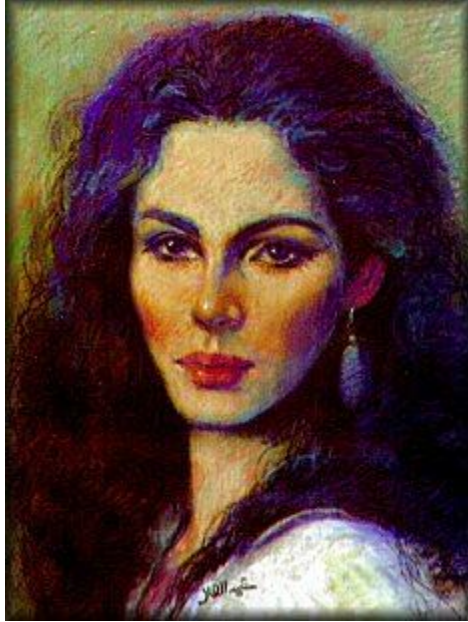


THE IDIOPATHIC PARKINSON DISEASE, A MAGNETIC RESONANCE IMAGING STUDY : CORRELATION WITH THE CLINICAL PICTURE AND THE PATTERN OF LEVODOPA RESPONSIVENESS

Metwally, MYM (2000): Ain Shams medical journal, VOL 51, No 1,2,3, pp 181-198 | www.yassermetwally.com

INDEX



- [SUMMARY](#)
- [INTRODUCTION](#)
- [MATERIAL AND METHODS](#)
- [RESULTS](#)
- [DISCUSSION](#)

SUMMARY

In the present study 20 patients with the clinical diagnosis of idiopathic parkinson disease are included. All patients were subjected to (1) full clinical examination and MRI study of the brain with a special focus on the midbrain and the basal ganglia . Based on the duration of the parkinsonian symptomatology and the clinical response to levodopa treatment, patients were classified into two main groups. Group (A) is characterized by short duration of the parkinsonian symptomatology and a good sustained response to levodopa treatment, while group (B) was characterized by a longer duration of the parkinsonian symptomatology and a fluctuant response to levodopa treatment. MRI demonstrated important structural changes at the level of the substantia nigra and the red nucleus in both groups, while structural changes at the level of the basal ganglia (putaminal hypointensity on the T2 weighted images) were demonstrated only in group (B) patients. The significance of the MRI findings, their probable aetiology and pathogenesis, their value in explaining the pattern of clinical levodopa responsiveness and their implications in the management of parkinson disease will be discussed.

INTRODUCTION

L-dopa treatment still remains the most effective agent for the symptomatic treatment of parkinson disease. Its remarkable success has made it the gold standard for which all new forms of therapy need to be compared. L-dopa therapy is far from perfect as it failed to stop the progression of the disease and it is frequently associated with the development of abnormal motor responses as the number of years of treatment mount and as the disease inevitably advances. Ultimately the clinical response to L-dopa becomes contaminated by motor response fluctuations to the extent that response fluctuations become increasingly difficult to live with and complex to manage. At this advanced stage, the response fluctuations to L-dopa become a part of the clinical disability of the disease. Controversies exist about what causes this dramatic shift of the patient response to L- dopa from a good

sustained response initially to a disabling fluctuant response after the lapse of a few years. Is it due to chronic levodopa therapy? or due to some structural changes induced by the natural progression of the disease. The aim of the study is to explore the existence of any structural changes, that can be picked up by MRI, and that can explain this peculiar pattern of clinical levodopa responsiveness among patients with idiopathic parkinson disease and to see whether any of these findings has any diagnostic, predictive or therapeutic implications in the management of parkinson disease.

MATERIAL AND METHODS

In the present study 20 patients with idiopathic parkinson disease are included, all patients were subjected to

1- Full clinical examination

2- MRI study of the brain with a special focus on the midbrain and the basal ganglia regions

1.5 tesla MRI apparatus was used and the study was done using the protocol previous described by Drayer et al , 1986 and Duguid et al , 1986 in the study of parkinsonian patients. This protocol include :

1-heavily T2 weighted MRI scan (repetition time(TR) of 2500-3000 and, echo time (TE) of 80 to 90 .

