Up - Dated Therapy Of Parkinsonism

An essay

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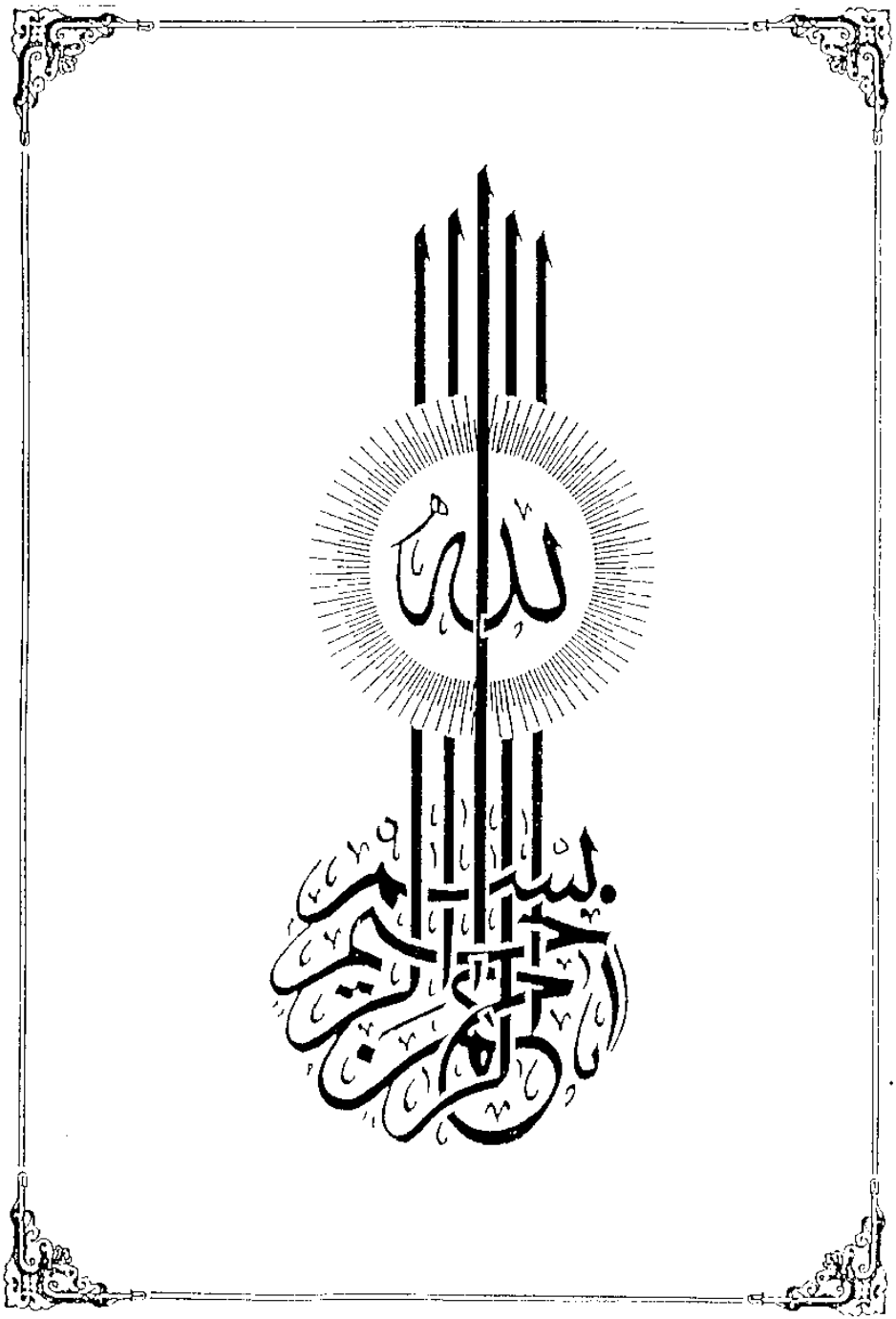

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"Introduction"

Parkinsonism is a comnon disorder which begins in later life with an average age of onset of 60 years.

