thickness 1.25 mm). In August 1983 levodopa treatment was stopped and was replaced by

bromocriptine. Up until August 1984, 17 months after the excision of the primary, there were no signs of recurrent melanoma.

Case 2

A female patient with Parkinson's disease had been treated with levodopa since 1971. In 1974 carbidopa was given in addition and in 1982 treatment with bromocriptine was given for short periods (the drug had to be withdrawn because of serious side effect). In November 1982, when 66 years old, a melanoma on the left shin was excised (superficial spreading type; level III; Breslow 0.75 mm). The lesion had been growing for over a year. Levodopa was continued. During the follow-up period of 22 months there was no recurrence.

Case 3

A 65-year-old female was found to have widespread metastatic melanoma with occult primary in May 1984. From 1975 she had been taking levodopa for Parkinson's disease and later, in addition, benserazide. In 1980 three pigmented lesions were excised from the face, but histology showed no malignancy. In 1981 low back pain commenced which gradually increased in intensity during the next few years. Eventually, in May 1984, when the pain had become unbearable, radiographs disclosed large defects in the sacro-iliac region. Cytology revealed melanoma. Multiple pulmonary secondaries were found. Histological review of the naevi removed in 1980 failed to show malignant features. Chemotherapy was started with dacarbazine, cisplatin and vindesine. Levodopa treatment was not discontinued.

Discussion

Parkinson's disease is a common disorder. During the last 15 years there must have been millions of patients with Parkinson's disease who have received

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Table Reported cases of melanoma and Parkinson's disease

Case no	Reference	Sex age (yr)	Location of primary	Time from initiation of levodopa therapy to melanoma diagnosis	Course
1	Skibba <i>et al</i> (1972) ¹	M 55	skin	(melanoma diagnosed 56 months previously)	levodopa discontinued; local recurrence and "multiple new primaries" after 4 months
2	Robinson <i>et al</i> (1973) ²	M 50	skin	concomittant	levodopa discontinued; died of melanoma after 10 months
3	Lieberman <i>et al</i> (1974) ³	M 70	skin	18 months	levodopa discontinued; no recurrence after 33 months
4	id	M 62	skin	(melanoma diagnosed 11 months previously)	cerebral metastases after 2 months
5	id	M 62	skin	(melanoma diagnosed 7 years previously)	no recurrence after 24 months
6	Fermaglich <i>et al</i> (1977) ⁴	M 71	skin	never received levodopa	—
7	Fermaglich (1978) ⁵	—	—	never received levodopa	—
8	id	—	—	8 years	—
9	Sober <i>et al</i> (1978) ⁶	M 48	skin	6 years	no recurrence after 9 months
10	Botteri <i>et al</i> (1979) ⁷	F 73	urethra	14 months	levodopa discontinued; died of melanoma after 11 months
11	Bernstein <i>et al</i> (1980) ⁸	F 74	skin	10 years	multiple satellites and "new primaries" 10 months later; then discontinuation of levodopa
12	van Rens <i>et al</i> (1982) ⁹	F 69	choroid	7 years	levodopa temporarily withdrawn; no recurrence after 12 months
13	id	F 53	choroid	4½ years	no recurrence after 7 months
14	id	F 70	ciliary body	11 months	no recurrence after 4 years
15	Abramson <i>et al</i> (1984) ¹⁰	M 67	choroid	approx 1 year	—
16	Rosin <i>et al</i> (1984) ¹¹	M 58	skin	approx 2 years	levodopa discontinued; no recurrence after 6 months
17	Rampen, present series	M 69	skin	18 months	levodopa temporarily withdrawn; no recurrence after 15 months
18	id	F 66	skin	11 years	no recurrence after 22 months
19	id	F 65	occult primary	9 years	—

long term levodopa therapy. Yet the reported cases of melanoma associated with levodopa treatment have been few. The table gives the data from the literature on the association of melanoma and Parkinson's disease. There have been four ocular melanomas (nos. 12–15) and one mucosal melanoma (no. 10). In two instances the site of origin was not recorded but presumably these were cutaneous melanomas (nos. 7 and 8). Our third patient had had an occult primary melanoma. Two patients never received levodopa (nos. 6 and 7). In patient no. 5 levodopa treatment was initiated 7 years after a melanoma had been successfully treated; 24 months later no relapse of the melanoma had occurred. Thus, there remain 16 patients, including our three cases, in whom there was an apparent time relationship between the emergence of melanoma activity (primary or metastatic) and levodopa treatment. Whether this relationship is a causal one or merely coincidental remains a matter of dispute.

The putative capacity of levodopa to induce melanomas should be questioned. As can be seen from the table, diagnosis of melanoma preceded the initiation of levodopa therapy in three patients (nos. 1, 4 and 5), whereas in a fourth case (no. 2) melanoma diagnosis coincided with the start of

levodopa therapy. Moreover, in six cases (nos. 3, 10, 14–17) the interval between the start of levodopa treatment and melanoma diagnosis was 2 years or less. Time lapses between exposure to incriminated carcinogens and clinical manifestation of tumours are considered to be many years (if not decades) in most malignancies and melanoma is probably no exception. It is therefore unlikely that levodopa played any role in the induction of melanoma in these six cases. Thus, there remain only seven patients in whom the time lapse between projected tumour induction and clinical manifestation of melanoma was long enough for levodopa to be considered as a potential carcinogen. This figure is meaningless in the light of the high number of patients under long-term levodopa therapy.