2- 5mm thickness MRI slices

Six age matched normals (mean age 57.3) were taken as controls for the radiological studies

RESULTS

- **Based on the clinical examination , patients were classified into two main groups**

Group (A) comprised 10 newly discovered patients with average duration of parkinsonian symptomatology of 8.7 months. Non of the patients had taken any antiparkinsonian medication before diagnosis. The mean age of this group was 55.7 years. The disease started by typical parkinsonian tremors that started unilaterally in 7 patient and bilaterally in 3 patients with left sided predominance. Hypokinesia and rigidity of variable degrees were present in all patients. Clinical examination did not reveal evidence of pyramidal, cerebellar, orthostatic hypotension or sphincter dysfunction in any patient. Also no evidence (based on clinical examination) of impairment of memory (recent or remote) was demonstrated in any patient .

All group (A) patients were given L-dopa in the dose of (300 mg TID) with very good clinical response in all patients, no other antiparkinsonian medications were given to any patient.

Group (B) comprised 10 known parkinsonian patients with average duration of symptomatology of 9.6 years and a mean age of 64.3 years. All patients were given L-dopa once diagnosed and non of the patients had taken any other antiparkinsonian medication during the course of their illness. The disease had a clinical picture and initial levodopa response identical to group (A). The only difference between group (A) and group (B) patient was the current response(after a mean period of 9.6 years) of group (B) patients to L- dopa that occurred after an initial good response. This was typically described by patients as follows :

"At first the patient did not feel the effect of individual doses and he might skip a single dose without noticing any loss of the therapeutic response. Later on recurrence of symptoms in the afternoon required the addition of another dose during this period and after the lapse of a few months to a few years the patient started to notice loss of sleep benefit (with recurrence of bradykinesia early in the morning) and an early morning dosing was thus required . Later on a clear wearing-off pattern is noticed by the patient and which required dosing at regular intervals all around the clock and the patient noticed persistent gradual decline in the dosing interval required to maintain a reasonable symptom control all around the clock ". Non of the patients examined were suffering from dyskinesia

or dystonia, also non gave a history suggestive of the on and off phenomenon.

It must be noted, however, that we are not talking about lack of response or state of levodopa unresponsiveness in group (B) patients, but rather a state of marked fluctuation of the clinical response, in an unexpected and unpredictable fashion, to levodopa. The response to levodopa ultimately became fragile and the initial good sustained response is hardly ever attainable.

- **Results of radiological studies**

- **Results in normal controls**

Using a high field strength (1.5 tesla) heavily T2 weighted MRI transverse scan in the regions of the midbrain and the basal ganglia the following were demonstrated .

1-Signal attenuation or hypointensity in the regions of red nucleus and the posterior part of the of the substantia nigra (pars reticularis). These structures are well defined and definitely separated by a region of a relatively higher signal intensity .

2- No signal hypointensity was seen in the region of the basal ganglia. Signal hypointensity in the internal capsule and the rest of white matter is due to the presence of myelin and the relative lack of water.

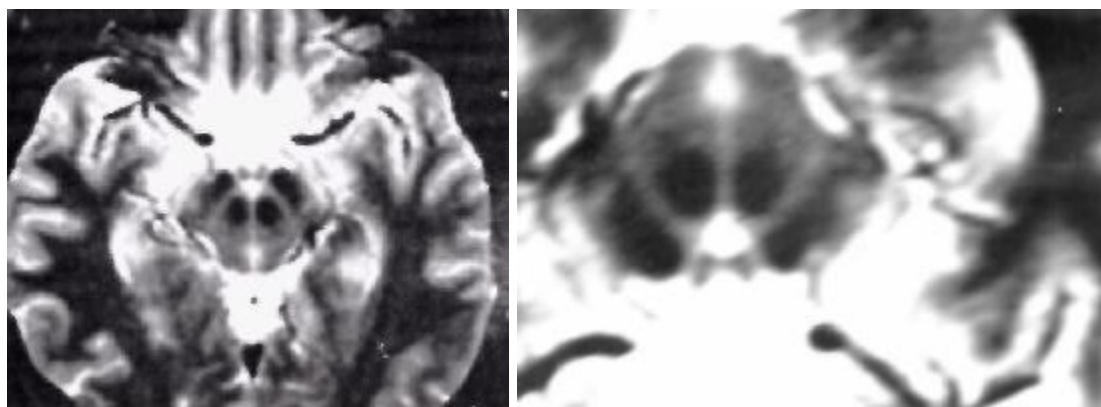


Figure 1. MRI T2 images showing the red nucleus and the substantia nigra as hypointense structures, notice the less hypointense band that separates them



