Parkinson's disease, levodopa-use and the risk of melanoma


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**A R T I C L E   I N F O**

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**A B S T R A C T**

Since the early 1970s, the literature has suggested an association between Parkinson's Disease (PD) and/or levodopa-use and an increased risk for the development of malignant melanoma. In some countries, this possible association has even led to a warning in the drug insert leaflet of the possible risk. Recently, five studies have been published that have investigated both associations and three conclusions can be drawn. Firstly, there appears to be an increased risk in the development of melanomas in patients with PD. Secondly, this increased risk is already present before the PD is diagnosed. Finally, it is unlikely that levodopa plays any role in this phenomenon. It is not known which factors are responsible for this increase in the development of melanomas in PD patients and this needs further investigation. We recommend the removal of the warning from the drug insert leaflet, since this can lead to unnecessary fear on the part of the patients and physician resistance to prescribing this medication.

1. Introduction

Levodopa is the cornerstone of treatment for Parkinson's disease (PD). Due to the fast and significant improvement in motor function after initiation of levodopa-therapy patients are able to function independently for a longer period of their lives [1]. It is mainly because of this fact that levodopa is considered to be the 'golden standard' in the treatment of PD [2]. Owing to the favourable effects on symptoms almost all PD-patients are treated with levodopa at all stages of the disease [1]. Unfortunately, chronic use of this medication has some disadvantages: after some time, fluctuations in motor response ('wearing off', 'on–off') and dyskinesias often occur [3]. These side-effects have been extensively discussed in the literature. An issue that has been raised since the early 1970s is the possible association between levodopa-use and the risk of developing a malignant melanoma. This topic has been explored extensively, but no clear conclusions have been drawn. In the last three years, five major studies with clear methodology and large study groups have been published [4–8]. We consider that these publications can be used to draw final conclusions. It is especially important to give a clear message about the association between levodopa-use and melanoma, since in several countries (USA, the UK, the Netherlands, New Zealand and Germany) drug insert leaflets mention the development of 'malignant melanoma' (even though 'rarely') as a side-effect of 'levodopa/carbidopa'; even though this statement is unproven [9–13]. Even the website of the 'European Parkinson's Disease Association' warns that patients with a history of melanoma should not take levodopa [14]!

In this review, we give an overview of the current knowledge about the relationship between both, PD and the risk on developing a melanoma and between levodopa-use and the risk of developing this malignancy.

2. Historical overview of the literature

The association between levodopa-use and the development of a malignant melanoma was first mentioned in 1972 [15]. A case-report described a 50-year-old man with PD who had developed a melanoma on the scapula before initiation of levodopa-therapy. The melanoma was removed surgically and there was no evidence of metastasis. Four months after initiation of the levodopa-therapy, pigmented noduli were removed from the site of the original melanoma. A 'recurrent melanoma' was diagnosed and the levodopa-therapy was stopped [15,16].

After this publication, several case-reports followed in the 1970s. It should be noted that all of these patients had a melanoma or a 'benign nevus' in the case history before initiation of levodopa-therapy [17]. Already in the 1970s, doubts were raised about the relationship between levodopa-use and melanoma development. A paper in 1978 described a database of 1099 patients with a primary melanoma: only one patient took levodopa [18].

In the 1980s and 1990s, several case-reports followed, summarized in a review in 1997 [19]. This review failed to answer...
the question about the relation between levodopa-use and the development of melanomas.

In 2003, a review was published that evaluated all the previous case-reports investigating the possible relationship between levodopa-intake and the development of a melanoma [20]. However, since only case-reports were used, no clear conclusions could be drawn. Larger study-populations and more clear methodology were needed to finally end the discussion that has already lasted over 30 years.

3. PD and the development of melanomas

Since 2005, three major epidemiological studies have been published that have investigated the association between PD and the development of melanomas.

