Visual hallucinations in the elderly associated with the use of levodopa

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Summary: Visual hallucinations are a well recognized unwanted effect of treatment with levodopa.⁸ Although many individual cases have been reported, there has only been one review previously published about this finding, and this did not discriminate age groups.⁸ We present five cases and briefly review the literature. It is important to enquire specifically about visual hallucinations in patients on levodopa therapy at follow up, as this otherwise potentially reversible side effect may be overlooked.

Introduction

Mental disorder in Parkinson's disease is a well known phenomenon. Mental dysfunction occurring with levodopa therapy varies from mild mood disorders to hallucinations.^{1–3} The widely differing prevalence of visual hallucinations in previous studies (between 5 and 30%^{4–9}) may be explained by a variation in predisposing factors, such as a history of psychiatric illness (including dementia), duration of therapy, or by the adverse effects of concurrent drugs. In a disease that is known to be progressive, the simplest explanation relates to the selection of patients under study – that is, newly diagnosed as opposed to secondary referrals. The present paper describes 5 patients with the disorder and a review of previous publications.

Patients and methods

From a total of 19 patients with Parkinson's disease admitted to an acute geriatric unit during a 3 month period, 5 had reported visual hallucinations whilst taking levodopa. These 5 cases are presented here (Table I).

Case 1

Female aged 72 with a previous history of depression, was admitted to hospital with repeated 'funny turns' and falls. She was known to have suffered from Parkinson's disease for at least three years, and

throughout this period had been maintained on Sinemet-110 five times daily (equivalent to 500 mg levodopa a day). Her compliance was poor. On examination she demonstrated increased tone in all limbs, with associated 'cog-wheel' rigidity, but no resting tremor. She showed no focal neurological signs and examination was otherwise normal. After admission, she subsequently developed visual hallucinations and persecutory ideas. Although these were initially attributed to a bereavement reaction, nevertheless, the Sinemet was slowly discontinued and benztropine 4 mg a day was substituted. She still continues to have intermittent visual hallucinations (confirmed by the nursing staff as well as her relatives). Her parkinsonian symptoms are stable on this medication.

Case 2

Female aged 81, with a two year history of Parkinson's disease and mild senile dementia. She had been commenced on Sinemet-110 six times daily (600 mg levodopa) early in her illness, and was still on this regimen at the time of her admission to hospital. She experienced an episode of visual hallucination which lasted 24 hours soon afterwards. The dosage of Sinemet was reduced and she did not suffer any further hallucinations.

Case 3

Male aged 74 with a 12 month history of Parkinson's disease, and rapid progression in the last 6 months. He was seen on a domiciliary visit which prompted his admission to hospital. He had no previous psychiatric history. He was initially treated with Madopar 625 three times a day (equivalent to 150 mg levodopa a

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Table 1 Details of therapy for all 5 patients

	Case number				
	1	2	3	4	5
Age (years):	72	82	74	70	81
Past history of psychiatric illness:	Depression	Symptoms of mild dementia	—	Dementia	Dementia
Duration of parkinsonian symptoms (months):	36	24	12	18	24
Other therapy at onset of hallucinations excluding levodopa:	—	Paracetamol Glibenclamide	—	Orphenadrine	Atenolol
Daily dose levodopa at onset of hallucinations:	500 mg	600 mg	300 mg	600 mg	300 mg
Duration of levodopa therapy (months):	36	24	2	7	24
Dose increase of levodopa before hallucinations?	Yes	No	Yes	No	No
Management of hallucinations:	Gradual replacement of Sinemet by benzotropine	Reduction in dosage	Reduction in dosage	None	Stopped levodopa
Relief of symptoms:	Complete	Complete	Complete	None	Uncertain

day), which was gradually increased to 125 Madopar three times a day (equivalent to levodopa 300 mg a day). Two months after starting treatment, he experienced an episode of visual hallucinations. Although maintained on the same dose, he did not report any further episodes; however, when his wife was interviewed recently, she admitted that he continued to experience further hallucinations. She claimed that these took the form of him seeing people walking through the room who were not actually present. As a consequence of this, it was felt necessary to reduce his dose of Madopar from 125 to 62.5 three times a day. Accordingly, his wife reported considerable improvement. In addition to the absence of hallucinations, his Parkinson's disease remains well controlled.

Case 4

Male aged 70, presented with an 18 month history of Parkinson's disease. Over the past two years he developed progressive dementia and confusion. For the first 9 months of his illness he was treated with orphenadrine 25 mg three times a day; however, because of persistent rigidity and tremor, his treatment was changed to two Sinemet-110 three times a day (equivalent to levodopa 600 mg a day). After 7 months of treatment, he developed visual hallucinations. He continued to be ambulant but suffered with rigidity and confusion. The same total dose of levodopa was maintained but spread more widely over the day

(Sinemet-110 three hourly). After two weeks on this regimen, the visual hallucinations and confusion became worse. For some weeks he did not receive his correct medication. He was then reinstated on two Sinemet-110 three times a day. He experienced no further episodes of visual hallucinations and his parkinsonian symptoms improved greatly.