Figure 2. MRI T2 normal images at the level of the midbrain (A) and the basal ganglia (B), notice that the pars reticularis of the substantia nigra and the red nucleus appear hypointense on the T2 weighted images because of iron deposition (A)

- **Results in group (A) patients**

1-Reduction in the region of the higher signal intensity that separates the red nucleus from the substantia nigra was observed in the region of the midbrain in all patients belonging to group (A) with the resultant that both

structured appeared smudged and in touch with each others.

2-The MRI studies at the region of the basal ganglia were identical to the age matched normal control and no pathological changes were observed in this region in group (A) patients.

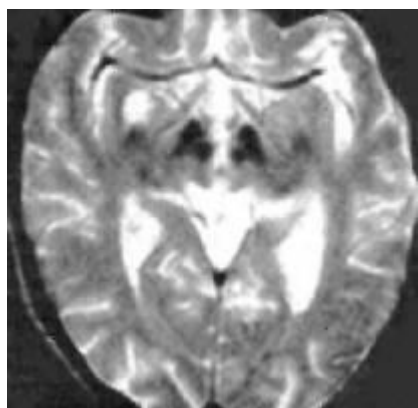


Figure 3. MRI T2 image showing reduction in the region of the higher signal intensity that separates the red nucleus from the substantia nigra

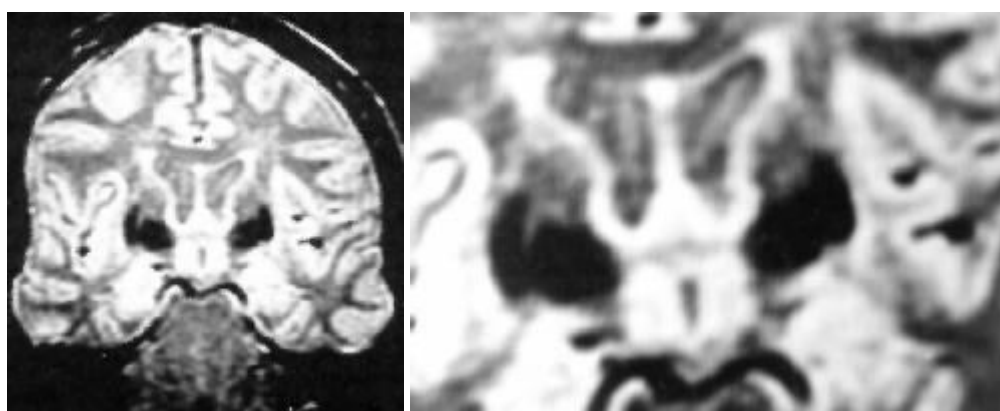


Figure 4. MRI T2 images showing narrowing of the high signal intensity area that separates the red nucleus and the substantia nigra with smudging of both structures

○ **Results in group (B) patients**

1- MRI results in the region of the midbrain were identical to those observed in group (A) patients .

2-Prominent signal hypointensity was observed in the region of the putamen in all group (B) patients.

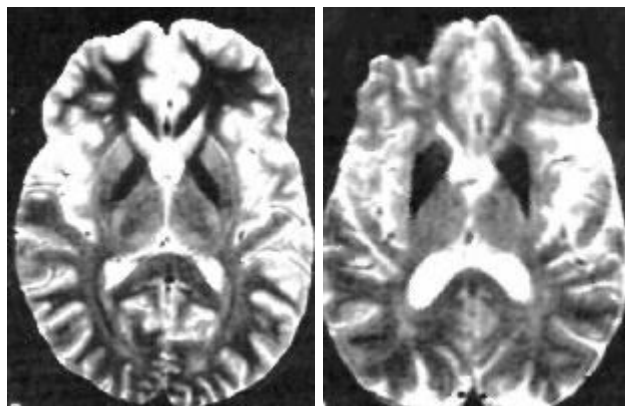


Figure 5. MRI T2 images at the level of the basal ganglia, left normal image, right a group (B) patient, notice the putaminal signal attenuation (B)

In general the only radiological difference observed between group (A) and group (B) patients was the putaminal signal changes that were observed in group (B) patients. It should also be noted that no significant central and /or

cortical atrophy was observed in any of the patients included in this study beyond that found in the age-matched normal control. Also no atrophic changes were observed in the brain stem or cerebellum in any patient.