Two case studies merit particular consideration. Skibba *et al* reported a male patient who developed several pigmented lesions within a few months of resuming levodopa treatment and 4 years after excision of a primary melanoma.¹ These lesions were located in the grafted area on the back and on the right shoulder, anterior chest wall, neck and scalp. Some were pea-sized subcutaneous nodules consistent with melanoma metastases. Other lesions exhibited junctional activity together with dermal invasion. These lesions were referred to by the authors

as "typical primary melanomas". However, the clinical behaviour of this melanoma with multiple cutaneous lesions emerging simultaneously in the region of the primary site suggests that all these lesions were in fact cutaneous secondaries. Epidermotropism is not a feature peculiar to primary melanomas but may occur in cutaneous metastases as well.¹²

A rather similar case was described by Bernstein *et al.*⁸ An elderly woman developed a level IV melanoma 10 years after she had been receiving levodopa and a decarboxylase inhibitor. The lesion, which was located on the scalp, was excised and a rotated skin flap was applied. The patient subsequently received local x ray therapy. Ten months later six tiny purple nodules arose within the area of the flap. The presence of epidermotropism led the authors to believe that these lesions represented local recurrences. One month later a 2 mm brown papule on the left foot was excised, exhibiting "moderately atypical melanocytes" in the epidermis only and a diagnosis of precancerous melanosis was made. Again 2 months later a flesh-coloured papule above the right eyebrow was excised. Primary melanoma was diagnosed. In this case the designation "distinct primary melanoma" for the foot lesion, showing no dermal invasion, is not borne out by the clinicopathological description. Also, the evidence furnished to classify the forehead lesion as a new primary is not firm. Differences between satellite and in-transit lesions and epidermotropic metastases on the one hand and primary melanomas on the other hand may be very subtle.¹² Slight acanthosis, absence of atypical melanocytes in the dermal vessels and tumour involvement of the entire dermis in a "nonzonal fashion" cannot be called characteristic features in favour of primary cutaneous melanoma. It is tempting to theorise that, where multiple local recurrences have emerged, a new lesion in the vicinity of the excision scar is not a new primary but also a sign of recurrent disease (satellite or in-transit metastasis).

Summarising the above it can safely be stated that the available literature data do not endorse the supposition that levodopa intake has an effect on malignant transformation of melanocytes. Likewise, there is no substantial evidence from the reported cases that levodopa therapy enhances melanoma growth. Thus far, two cases have been reported showing melanoma relapses after 4 and 2 months of levodopa therapy, respectively (nos. 1 and 4). These two cases prompt little concern and should be regarded as coincidental. In our third patient low back pain started 6 years after initiation of levodopa. The pain gradually intensified and after 3 years (!) metastatic melanoma was diagnosed. In

this instance levodopa does not seem to have exerted a detrimental influence on the course of the melanoma and might even have been growth restraining.

Growth exacerbation of melanoma due to levodopa is often explained by the role levodopa plays in the biosynthetic pathway of melanin, in which it serves as a substrate for the rate-limiting enzyme tyrosinase.¹³ However, a distinction should be made between melanogenesis and tumour growth rate. Stimulation of the metabolic pathway for melanin synthesis by levodopa administration implies the augmentation of a highly differentiated function of the melanocyte. Where melanogenesis is activated, cell replication is probably impeded. Although melanogenesis and mitotic activity are not necessarily mutually exclusive, it is conceivable that melanocytes that are productive (melanin synthesis) are not at the same time re-productive (cell replication). Certainly, undifferentiated, that is amelanotic, melanomas are among the fastest growing human tumours. It is therefore anticipated that if levodopa has any effect on melanoma growth, it would be an inhibitory one since it stimulates melanogenesis. Wick *et al* have in fact demonstrated that levodopa is "toxic" to melanoma cells.¹⁴

Should patients with Parkinson's disease receiving levodopa be monitored for the development of melanomas? Several authors imply that vigilance is required.^{3,8,10} In our opinion, the advice to search for melanomas in all patients on levodopa is impracticable. In the light of present knowledge the expected number of melanomas to be found on routine examination of these patients is extremely few. Moreover, delicate changes in pre-existing moles are difficult for the non-dermatologist to interpret. Should dermatologists then be burdened with the regular control of all patients with Parkinson's disease taking levodopa? We are inclined to admit that the answer is no.

The second question is whether patients who use levodopa and in whom a melanoma is encountered should discontinue taking the drug? Some authors adhere to such an approach.^{3,4,15} This attitude has been challenged by Sober and Wick.^{6,16} Since the exact influence of levodopa on the behaviour of melanoma is unsettled, it would seem prudent to try an alternative drug like a dopaminergic agonist. However, if control of Parkinson's disease with a dopaminergic agonist is less satisfactory than with levodopa, there should be no hesitation in returning to its use.

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