Uveal Malignant Melanoma and Levodopa Therapy in Parkinson's Disease

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Abstract: Of three patients who used Levodopa as therapy in Parkinson's disease, two developed a malignant melanoma of the choroid, the third a malignant melanoma of the ciliary body. The possible connection between Parkinson's disease, Levodopa therapy and malignant melanoma, until now only described for cutaneous melanomata, will be discussed. [Key words: Levodopa, Parkinson's disease, uveal malignant melanoma.] *Ophthalmology* 89:1464–1466, 1982

Skibba et al¹ first reported the case of a patient with Parkinson's disease and a cutaneous melanoma who developed a local recurrence of this melanoma together with multiple primary skin melanomas two months after starting Levodopa therapy. Several more reports suggesting a relation between malignant melanoma, Parkinson's disease and Levodopa therapy have appeared.^{2–5} Because of this the manufacturer of Levodopa-containing drugs advises in The Netherlands not to use Levodopa in patients with melanomas or with undiagnosed melanomatous lesions.

We reported the case of a patient with a choroidal malignant melanoma, Parkinson's disease, and Levodopa treatment at the annual Dutch ophthalmology meeting. This case is presented here, together with another two Belgian cases with this combination.

CASE REPORTS

Case 1. A 69-year-old Caucasian woman came to the outpatient department with an amblyopic right eye and a retinal

detachment in the left eye secondary to a large presumed choroidal malignant melanoma. A general check-up showed no signs of metastasis. She was known to have had Parkinson's disease for the past 12 years. For the last seven years she had been taking 250 mg Levodopa tid, 25 mg Carbidopa tid, and biperiden. As the left eye still had 20/20 vision we decided to wait until growth of the tumor was verified. Later on, the patient refused the proposed enucleation till the visual acuity dropped to hand movements two months after the first visit to the hospital. Microscopical section of the tumor showed a choroidal spindle-cell B malignant melanoma with extraocular expansion (Fig 1). Twelve months after the enucleation, there were no signs of metastasis, and the patient continues to do well. Withdrawal of the Levodopa therapy caused so much discomfort that the drug had to be prescribed again, in an even higher dose than before.

Case 2. A 53-year-old Caucasian woman with a 4½-year history of Parkinson's disease had been taking 250 mg Levodopa tid along with methixene HCl 5 mg and ocymetaphine 100 mg tid since the onset of the disease.

The visual acuity of the right eye temporarily dropped to 20/200 because of a retinal detachment secondary to a tumor on the nasal side of the optic disc, but regained 20/20 again through a spontaneous disappearance of the exudation. The left eye had full vision.

After enucleation of the right eye, a spindle-cell choroidal melanoma was diagnosed. Histology showed mainly fusiform and round cells. The patient is well, seven months after the operation, and the left eye shows no signs of a tumor.

Case 3. A 70-year-old Caucasian woman with Parkinson's disease had been treated with 125 mg Levodopa and 25 mg benzeradine tid since January 1977. Eleven months later a tumor was found in the right eye that still had full vision.

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Figs 1. *Top*, case 1. Malignant melanoma of choroid with extrabulbar extension (hematoxylin-eosin, $\times 80$). *Bottom*, same tumor, spindle B (hematoxylin-eosin, $\times 800$). Courtesy A. B. de Haan, MD

The enucleated eye had a malignant melanoma arising from the ciliary body, consisting mainly of round cells with some epithelioid cells to a lesser degree. No tumors have been found till now, four years later.

DISCUSSION

The relation among Parkinson's disease, Levodopa, and cutaneous melanomas is full of controversy. A statistically nonsignificant increase in the incidence of cutaneous melanomas in Parkinson's disease was reported by Fermaglich et al.⁴ Sober and Wick,^{6,7} however, found only one patient who had used Levodopa and only one patient with Parkinson's disease in a group of 1099 patients with primary cutaneous malignant melanoma. Beardmore and David⁸ reported that 3.9% of 1444 patients with cutaneous melanoma had multiple primary melanomas, so there is a possibility that the patients described by Skibba et al.¹ and Bernstein et al.⁵ fall into this category.

A possible tumor-inducing or stimulating effect of Levodopa on melanoma cells had been suggested,³ but in contrast, a growth inhibiting effect on human melanoma cells in vitro and on mouse melanoma cells in vivo was reported by Wick.^{9,10} The melanin formation is dependent on a metabolic pathway that is impaired in Parkinson's disease. Thus, one could expect the melanin formation to be decreased, resulting in a lower incidence of melanin forming tumors in Parkinson patients compared to a normal population.

In The Netherlands the incidence of uveal malignant melanoma is 0.8 per 100,000 per year.¹¹ About 30,000 people have Parkinson's disease (1–2‰), and approximately 12,000 of them are taking Levodopa-containing drugs. According to these figures the chance of getting a malignant melanoma through Levodopa therapy would be increased if in ten years more than one patient would have this combination. Although the Belgian population is slightly smaller, these data would be appropriate for that country as well. Barbeau¹² mentioned a possible increase in malignancy in patients on Levodopa therapy, but all articles reported here did not cause Parkes¹³ to mentioning malignancies in his review article on adverse effects of anti-Parkinson drugs.

We report these patients, although we are not convinced about the connection between malignant melanoma, Parkinson's disease and Levodopa treatment. Our three cases are dealing with uveal melanomas, which differ from cutaneous melanomas in their clinical aspects as well as in their microscopical appearance.¹⁴ It may be, however, that more patients with Levodopa therapy and uveal malignant melanoma will be found once this has been reported in the ophthalmologic literature.

Up till now we have found no reason to discontinue Levodopa treatment in Parkinson's disease, but some authors advise bromocryptine as a dopaminergic agonist⁷ instead of Levodopa.

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