Both putaminal and nigral involvement were concomitantly demonstrated in every single patient belonging to group (B) and putaminal involvement was not demonstrated in any patient without concomitant nigral involvement.

It should also be noted that the MRI signal changes were always bilateral and fairly symmetrical in all group A , B patients .

Table 1. Patterns of MRI T2 involvement in idiopathic parkinson disease

MRI pattern	Description	Aetiology
The nigral pattern of involvement	Smudging or blurring of border between the substantia nigra and the red nucleus so that both structures appear in touch with each other	Iron accumulation in the pars compacta of the substantia nigra will cause signal attenuation in the region that formerly had a higher signal because it was relatively devoid of iron , thus explaining the signal changes observed in the midbrain of parkinsonian patients
Putaminal pattern of involvement	putaminal hypointensity	deposition of iron in the degenerated putamen

DISCUSSION

Levodopa combined with carbidopa remains the most effective approach to the symptomatic relief of idiopathic parkinson disease. Over time, however, an increasing number of parkinsonian patients evidence motor complications, notably motor response fluctuation and abnormal involuntary movement. Chase et al, 1989; Obeso et al, 1989. Dopaminergic treatment of parkinsonian patients is composed of two main stages, an initial honeymoon stage in which the patient's response is typically good, to be followed after the lapse of a few years by another stage in which the clinical response is plagued by response fluctuation and involuntary movement. The progression from one stage to the other stage is almost invariable in every single patient. Lees, 1989. Motor complications of dopaminergic treatment is mainly due to striatal, mainly putaminal, degeneration (as a part of the natural progression of the disease) following degeneration of the nigral dopaminergic projections. In addition, pathological modification of striatal receptors, partially related to the nonphysiological delivery of levodopa in a continuous pulsatile mode, might be responsible for the various types of dyskinesias observed in the second stage . Lees , 1989

As a point of departure, a quick overview of the peripheral and central Pharmacokinetics of levodopa will be presented. Levodopa is mainly absorbed from the duodenum and the proximal small intestine and factors which enhance gastric emptying enhance levodopa absorption and vice versa. The half life time of the circulating L-dopa is very short (about 90 minutes) and this half life time is almost doubled if a peripheral decarboxylase inhibitor (carbidopa) is used. Chase et al, 1989, L-dopa is decarboxylated in the dopaminergic neurons of the substantia nigra into dopamine. The dopamine is stored in the presynaptic terminals in the corpus striatum (mainly the putamen). Dopamine is normally stored in presynaptic vesicles termed chromaffin granules and is released into the synaptic cleft by a calcium dependant process, however dopamine formed by decarboxylation of exogenous L-dopa is not incorporated into the normal storage pool in the chromaffin granules but rather is accumulated in the cytosol of the presynaptic terminals until delivered into the synaptic cleft . Chase et al, 1989; Obeso et al , 1989; Juncos, 1992; LeWitt, 1992

Dopamine in the synaptic cleft is driven (by continuous release) from the presynaptic store and subsequently its

concentration remains constant so long as the striatal storage capacity remains within reasonable limits. In this way striatal dopamine availability does not depend on the plasma levodopa level and the concentration of striatal dopamine remains fairly constant in the face of the wild fluctuations and swings of plasma levodopa level that normally occur due to the short half life time of levodopa. Chase et al, 1989; Obeso et al , 1989 Early in the disease the striatal storage capacity of dopamine will buffer the peripheral oscillations of L-dopa level and will transform the intermittent pulsatile delivery of L-dopa into a sustained clinical response (by maintaining a constant concentration of dopamine in the synaptic cleft) . In this way the clinical response is not directly related to, or dependant on, the peripheral plasma concentration of L-dopa. Chase et al, 1989; Obeso et al , 1989;Juncos, 1992; LeWitt, 1992