The incidence increases with age, leading to the suggestion that, every one would develop parkinsonism if they lived long enough. Because of the late onset of the illness, the prevalence increases to 1 in 100 if one looks at the population that is older than 55 years of age. Men are slightly affected more commonly than women.

About 85%of cases of parkinsonism are idiopathic. The pathologic hallmark of idiopathic parkinsonism is currently considered to be the degeneration of neurons in the substantia nigra pars compacta whose axons terminate in the caudate and putamen (striatum) and release dopamine as their synaptic neurotransmitter. Neuronal degeneration occurs less consistently and severly in other areas of the central nervous system and accounts for other features associated with idiopathic parkinsonism.e.g. Autonomic dysfunction and cognitive changes.

The therapy of parkinsonism is challenging yet rewarding because most patients are moderately to markedly improved by therapy.

Levodopa still remains the main stay of therapy for parkinsonism.

An estimated 85% of patients with idiopathic parkinsonism respond to some extent to levodopa.

Unfortunately, the therapeutic effect is not sustained. After 5 years of treatment with maximum tolerated doses, approximately one - third of patients have deteriorated to their pre - treatment level of disability, and a further third show even greater incapacity.

The new stratgies in use of antiparkinsonian drugs to achieve the following goals :-

- Optimization of the motoric activity.
- Prolongation of the on - period.
- Levelling of fluctuation.

Aim of the work :-

- Early diagnosis of Parkinson's disease and possible neuroprotective therapy.
- To find the best strategies for controlling motor disabilities and other symptomatology for example psychiatric symptoms and autonomic symptoms with least possible side effects.
- Future therapies.

Functional anatomy of the basal ganglia

The basal ganglia form a conglomerate of nuclei in the telencephalon (the Corpus striatum), diencephalon. (the sub-thalamus) and midbrain (the substantia nigra and pedunculopontine nucleus).

The corpus striatum includes the globus pallidum, the striatum (the caudate nucleus and putamen), the nucleus acumbens septi, the olfactory tubercle and part of the substantia innominata. (keith E. Webester, 1975). The corpus striatum can be divided roughly into a dorsal division related principally to the somatic central nervous system and a ventral division related principally to the limbic system.

The basal ganglia exert their influence largerly, but not exclusively through the supplementary motor cortex. The other most significant areas of influence appaer to be the non motor association cortex and the superior colliculus, both controlled through the substantia nigra pars Reticularis. So that, disorders of this system will be productive not only of relatively simple motor symptoms, but of more complex motor disruption (e.g. of motor planning and strategies) as well as including perhaps, congnitive and even perceptual. (webester, 1975).

Connections of the basal ganglia :

1 - Connections of the dorsal division of the corpus striatum:

- The striatum (caudate - putamen) recieves its major afferents from three sources:

(a) The largely dopaminergic input from the substantia nigra.

(b) The glutaminergic input from the entire neocortex.

(c) The cholinergic inputs from the intralaminar and ventrolateral ventro anterior nuclear complexes of the thalamus (Bjorklund and lindvall. 1984). There fore, the striatum has available to it all extero ceptive information and a proportion of proprioceptive inputs,

together with information about processing in the association cortex and some limbic structures.

- The striatum sends efferents to two targets:

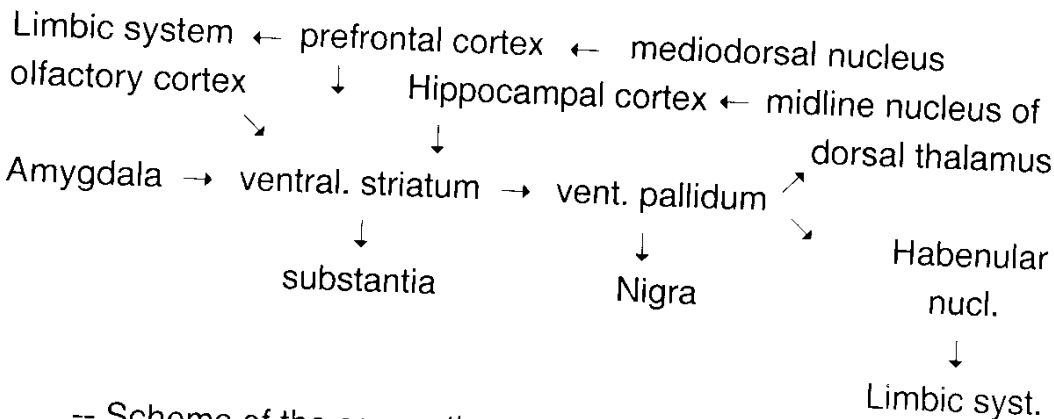
- The Globus pallidus and the substantia nigra. (Carpenter and peter, 1972).

2 - Connections of the ventral division of the corpus striatum:

- The ventral striatum (olfactory tubercle, nucleus accumbens and neighbouring parts of the caudate nucleus and putamen) recieve cortical inputs from the cingulate, hippocampal and prefrontal cortices,. as well as from the amygdala and olfactory cortex, and project via substance p- utilizing fibers from the ventral pallidum.

- The output from the ventral pallidum to the dorsal thalamus reaches the mediodorsal nucleus which projects back upon the prefrontal cortex.

- Ventral pallidal efferents also reach the subthalamic nucleus and thus the substantia nigra (which also receives afferent directly from the ventral striatum). (Graybiel, 1984).



-- Scheme of the connections of the ventral striato-pallidum

The biochemistry of parkinson's disease

Biochemically, selective degeneration of the dopaminergic mesostriatal system is the salient feature of the illness profoundly disturbing transmission of information through the basal ganglia. However, it is now known that the pattern of biochemical changes within the brain is far more complex than previously thought and the consequences of dysfunction in other neurotransmitter systems (noradrenergic, serotoninergic, cholinergic, peptidergic....) must also be taken into consideration.

Degeneration of the dopaminergic system:

In Parkinson's disease, the dopamine deficieny appaers to have four essential characterstics:

1 - The decrease in dopamine levels is more severe in the putamen than in the caudate nucleus.

2 - The Mesostriatal system is more affected than mesocortico limbic system.

3 - The dopamine deficieney does not seem to be generalized, however, although there are diffuse and marked reductions in dopamine concentrations in several cerebral regions.

4 - The Reduction in dopamine levels vary considerably in different structures in the same individuals and also from one patient to another. This might account for the considerable variation in symptomatology within the parkinsonian population (Yvis Agid, 1984).

Dysfunction of non-dopaminergic systems in Parkinson's disease:

a: Partial degeneration of noradrenergic systems:

In Parkinson's disease concentration of Noradrenaline and MHPG (3 - methoxy -4- hydroxyphenol - glycol, its main metabolite) as well as the activity of dopamine beta - hydroxylase (the enzyme

specific for the synthesis of Noradrenaline) are decreased in cortical and subcortical areas. (scatton et al., 1983). In addition, noradrenergic fibers projecting to the spinal cord are apparently damaged as indicated by a 50% reduction in the noradrenaline content of the dorsal and ventral horns of the lumbar spinal cord. (scatton et al., 1986). Cerebral noradrenaline deficieney might play a role in the development of depression in parkinsonian patients, since tricyclic antidepressants, known to increase noradrenergic transmission by inhibiting the uptake of the amine, are effective in treating these symptoms.

b : Degeneration of serotoninergic systems:

In Parkinson's disease concentration of serotonin and 5 - HIAA (5 - hydroxy - indol - acetic acid) are decreased in several regions of the forebrain, including the basal ganglia, hypothalamus, hippocampus and frontal cortex (scatton et al. 1983). central serotoninergic deficiency might be involved in depressive symptoms (Mayeux et al. 1984).

c : Degeneration of the cholinergic systems:

- From the pathophysiological point of view, the sparing, even if partial, of striatal cholinergic interneurones in contrast with gross dopaminergic deficiency, might explain the efficacy of anticholinergic medication on motor symptoms of the disease. it is usually accepted that the loss of dopaminergic inhibition on cholinergic neurones causes cholinergic hyperactivity in the striatum.

