Treatment of blepharospasm with levodopa

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Mechanism of production of Parkinsonian symptoms

The clinical features that result when the 'extrapyramidal' motor system is involved in disease are often highly characteristic, but unfortunately not yet well understood. Explanation of symptoms of Parkinson's disease is difficult not only because of their complexity but also by difficulties in interpreting the pathological material. There are a few pathological changes, the most consistent appearing to be the loss of nerve cells from the substantia nigra and of myelinated fibres from the globus pallidus and depletion of dopamine in the globus pallidus. However, it is important that the clinical features are recognized before attempts are made to understand the underlying mechanism of production of symptoms in the light of present knowledge.

One of the commonest and earliest symptoms of parkinsonism is tremor consisting of rhythmic alternating movements of opposing muscle groups with a frequency of about 6/sec. The tremor is usually confined to one hand or less commonly the foot and can spread with varying degrees of rapidity to the other limbs, head and jaw. The tremor is present when the patient is at rest and is commonly suppressed during voluntary movement.

The major disability is disorder of voluntary movement, akinesia. This results in small and cramped hand-writing, difficulty in fastening buttons and shoe laces, difficulty in rising from a chair, slowness in walking, etc. Frequent falls are not uncommon. Muscle rigidity is present except in the very early cases and can be demonstrated on passive flexion and extension of the wrist or elbow. In parkinsonism, the facial muscles exhibit an unnatural immobility. Depression also appears to be an integral symptom of the disease.

There are some characteristic features in post-encephalitic parkinsonism. The rigidity is disproportionate in severity. Ocular symptoms and signs are common. Blepharospasm may be severe enough to prevent useful vision. There may be oculogyric crises. Pupillary abnormalities, ocular palsies and increased tendon jerks may also be present. It is now thought arterio-sclerosis plays no part in the aetiology of parkinsonism. Drug-induced parkinsonism due to prolonged use of phenothiazines or reserpine is seldom severe and very often is reversible.

It is now recognized that reserpine will deplete dopamine in the basal ganglia and produce parkinsonism in man. The depletion of dopamine in the globus pallidus found at post mortem suggests that an attempt to restore normal concentrations of dopamine in the basal ganglia could be helpful in parkinsonism. Dopamine will not cross the blood brain barrier, but levodopa (L-dopa) will, and has been found to be effective in controlling the symptoms of parkinsonism. It is possible that the symptoms of parkinsonism arise in some way from loss of neurones in the substantia nigra that liberate dopamine as a transmitter substance in the globus pallidus, and that this is normally balanced by other fibres liberating acetylcholine.

It has been suggested that blepharospasm could be a nociceptive reflex normally inhibited by dopamine, and that this inhibition is lost in patients suffering from parkinsonism. The loss is functional but can be corrected by dopamine acting in the striatum. Klawans and Erlich (1970) suggest that blepharospasm may be due to nociceptive reflex initiated by stimuli such as strong light, gusts of wind, cigarette smoke, etc. This closure is spontaneous and can vary from fibrillar twitching of a few fibres of the orbicularis oculi to severe, prolonged and painful contractions of both orbicularis muscles.

Three patients suffering from parkinsonism with blepharospasm were treated with L-dopa. In all three, there was considerable improvement in parkinsonism as well as blepharospasm, and in two cases the blepharospasm was reversed within 4 weeks of starting treatment. In all three there was a remarkable improvement in the depression.

Case 1

L.B. is a 70-year-old male with a 3-year history of parkinsonism. Initially, stiffness and slowness of movements with masked facies were noted. Over the last 2 years, he developed cogwheel rigidity, tremor of hands, difficulty in initiating movements, shuffling gait and poor balance. Recently, difficulty in initiating and carrying out movements became so
much worse that he found it difficult to get out of a chair and walk about inside the house and also he was having frequent falls. He was depressed. His voice became weak and speech was low pitched and almost inaudible. For the last 3 months, he was having episodes of involuntary closure of both eyes associated with pain which was gradually getting worse. At times, he had to keep the eyes open manually. When the eyelids were held open, vision and extraocular movements were normal.

His past history includes a moderate hypertension (200/115 mmHg) but no encephalitis. Neurological examination revealed that the patient was reasonably alert. Cranial nerves, sensations and deep tendon reflexes were within normal limits. There was marked bradykinesia (had great difficulty in getting out of the chair, as mentioned earlier), positive glabellar tap in addition to other features of parkinsonism previously mentioned. Episodes of involuntary eye closure, and also the fact that he had to open the eyelids manually, were observed during examination of the patient.

Medication for the last few years was benzhexol 4 mg t.d.s. The patient was placed on oral L-dopa 250 mg b.d. which was gradually increased by 250 mg every 3–4 days until a total daily dosage of 2.5 g was reached. Benzhexol was continued as before. Within 4 weeks of treatment the patient made a considerable improvement—blepharospasm completely disappeared, rigidity much reduced and there was slight improvement in the tremor of the hands. Great improvement in bradykinesia was noticed and he was able to get out of a low chair and was able to walk along the corridor quite well. Balance improved and he had no further falls. Speech became distinct. He had a feeling of well-being and became cheerful (depression lifted).

No side effects from L-dopa were observed.