However with progressive denervation / degeneration of the corpus striatum, the storage capacity of the brain to dopamine is reduced to a critical level and the brain is no longer capable of buffering the peripheral oscillations of L-dopa level by continuously releasing dopamine into the synaptic cleft to maintain a constant concentration of it . The concentration of dopamine in the synaptic cleft will fluctuate with fluctuation of the plasma level of L-dopa and peripheral kinetics of L-dopa become of paramount importance. Under such circumstances the duration of the antiparkinsonian action of L-dopa diminishes, ultimately to the point where clinical fluctuations become a direct reflection of the variations of the plasma concentration of L-dopa. Chase et al, 1989; Obeso et al , 1989; LeWitt, 1992 ;Goetz and Diedwerich 1992 Diminished storage capacity of the corpus striatum to dopamine in advanced parkinson disease was described by PET studies . Eidelberg , 1992

The initial stage of good response to -L-dopa probably coincide with the stage where pathological changes are confined to the substantia nigra with a reasonable striatal storage capacity, however when pathological changes extend to involve the putamen (progressive putaminal denervation and degeneration) with the resultant of reduction of the storage capacity of the brain to dopamine, the initial good sustained response to L-dopa is replaced by an unexpectedly fluctuant response that oscillates with oscillation of the plasma concentration of L-dopa .Obeso et al, 1989; LeWitt, 1992 ;Goetz and Diedwerich 1992

This is consistent with our radiological findings since group (A) patients (with a good sustained clinical response to L- dopa) was characterized by signal changes confined to the region of the substantia nigra with putaminal sparing, while the putamen was involved, in addition to the substantia nigra, in all group (B) patients, this group was characterized by a fluctuant clinical response to L-dopa. Group (B) patients had more advanced disease, with a longer duration of clinical symptomatology compared with group (A) patients .

MRI thus appears able to divide patients presenting with idiopathic parkinson disease into a nigral and a striatal type based on the appearance of signal attenuation in the putamen. Patients with striatal parkinsonism are likely to have more advanced disease with degeneration of striatal neurons and presynapsis and with reduction of the brain storage capacity to dopamine. The reduction of the storage capacity probably accounts for the fluctuant response of those patients to levodopa. By contrast, patients with nigral parkinsonism generally have an early disease in which degeneration is confined to the nigra. These patients do not have signal attenuation in the putamen exceeding that found in age-matched controls. This reflects preservation of striatal neurons and their dopamine receptors and accounts for the capacity of those patients to respond to levodopa replacement therapy in a sustained pattern.

It should also be noted that the MRI findings might even have a predictive significance and patients with the idiopathic parkinson disease who do not have putaminal hypointensity on the MRI T2 studies are believed to show good sustained clinical improvement to levodopa therapy, while patients with putaminal hypointensity do not show this good clinical response. Putaminal hypointensity is regarded as a radiological sign of bad prognostic significance in so far as the clinical response to levodopa is concerned. Olanow et al, 1990

The T2 signal hypointensity that was normally demonstrated at the midbrain level is due to normal iron deposition in the red nucleus and the pars reticularis of the substantia nigra. The more dorsal pars compacta of the substantia nigra is relatively devoid of iron and subsequently appears isointense to the gray matter, and this probably constitute the band "with a higher signal intensity" that is normally seen between the red nucleus

Our findings in parkinsonian patients are consistent with the findings of Duguid et al, 1986; Rutledge et al, 1987; Braffman et al, 1988; Olanow et al, 1989; Huber et al, 1990; Drayer, 1995. The MRI signal changes reported in idiopathic parkinson disease is thought to reflect iron accumulation associated with neuronal degeneration. Rojic et al , 1965; Earle , 1968; Dexter et al, 1989; Jellinger et al, 1990; Hirsch et al, 1991; Sofic et al, 1991. Iron accumulation in the pars compacta of the substantia nigra will cause signal attenuation in the region that formerly had a higher signal because it was relatively devoid of iron, thus explaining the signal changes observed in the midbrain of parkinsonian patients. Duguid et al, 1986; Olanow and Drayer, 1987; Olanow et al , 1989; Olanow et al, 1990; Huber et al, 1990. High -field strength MRI might be a mean of studying and evaluating iron concentration and distribution in the brain of patients with parkinson disease. Brittenham et al, 1982; Brooks et al, 1989; Hirsch et al , 1991; Sofic et al, 1991.