- Damage to the cholinergic innominato - cortical pathway might be implicated in the pathophysiology of dementia. A common terminal feature of Porkinson's disease.

- The role of cortical cholinergic deficiency in the genesis of intellectual impairments is underlined by the fact that drug - induced memory disorders are seen more frequently in patients recieving anticholinergic medication. (sadeh et al., 1982).

d - Preservation of the GABA ergic systems?

It is difficult to draw firm conclusions concerning the state of GABA ergic systems in Parkinson's disease · Glutamic acid decarboxy lase (GAD) activity has been reported to be decreased in large parts of the brain, especially the basal ganglia and the cerebral cortex. (Mc Geer et al., 1973).

Decreased GABA concentrations have been found also in the cerebro spinal fluid of parkinsonians. (Manyam, 1982).

Restoration of nigral GAD activity and CSF GABA levels normal in patients on long-Term Levodopa treatment has been found (De Long et al., 1984).

e - Dysfunction of peptidergic systems:

Among the numerous neuronal markers that are abnormal in Parkinson's disease (Javoy - Agid et al., 1984) five neuropeptides are of particular interest:

Cholecystokinin (CCK-8), met. enkephalin, leu-enkephalin, substance-p and somatostatin and CRF. Most of the CCK-8 containig neurones appaer to be preserved in parkinsonism, at least as indicated by brain concentrations which are generaily normal. A decrease of CCK-8 concentrations, of the order of 30% in the substantia Nigra might, however, reflect degeneration of CCK-8 containing neurones (Studler et al., 1982).

Brain levels of methionine - enkephalin and leucine - enkephaline are usually normal in most brain regions in Porkinson' disease although decrease in Methionine - enkephalin of about 70% in the substantia Nigra and the ventrotegmental area and about 30% in the putamen and pallidum have been detected. (Taquet et al., 1983). Leucine - enkephalin Levels are also reduced to about 30 - 40% in the putamen and pallidum indicating involvement of an enkephalinegic putaminopallidal system in this disease.

Substance P concentrations were found to be decreased (in the order of 30 - 40%) only in the pallidum and substantia Nigra. (Rinne et al., 1984). Somatostatin levels are not altered in cortical areas, a 30-50% decrease in the frontal cortex and hippocampus has been confirmed in cases where there was clinical evidence of inttellectual deterioration (Epelbaum et al., 1983).

Decreased levels of corticotropin releasing factors were found in the cerebral cortex of parkinsonian patients (whitehouse et al., 1987) but not in the hypothalamus (conte-Deuolx et al., 1985).

However, It is not possible to conclude that changes in peptide levels in the parkinsonian brain are directly related to clinical signs. However the selective alterations in cortical somatostatin in patients with dementia suggests that somatostatinergic dysfunction plays a role in intellectual deterioration particularly as similar changes have been observed in Alzheimer's disease.

Finally, it is premature to consider therapeutic modification of central peptidergic transmission, although this ultimately might be envisaged.

Etiology and pathogenesis of Parkinson's disease

(Joseph Jonkovic. 1993).

Despite Tremendous advances in the treatment of Parkinson's disease, its cause is as much a mastery to day as when it was first described in 1817. In fact, the question has been raised as to whether Parkinson's disease is actually a disease as opposed to a syndrome. Although there is a characterstic clinical and pathological picture of Parkinson's disease, variations in clinical experience exist, indication that there are subtypes within the disease., these subtypes may themselves represnt different diseases. Further more, a disease-specific biologic marker for Parkinson's disease has yet to be identified.

- Parkinson's disease : disease or syndrome?