Case 5

Female aged 81 presented with a two-year history of resting tremor and akinesia. During this period, she was treated with Sinemet 110 (equivalent to 300 mg levodopa a day). She had developed visual hallucinations 2 months before being seen and her general condition had been progressively deteriorating. Her general practitioner had discontinued her treatment.

Upon admission, she demonstrated a pill rolling tremor, cog-wheel rigidity, a festinant gait, and her Newcastle abbreviated mental test score for dementia was 0 out of ten, the normal score being 9–10/10. She had had a previous score of 8/10. She was initially very confused and agitated, but was gradually calmed on promazine 75 mg three times a day, later reduced to 25 mg three times a day. At the same time she was recommenced on Sinemet Plus three times a day (equivalent to 300 mg levodopa a day). She has made a good recovery, walking unaided. The promazine has been discontinued, and she does not appear to have experienced any further visual hallucinations.

Discussion

The prevalence of visual hallucinations in patients receiving levodopa therapy varies between 5% and 30% in different studies reporting this condition.⁴⁻⁹ In our study over a period of three months, a total number of 19 patients with Parkinson's disease were seen, giving an overall incidence of 26%. However, the findings of a retrospective study of such a limited number of admissions cannot be a reliable measure of incidence or prevalence of the disorder or of predisposing factors. The variation in prevalence in the different studies may be explained firstly by the selection of the patients being studied, secondly by the progression of the disease itself, and lastly by the fact that some studies do not exclude patients with known psychiatric disease such as dementia. Perhaps because of this, it was recently suggested that dementia is a contraindication for the use of levodopa.¹⁰

The incidence of psychiatric disorders precipitated by levodopa in a random population with Parkinson's disease increases with a previous history of psychiatric illness in the patient, or in a first degree relative of the patient.¹

In an eight year prospective study, Sweet *et al.*⁶ found that 18 out of 104 patients with Parkinson's disease suffered mental disorder associated with levodopa therapy. Only 6 of them did not suffer mild to severe dementia at the beginning of the study. The symptoms of the 12 patients with dementia initially were observed to undergo subsequent deterioration.⁶

The incidence of visual hallucinations positively correlates with both the dose¹¹ and the duration of treatment^{6,8,12} as well as the severity and progress of the disease. Visual hallucinations are not only experienced with levodopa therapy, an even higher incidence has been reported with bromocriptine, although this may be due to the greater severity of the disease in those patients requiring treatment with bromocriptine. Anticholinergics and selegiline also have a recognized association with visual hallucination.^{13,14,15}

Other treatments not associated with Parkinson's disease have been suspected of causing visual hallucinations. These include psychotropic drugs such as tricyclic anti-depressants and benzodiazepines, cardiovascular agents such as digoxin and beta blockers, as well as various analgesics including pentazocine, indomethacin and salicylates.¹³ It is therefore mandatory to obtain a comprehensive and full drug history from any patient complaining of visual hallucinations.

There are several pathophysiological theories to explain visual hallucinations associated with levodopa therapy. It has been suggested that dopamine may produce mental disturbances by interfering with structures within the limbic system, which utilize dopamine receptors. Alternatively, it is possible that levodopa may compete with serotonin (5-hydroxytryptamine) for L-aromatic amino acid decarboxylase in brain tissue, or by displacing serotonin in serotonergic granules and acting as a false transmitter at serotonergic receptor sites.¹⁶

Visual hallucinations are therefore a well recognized unwanted effect of levodopa, which may easily be overlooked. It is important to recognize this symptom as it is potentially reversible. Hallucinations are often relieved simply by reducing the dose of levodopa, however this also often decreases the effect of levodopa on the motor symptoms of Parkinson's disease.¹¹ An alternative method of managing levodopa-induced hallucinations is to either totally discontinue the levodopa treatment or to reduce the dose and introduce L-tryptophan.^{11,17} However the use of other dopaminergic drugs, such as bromocriptine, has not been shown to be useful.^{14,15} Bromocriptine ameliorates the on-off phenomenon in some patients, but psychiatric symptoms may well become worse. The use of dopaminergic blocking agents such as phenothiazines and butyrophenones may decrease some of these side effects, but since these agents block all dopaminergic receptors unselectively, it is probable that the parkinsonian symptoms will be exacerbated.

Levodopa is the treatment of choice in the elderly patient with Parkinson's disease; it should be administered in the lowest dose required to satisfactorily control the motor symptoms. Anticholinergic agents have a greater incidence of side effects, particularly in those parkinsonian patients with associated dementia.²⁰ However, even with lower doses of levodopa, a watch must be kept for the emergence of any side effects, especially in those patients who have been taking this medication in the long term.²¹

In summary, visual hallucinations are an important unwanted effect of treatment with levodopa, which may be much more common than previously reported. With an increasing elderly population, this side effect should be more widely considered. It is essential to specifically enquire whether these patients experience visual hallucinations, when they are seen in clinics or on ward rounds, since a serious and potentially treatable side effect may otherwise go unnoticed.

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