Although Olanow, 1992 considered the possibility that putaminal parkinson disease is probably more likely to be a part of the parkinson plus syndrome (multisystem atrophy) and might not be considered as an advanced stage of one and the same disease (the idiopathic parkinson disease) that starts with involvement of the substantia nigra and extends, later on, to involve the putamen, however our findings argue against this possibility because of the following factors:

- The initial clinical presentation of group (B) patients were identical with the clinical presentations of group (A) patients with unilateral or predominately unilateral resting tremors and initial good response to treatment, this is not consistent with the clinical presentation of the parkinson -plus syndromes. Quinn, 1989
- Complete absence of pyramidal, cerebellar or autonomic clinical manifestations, also there was no evidence of any sphincter troubles, gaze palsy or clinical evidence of dementia in any patient belonging to group (B). These signs are mandatory for the diagnosis of multisystem atrophy. Lees , 1989; Quinn, 1989
- There was no radiological evidence of brain atrophy in any patient belonging to group (B), brain atrophy is almost invariable in **multisystem atrophy**. Drayer , 1995
- The MRI signal changes concomitantly seen at the midbrain level in all group (B) patients (smudging or blurring of border between the substantia nigra and the red nucleus) is typical for the idiopathic parkinson disease as a primary disorder of the pars compacta of substantia nigra and has not been reported in multisystem atrophy (parkinson-plus syndromes). Drayer , 1995
- Patients belonging to the parkinson-plus syndromes are likely to be levodopa resistant (unresponsive) from the very start of the disease rather than to be initially responsive , in a sustained pattern, to levodopa and then to have this sustained response replaced by a fluctuant one after the lapse of a few year. Chase et al, 1989; Obeso et al , 1989; Lees, 1989 ;Quinn, 1989; Patients belonging to group (B) can not be described as being unresponsive but rather they ultimately become plagued with daily oscillation in levodopa responsiveness. This pattern of levodopa responsiveness is typical (and almost invariable in every single patient) of the idiopathic parkinson disease. Chase et al, 1989; Obeso et al , 1989

Accordingly we regard the nigral and the putaminal stages (as demonstrated radiologically) as two pathological stages of one and the same disease (the idiopathic parkinson disease). Progression from the nigral stage to the putaminal stage is almost invariable in every single patient. This view point is consistent with the view point of Rutledge et al, 1987; Braffman et al, 1988; Chase et al, 1989; Duguid et al, 1986; Obeso et al , 1989; LeWitt, 1992. Progression was attributed to the natural history of the disease, however others attributed this progression, at least in part, to chronic levodopa therapy, as levodopa metabolism generates hydroxyl free radicals and hydrogen peroxide which can induce nerve damage. Goetz and Diedwerich 1992. Others, however, negated this possibility stating that levodopa has no neurotoxicity. Chase et al, 1989; Duguid et al, 1986; Obeso et al , 1989

However when putaminal involvement is demonstrated radiologically in the absence of nigral involvement,

especially in a levodopa resistant patient, (and this has never been the case in any of our patients) one might consider the possibility of multisystem atrophy in the appropriate clinical context. When both putaminal and nigral involvement are concomitantly demonstrated in any single patient, this must be regarded as an advanced stage of the idiopathic parkinson disease. Lees, 1989 ; Quinn, 1989; Drayer, 1995. See table (2)

Table 2.

MRI signal changes	Description	Pattern of levodopa response
Only nigral MRI T2 signal changes	Early idiopathic parkinson disease with intact striatal storing capacity to dopamine	Good sustained response to levodopa
Concomitant nigral and putaminal MRI T2 signal changes	Advanced idiopathic parkinson disease with impaired striatal storing capacity to dopamine	Fluctuant unsustained response to levodopa
Only putaminal MRI T2 signal changes	Parkinson -plus syndromes (multisystem atrophy)	Levodopa-resistant

It is important to consider the significance of iron accumulation in the nigra and striatum in patients with parkinson disease. Iron promotes oxidation reactions and the formation of cytotoxic free radicals, which may contribute to lipid peroxidation, neuronal degeneration, and parkinsonism. Olanow 1990 Using different techniques, several laboratories have confirmed an increase in iron concentration in the substantia nigra pars compacta of patients with Parkinson's disease. Dexter et al, 1989; Hirsch et al , 1991; Sofic et al, 1991. The increase in iron is largely in the Fe³, (ferric) rather than Fe² (ferrous) form, indicating oxidant stress. Sofic et al, 1988 One study also indicates that ferritin, the binding protein for iron, is reduced in the brain of patients with Parkinson's disease, implying that iron in the brain is unbound and in a form in which it can promote oxidation. Dexter et al, 1990.