**Case 2**

I.W. is a 68-year-old female. She has a 10-year history of parkinsonism and has received hospital treatment for at least 5 years. Initially, no rigidity but fairly gross tremor of the hands was noted. She had been having frequent falls. Gradually the tremor of the hands became more marked and also the tremor of the jaw appeared. Masked facies, frequent involuntary closure of eyelids (blepharospasm), some cogwheel rigidity, bradykinesia (great difficulty in getting out of chair unaided), poor balance and positive glabellar reflex were noted. There was also shuffling gait, anteropulsion and retropulsion and the body became stooped. There was excessive salivation.

Her past history includes depression but no history of encephalitis.

Neurological examination revealed the patient to be very alert and well orientated with both recent and remote memory intact. She was unable to rise by herself from a seated position. Deep tendon reflexes were normal and symmetrical. Examination of cranial nerves and sensations revealed no abnormality. She was depressed. The features of parkinsonism which were present are already mentioned.

Medication for the last few years was benzhexol, orphenadrine and benztropine methanesulphonate, imipramine (for depression) and amantidine for the last year. She was started on a small dose of L-dopa, 250 mg b.d. which was gradually increased to a total daily dosage of 2 g. At the same time all other medications were withdrawn as the patient was reluctant to take them. Within 4 weeks of treatment with L-dopa, there was a considerable improvement in her bradykinesia and she was able to get up from a low chair unaided and was able to walk fairly steadily. The incidence of falls became much less. There was a marked improvement in her depression. Blepharospasm completely disappeared. No change in tremor was noticed. Palmo-mental and glabellar reflexes were reversed.

The only side effect noticed was slight drowsiness.

**Case 3**

G.R. is a 73-year-old male with a 4-year history of parkinsonism. Marked facies, tremor of right hand, cogwheel rigidity of all the limbs, marked bradykinesia (was recently virtually confined to bed and chair) and frequent uncontrollable blinking of both eyes (blepharospasm) were noticed. He had stooped posture, confusion and marked depression. No history of encephalitis.

Neurological examination revealed moderate mental impairment (scored 6/10 on mental status questionnaire test). Sensations were within normal limits. Cranial nerves and deep tendon reflexes revealed no abnormality. Postural stability was not tested because the patient was unable to stand without assistance.

He was commenced on L-dopa 250 mg b.d. which was gradually increased every 3–4 days by 250 mg until a daily dosage of 2–250 g was reached. Initially, no improvement was noticed. Later, a gradual improvement took place and in about 6–8 weeks bradykinesia improved considerably and he was able to get out of a chair and walk along the corridor unaided. His confusion improved and he became cheerful (depression lifted). Blepharospasm was less but still present. Rigidity was reduced and there was no significant change in tremor. He still had positive palmo-mental and glabellar reflexes. His balance was much improved.

The only side effect was increased sexual desire but he did not require any treatment for this.
Discussion

Blepharospasm is an unusual manifestation in parkinsonism but this has been a well recognized symptom of the disease (Klawans and Erlich, 1970). In some cases, blepharospasm may be so severe as almost to prevent useful vision and may also be associated with painful contractions of the muscles of the eyelids. It is more frequent in post-encephalitic than idiopathic parkinsonism.

The first patient presented with difficulty in useful vision and pain in the eyes which was relieved within a short period following commencement of treatment with L-dopa. With regard to the other two cases, life became more comfortable when blepharospasm was relieved. In all these patients, there was also remarkable improvement in parkinsonism, depression and general condition (i.e. a feeling of well being).

L-dopa now seems to be a major therapeutic advance and most effective treatment of Parkinson’s disease, particularly for the akinesia and parkinsonian blepharospasm. Although all the patients (in this series) were elderly, a daily maintenance dose of about 2 g of L-dopa was tolerated and there were no significant side effects.

It was interesting to observe that in two cases the initial positive glabellar reflex was reversed following treatment. It has been suggested that the reversal is secondary to the re-establishment of dopamine inhibition of the neurones of the striatum (Klawans and Goodwin, 1969).

Acknowledgments

I wish to thank Miss Fairweather, the librarian, and Mrs V. S. Pawson, medical shorthand-typist, for their help.

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Case reports

Penile Parkinsonism

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Summary

Priapism following the administration of the tranquilizer pericyazine (Neulactil) is reported. No other aetiology was found after full investigation. The condition resolved during treatment with intravenous benzotropine (Cogentin). An attempt has been made to explain the aetiology and rationalize the treatment given.

Case report

History

A 37-year-old Caucasian paper merchant presented to the accident and emergency department with a persistent painful erection for 48 hr. The onset of the priapism occurred following the administration of a prescription for pericyazine (Neulactil) 25 mg t.d.s. The patient had taken the first tablet, retired to bed and had sexual intercourse. He awoke the following morning with priapism, and continued to take the tablets for a further 24 hr. The tablets were prescribed for anxiety following a domestic disturbance. There was no relevant previous medical history and he had otherwise enjoyed good health.

Clinical examination

A fit looking, well nourished man in considerable pain. Apyrexial with no lymphadenopathy, the cardiovascular and respiratory systems were normal.


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doi: 10.1136/pgmj.50.586.521

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