In the first study, from a retrospective cohort-view, the incidence of the development of melanomas in PD was investigated in 14,088 PD patients from the ‘Danish National Hospital Register’ (a register that contains all the PD diagnoses between 1977 and 1998), as compared with the ‘standardised incidence ratio’; the estimated incidence for the development of melanomas in the general population [7]. It was found that in the PD group, 1282 cases of cancer were reported in the ‘Danish Cancer Registry’. In the general population, a total of 1463.9 cases could be expected. The study concluded that there is a significant risk reduction of 12% of the development of tumours in patients with PD. Surprisingly, certain types of tumours like the malignant melanoma, arose 95% more often than could be expected (44 observations, compared with 22.5 cases that could be expected).

Because of these remarkable findings, this study was extended in 2006 by the same group [6]. The main purpose was to find out what factors play a role in the development of the melanomas: if levodopa-use itself is the main factor, the increased incidence of melanomas in PD would only be found after initiation of levodopa-therapy. However, if other PD-related factors were responsible (genetics or environment), the increased incidence would already be found earlier, possibly even before the PD has been diagnosed or at least before initiation of any therapy. In a retrospective patient-control study, patients with PD diagnosed between 1986 and 1998 from the same ‘National Hospital Register’ (8090 patients) were individually linked to a control person of the same gender and age (32,320 persons in total), obtained from the ‘Danish Central Population Register’ (a register with base information of all 5.3 million citizens of Denmark). Both groups were verified in the ‘Danish Cancer Registry’ for the presence of tumours, including malignant melanomas, which were diagnosed before the PD had been diagnosed in the patient group. In this group, from 8090 patients, 966 patients (11.94%) had developed some form of cancer before being diagnosed with PD. In the control group, from the 32,320 persons, 3734 persons (11.55%) had developed some form of cancer. The endpoint in this group was diagnosis of PD in the patient that was linked to the control person. The first conclusion was that there was no significant difference in the development of tumours overall between both groups. However, when a difference was made between certain forms of cancer, it turned out that malignant melanomas were seen in 0.57% of the PD population, against 0.40% in the control group (44% more in PD patients than in a control group, being statistically significant). A remarkable finding was that this increased risk was mainly found in the year before PD was diagnosed.

If both articles are summarized, it can be concluded that there is an increased risk in developing malignant melanomas in patients with PD. Because this increase was found before PD was diagnosed and before a specific therapy had been started, the association between levodopa-use and the development of melanomas is unlikely.

The relationship between malignant melanomas and PD was again examined in 2007 in a patient-control study using the database of the ‘Physician’s Health Study’ (a placebo-controlled trial on the effect of aspirin and β-carotene on the prevention of cardiovascular diseases and cancer, using 22,071 male participants in the US) [5]. In this study, 487 participants developed PD (during a follow-up period of 23 years). For every patient, a control person of the same age, being free of cancer when the PD was diagnosed in the study group, was linked. In the total group of 974 participants (two groups of 487 persons), a total of 121 tumours developed during 5.5 years of follow-up. Of this total, 68 cases came from the control group and 53 from the PD group. This indicates that overall, cancer is seen less in the PD group (11%) as compared to the ‘healthy’ control group (14%), with an (insignificant) relative risk (RR) of 0.84. However, patients with PD appeared to have a significantly increased risk for the development of malignant melanomas, with an RR of 6.15 (9 cases in the PD group against 0 cases in the control group).

4. Levodopa-use and the development of melanomas

A retrospective patient-control-study investigated whether the increased incidence of melanomas in PD patients could be explained by levodopa-use [8]. From a more recent file of the ‘Danish Hospital Register’, PD patients were extracted who had developed a malignant melanoma. At the end of 2002, a total of 48 cases had been described. Each of these patients was linked to 4 control persons of the same age and sex. In this study, the RR to develop a malignant melanoma appeared to be 85% higher when a patient developed PD, as compared to ‘healthy controls’.