Histologic studies using Perls' stain and x-ray micro- analysis confirm findings of increased iron in the pars compacta of patients with Parkinson's disease. Hirsch et al , 1991; Jellinger et al, 1990 The potential of iron to damage neurons can be demonstrated by studies that show that infusion of iron into the substantia nigra can induce a dose-dependent degeneration of dopamine neurons and a reduction in ipsilateral dopamine striatal markers. Sengstock et al, 1991 Furthermore removal of iron by iron chelators attenuates the dopamine neuronal damage induced by 6-hydroxydopamine. Ben-Schachar et al, 1991

It is not known why iron increases in idiopathic parkinson disease. The possibility that iron might accumulate as a consequence of degeneration resulting in gliosis and leaking of iron from pools of intracellular ferritin should be considered. Signal attenuation presumably caused by iron accumulation has been observed in other degenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), choreas, and multiple sclerosis. Drayer, 1988 Iron does not accumulate, however, in the nigra of patients with progressive supranuclear palsy despite prominent neuronal degeneration .Hirsch et al, 1991 Further even if iron accumulation is consequent to neuronal damage, it can still create an environment in which secondary oxidation damage can occur leading to ongoing neuronal degeneration. Iron accumulation through either primary or secondary mechanisms can promote free radical production and possibly neuronal degeneration. Halliwell and Gutteridge 1988; Olanow, 1992

The nigral pattern of involvement (smudging or blurring of border between the substantia nigra and the red nucleus) might be regarded as a "biological marker with diagnostic significance" for the idiopathic parkinson disease, as it was uniformly demonstrated in all patients included in the study and it has not been demonstrated in other diseases with parkinsonian features (such as multisystem atrophy) or other degenerative disorders of the CNS . Drayer , 1995 It is well known that the idiopathic parkinson disease is a primary disorder of the pars compacta of the substantia nigra, and as mentioned above, the nigral pattern of involvement is due to selective affection of the pars compacta of the substantia nigra and to the best of our knowledge no neurological diseases, other than the idiopathic parkinson disease, behave in such a way .However more studies are needed to delineate

the exact specificity of this radiological sign in the diagnosis of idiopathic parkinson disease

Should this nigral pattern of involvement prove to be specific to idiopathic parkinson disease, then this might help in the differential diagnosis of difficult cases on one hand, and on the other hand the timing of appearance of this sign might have serious implications, because if this radiological sign antedates the onset clinical symptomatology in parkinson disease then it will be possible to take preventive measures that can delay or even prevent any further progression of the disease and subsequently prevent or delay the occurrence clinical symptomatology once this radiological sign is discovered Presymptomatically (for example by giving antioxidant medications as will be described later) .

It is well known that the degenerative & pathogenic process of parkinson disease antedates the clinical symptomatology by so many years -by studying the incidence of lewy bodies, the pathological markers of parkinson disease, in the substantia nigra of persons who died without established parkinson disease Forno, 1969; Gibb and lees 1989 estimated the presymptomatic period to be as long as 30 years- and subsequently this radiological sign (should it prove to be specific to parkinson disease) can be regarded as a marker of increased susceptibility for the development of parkinson disease in asymptomatic individuals once discovered at this stage. Presymptomatic diagnosis of parkinson disease has always been a dream and indeed more researches are needed in this respect.