Evidence for disease.	Evidence for syndrome.
1 - Characterstic clinical symptoms	- Variable clinical expression
Tremor, rigidity, bradykinesia	- Idiopathic parkinsonism
2 - Characterstic pathologic features	neurofibrillary tangles, but without
- Depigmentation of substantia Nigra	lewybodies, had been noted
- Parsence of Lewy bodies.	- No specific biologic marker for
	Parkinson's disease

Anumber of hypotheses have been proposed regarding the etiology and pathogenesis of Parkinson's disease, the symptoms of which are known to appaer following the loss of at least 80% of do-paminergic neurons in the substantia nigra. of these hypotheses, the four most prominent are the accelerated aging theory, the toxin theory, genetic predisposition theory, and the oxidative mechanism theory.

The accelerated aging theory

Holds that, normal age-related attrition of dopaminergic neurons occur in all individuals, but that the process is accelerated in parkinsonian patients. evidence in favor of this theory includes the loss of anti oxidative protective mechanisms, which is known to be age related. for example, in both aging and Parkinson's disease, there is a decrease in glutathione peroxidase and catalase. In addition, the proess is known to result in an increase in monoamine oxidase and an accumulation of melanin, both of which contribute to the loss of dopaminergic neurons. Evidence against the accelerated aging theory includes the finding that while monozygotic twins age at the same rate, both do not necessarily develop Parkinson's disease. Furthermore, studies show that the incidence of Parkinson's disease peaks at age 67 and then decreases, suggesting the disease is not age specific. Furthermore, age related motor symptoms do not respond to levodopa. Propably the most convincing evidence against aging as an important factor in the pathogenesis of Parkinson's disease is the finding that in normal aging the lateral tier of substantia Nigra is relatively spared, but this area is specifically involved in Parkinson's disease.

According to the toxin theory

An extrinsic or intrinsic toxin selectively destroys the dopaminergic neurones. Providing support for this theory are a number of toxins known to induce parkinsonian symptoms, such as 1 - methyl - 4 - phenyl - 1, 2, 3, 6 - tetra hydropyridine (MPTP). Neuroleptic drugs are also known to induce parkinsonism, parhaps by blocking dopamine receptors and/or by exerting toxic effects on the dopaminergic neurons. In addition, there is some correlation between Parkinson's disease and exposure to pesticides, rural living, drinking well water, and exposure to heavy metals. Recently, dopamine antibodies have been theorized as having the potential to block the effects of dopamine or exert a toxic effect on the

substantia nigra, on the other hand, no clearly defined clusters of Parkinson's disease cases have been identified. furthermore, the relatively low frequency of cancer in Parkinson's disease patients argues against excessive toxin exposure.

Until recently, **Genetic factors** have been thought to play little or no role in the pathogenesis of Parkinson's disease. This belief was based on studies that showed a low frequency of concordant Parkinson's disease among monozygotic twins. However, 15-20% of Parkinson's disease patients have a first degree relative with tremor and other parkinsonian symptoms. In addition a number of related individuals have been identified as having autosomal - dominantly inherited Parkinson's disease. Furthermore, some evidence indicates that the repair mechanisms of DNA may be defective in Parkinson's disease patients.

Receiving perhaps the most support to date is **(the oxidative mechanism theory)** of Parkinson's disease, Pathogenesis. According to this theory, free radicals are generated from the oxidation of dopamine and as a result of increased iron and the loss of normal protective mechanisms. Among the evidence supporting this theory is the increase of toxic Free iron in the substantia nigra of Parkinson's disease patients and corresponding decrease in ferritin, which normally chelates iron.

Evidence to support oxidative mechanisms in the pathogenesis of parkinson's disease:

- MPTP must be oxidized to MPP^+ to exert neurotoxicity.

- Increased iron has been demonstrated in the substantia nigra of Parkinson's disease brains.

- Ferritin, glutathi one and glutathi one peroxidase are decreased in the substantia nigra of Parkinson's disease brains.

- Lipid peroxidation is increased in the substantia nigra of Parkinson's disease brains.