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COMPLICATIONS OF LONG TERM THERAPY OF LEVODOPA

A THESIS

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R. R

By

RAGAA RAGY MATTA
M.B., B.Ch.

30269

Supervised By:

Prof. Dr. YOUSEF ALI ABOU ZEID
Professor of Neurology, Faculty of Medicine
Ain Sham University



Dr. MONA ABDEL-HAMED RAAFAT
Lecturer of Neurology, Faculty of Medicine
Ain Shams University

AIN SHAMS UNIVERSITY
FACULTY OF MEDICINE

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INTRODUCTION

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The drug treatment of parkinson's disease has progressed through 3 main stages:

First, the use of anticholinergic drugs and amantadine, then the introduction of levodopa and its association with peripheral decarboxylase inhibitors, and finally the use of direct acting dopamine agonist drugs. Levodopa, however, remains the most effective single drug in parkinson's disease, unfortunately the side effects associated with long term levodopa treatment today constitute an important unwanted delayed effect "positive" side effects such as involuntary movements and psychiatric disorder remain difficult to manage without causing an increase in parkinsonian immobility, and led to new classification of these side effects.

New lines of managements had also been developed to overcome the side effects, thus we read nowadays about giving the drug in more frequent doses. The use of dopamine agonist drug, drug holiday.

AIM OF THE WORK

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Is to review the side effects encountered with long term therapy with levodopa, carbidopa.

This will include study of the pharmacology of the drug-side effects and if possible, the methods used nowadays in their management.

The review will be closed by our comment on that subject.

BASAL GANGLIA

ANATOMY OF THE BASAL GANGLIA:

Although many different discrete nuclei with complex interconnections are included in the concept of the basal ganglia, the latter have a relatively simple core structure, the strio-pallidal complex. The striatum (caudate nucleus and putamen) receives the major inputs into the basal ganglia from four sources:

1. Most area of the cerebral cortex.
2. The midline intralaminar thalamic nuclei in particular centrum medianum and the parafacicular nucleus
3. The zona compacta of the substantia nigra.
4. The raphe nuclei of the mid brain.

The striatum is the receiving area of the striopallidal complex, and it sends efferents to the pallidum which comprises not only the globus pallidus but also the zona reticulata of the substantia nigra. The pallidum is the major output center of the striopallidal complex, sending efferents to the thalamus and brainstem, whence influence can pass back to the cortex and down to the spinal motor apparatus.

The inner segment of the globus pallidus projects to three thalamic areas:

1. That part of the ventral nucleus formed by the nuclei ventralis lateralis and ventralis anterior.
2. The centrum medianum.
3. The lateral habenular nucleus.

Projection from ventralis anterior - ventralis lateralis complex end both in the motor cortex (area 4 and 6) and probably also extensively in other frontal areas. The nigrothalamic projection also might be expected to influence large area of the cerebral cortex, for it relays in the ventromedial thalamic nucleus. Widespread descending projections from the zona reticulata of the substantia nigra include a large nigrothalamic projection to the deeper layers of the superior colliculus.

Whatever function the basal ganglia exerts must depend upon the information the striatum receives from the cerebral cortex and midline thalamic nuclei. The corticostriate and thalamostriate pathways probably are excitatory to the small "spiny neurons" which form the bulk (more than 90%) of the interneuronal apparatus of the striatum (Carpenter M.B., 1976). However, whatever transformation the striatum makes to its cortical and thalamic inputs cannot occur without concurrent activity in the dopaminergic nigrostriatal input. The axon

terminals of the nigrostriatal dopaminergic pathway make axospinous synaptic contact with the same cells on which the thalamostriate and corticostriate terminals also make synaptic contact. There is great electrophysiologic debate as to whether these dopaminergic nigrostriatal inputs are excitatory or inhibitory, but in functional terms their impact is likely to produce inhibition. The massive ascending dopaminergic pathway, from midbrain to striatum thus occupy a pivotal role in normal striatal activity.

In parkinson's disease these dopaminergic nigrostriatal neurons are virtually destroyed which must lead to gross disruption of normal striopallidal activity. This is the argument which makes parkinson's disease the clinical "test bed" against which all theories of basal ganglia function must be measured.

PHYSIOLOGY OF EXTRAPYRAMIDAL SYSTEM:

The extrapyramidal system has in the past usually been assumed to consist of motor mechanisms of the C.N.S. excluding those of pyramidal tract. However, anatomic and physiologic separation of extrapyramidal from pyramidal tract system has become increasingly more difficult. The extrapyramidal system has come to be as a functional rather than anatomic unit

and, as such, may be said to be composed of extrapyramidal portions of cerebral cortex, thalamic nuclei connected with striatum, corpus striatum, subthalamus, rubral and reticular systems.

The extrapyramidal system, in contrast to the more direct pyramidal system, reaches segmental levels of distribution after many detours with neuronal chains synaptically interrupted in basal ganglia, subcortical ganglia, and reticular areas.

The extrapyramidal system may be regarded as a functional system with 3 layers of integration cortical, striatal (basal ganglia) and tegmental (mid brain). The bulboreticular inhibitory and facilitatory areas receive fibers from cerebral cortical area, the striatum, and anterior cerebellum. The principal functions of the extrapyramidal system are concerned with associated movements, postural adjustments, autonomic integration, tone, motor function and equilibrium regulation.

Lesion at any level may obscure voluntary movements and replace them with involuntary movements.

Clinically important syndromes caused by dysfunction of the extrapyramidal system include the following:

(1) Parkinsonism in which resting tremors and rigidity occur, the primary disorder is frequently in the globus pallidus, its cortical projection, the substantia nigra, or the reticular substance of midbrain

(2) Involuntary movements: athetosis, chorea, and torsion spasms are frequently associated with lesions of the caudate nucleus and putamen of the striate bodies and the midbrain nuclei. The pathophysiology of diseases of the extrapyramidal system is obscure. In general, it is felt that release from suppressor circuit action may occur. Operative measures aimed at interfering with an unsuppressed, relatively overactive circuit (Brodmann area 6 and the extrapyramidal system) or the precentral motor area that this circuit in turn affects may be helpful in overcoming annoying clinical symptoms. Thus, removal of area 6 and 4 or of area 4 alone has overcome severe hemiballism (one-sided jerking and twitching), athetosis or tremor.

Surgical or chemical destruction of globus pallidus or the ventrolateral nucleus of the thalamus may ameliorate involuntary movements in patients with dystonia or parkinsonism. Connection between the gamma loop and the extrapyramidal system seems quite likely, since extrapyramidal system disease may result in hypokinetic