The study was later extended: all the records of the 48 PD patients who had developed melanomas, and the records of 172 randomly selected patients from the great Parkinson-file were selected. The patients were divided into three groups (‘probable PD’, ‘possibly PD’ and ‘Parkinsonism’) and the medication history was studied. It was found that in the group of patients with a ‘probable PD’, the RR to develop a melanoma was increased fourfold, as compared to the ‘possible PD’ groups.

When the medication history of the different groups was compared, it was found that the cumulative levodopa-intake until the melanoma was diagnosed, was 1495 kg in patients with a malignant melanoma, and 1307 kg in the control group. The RR for a malignant melanoma per 1000 kg of cumulative levodopa-dose appeared to be 1.0. When a distinction was made in cumulative levodopa-dose ((1) <600 g, (2) >1370 kg or (3) in between), the RR remained 1.0 in all the groups. It was concluded that levodopa-use does not contribute to the risk of developing a malignant melanoma.

These findings were confirmed in an extraction of the DATATOP trial (a study on the effects of selegiline and tocopherol on the progression of PD), where in a retrospective cohort-study the incidence of malignant melanomas was determined [4]. A total of 800 patients contributed to this study. It was found that in 3691 person-years, 5 cases of melanomas appeared (which results in an incidence of 1.4 cases per 1000 person-years). Since in a ‘standard population’ a total of 1.5 cases could be expected in the total of 3691 person-years, the ‘standard event ratio’ (SER) for PD-patients (the chance of developing a malignant melanoma) is 3.3 times increased. Of these five cases, two occurred before initiation of levodopa-therapy (incidence of 1.2 per 1000 person-years, with an SER of 3.2) and three cases were found after 1, 6 and 19 months after initiation of levodopa-therapy (incidence of 1.4 per 1000 person-years, with an SER of 3.4). Therefore, this study also confirms the increased incidence in the development of malignant melanomas in PD patients, but it is unlikely that levodopa is responsible for this finding.
5. Discussion

The possible association between levodopa-use and the development of malignant melanomas has been described since the 1970s [20].

When the results of the aforementioned studies have been evaluated and combined, the following conclusions can be drawn. Recent studies investigating large cohorts show an increased risk of the development of malignant melanomas in patients with PD. The RR’s appeared to be 50% higher than in ‘healthy’ controls (Table 1). This risk is not increased from the moment of diagnosis: PD is already increased before diagnosis. This would suggest that even before PD is clinically manifest, there are already factors that increase the risk of developing a melanoma. Finally, there does not seem to be an association between levodopa-use and the development of melanomas [4,8]. The chance of developing a malignant melanoma is already increased before initiation of levodopa-therapy. This risk proceeds after initiating the therapy, but not in a way that levodopa itself contributes to the risk.

Therefore, the warning of an increased risk of developing a melanoma when levodopa is prescribed, and the warning of melanomas in the previous history as a contra-indication for prescribing levodopa, in the drug insert leaflets in several countries, and the warning of the ‘European Parkinson's Disease Association’ seem unfounded. There is no proof at all that this warning is legitimate and may lead to unwillingness to prescribe on the part of physicians and reluctance to take the medication because of the fear of malignancies on the part of patients.

The question remains as to which factors do contribute to the increased risk of malignant melanomas in PD patients. At this time little is known about this subject, but there are some hypotheses. It could be possible that there is a genetic profile that contributes to both the development of melanomas and the pathology found in the substantia nigra at PD [21]. Possibly, there are also social-economic factors involved, for example: the risk of melanoma development appears to be increased with an increased exposure to UV [22–24]. These factors should be investigated in a study in which special genes and environment-factors for the development of melanomas are compared in a validated setting.

6. Conclusion

There is a proven increased incidence in the development of melanomas in patients with PD, both before and after diagnosis. There does not seem to be an association between levodopa-use and the development of melanomas. It is not known which factor(s) do contribute to this increased incidence.

References