Our radiological findings have major therapeutic implications in the management of parkinson disease as follow : (for more details about the drug treatment of parkinson disease the reader is referred to the corresponding chapter)

In the more advanced stage of parkinson disease with putaminal involvement, and with the resultant of reduction of the storage capacity of the brain to dopamine, peripheral kinetics of levodopa should play an important and a key role. As the patient's response to levodopa will oscillate with oscillation of the serum level of levodopa, factors which help maintain a steady state serum level of levodopa will ameliorate this response fluctuations, these include :

1-As levodopa is absorbed from the duodenum and the proximal small intestine, factors which enhance gastric emptying will enhance levodopa absorption. High protein diet might delay levodopa absorption

2-The use of sustained release levodopa medications can help maintain a steady-state serum level of levodopa and ameliorate the response fluctuations in advanced parkinson disease. LeWitt, 1992

3-The use of duodenal infusion of levodopa can enhance levodopa absorption by bypassing the stomach, as delay in gastric emptying might delay levodopa absorption and might be the cause of serum level fluctuations of levodopa. LeWitt, 1992

4-The use dopaminergic agonist medications, such as bromocriptine, that act directly on the postsynaptic receptors, in this way the malfunctioning presynaptic storage pool is bypassed. Goetz and Diedwerich 1992

It should be noted, however, that many of these maneuvers were used in group (B) patients and although some of the patients did report definite clinical improvement, however this improvement was limited and of short duration and non of patients were back to the honeymoon initial stage of the disease during which the patient do not perceive the onset and decline in drug action and improvement from a single dose in the morning can last the entire day despite the rise and fall of levodopa serum level. It looks like that prevention, or at least delay, of disease progression from the nigral stage to the putaminal stage once parkinsonism is initially diagnosed is the only practical solution in so far as helping these miserable patients is concerned .

In the face of the accumulating data that neuronal damage, in parkinson disease, is caused by the cytotoxic free radicals, the role that can be played by antioxidant therapies (therapies that diminish free radical formation), in the protection of residual neurons and in the delay or even prevention of Parkinson's disease progression, becomes quite apparent. The parkinson study group, 1989 has demonstrated that the monoamine oxidase B (MAO-B)

inhibitor, deprenyl, which partially blocks free radicals generated from dopamine metabolism, delays the development of disability in patients with early Parkinson's disease. Cytotoxic free radicals scavengers should probably be administered concomitantly with dopaminergic medications to every newly discovered parkinsonian patient in the hope of delaying, or even preventing, disease progression .

There is also evidence that trophic factors can induce the growth of dopamine neurons in tissue culture, Hyman et al, 1991 attenuate methy l-4-pheny l-1,2,3,6-tetrahydropyridine (MPTP) damage to dopamine neurons in tissue culture, Drayer 1988 and possibly induce sprouting of dopamine terminals in patients with Parkinson's disease following transplantation. Bohn et al, 1987 These observations suggest the possibility that protective or restorative therapy for patients with Parkinson's disease may be forthcoming and that early accurate and even presymptomatic detection may be of great importance.

REFERENCES

-Ben-Schachar D, Eshel G, Finberg JPM, Youaim M: The iron chelator deferrioxamine (desferal) retards 6-hydroxy dopamine-induced degeneration of nigral striatal dopamine neurons. *j Neurochem* 56:1441-1444, 1991

-Bohn MC, Cupit L, Marciano F, Gash DM: Adrenal medulla grafts enhance recovery of striatal dopaminergic fibers. *Science* 237:913-916, 1987

-Braffman BH, Grossman RI, Goldberg HI, et al: NM imaging of Parkinson's disease with spin-echo and gradient-echo sequences. *AJNR* 9:1093-1099, 1988

-Brittenham GM, Farrell BE, Harris JW: Magnetic susceptibility measurements of human iron source. *N Engl J Med* 307:1671-1675, 1982

-Brooks DJ, Luthert P, Gadian D, Marsden CD: Does signal-attenuation on high-field T2-weighted MRI of the brain reflect regional cerebral iron deposition? Observations on the relationship between regional cerebral water proton T2 values and iron levels. *j Neuro Neurosurg Psych* 52(1):108-111, 1989

-Chase AM, Baronti f, Fabbrini J, Heuser IJ, et al: rationale for continuous dopaminergic therapy of parkinson disease. *Neurology* ,39 (suppl 2) :7-10,1989

-Dexter DT, Carayon A, Vidailhet, et al: Decreased ferritin levels in brain in Parkinson's disease. *j Neurochem* 55:16-20, 1990

-Dexter DT, Wells Fr, Lees AJH, et al: Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. *j Neurochem* 52:1830-1836, 1989

-Drayer BP: Degenerative disorders of the central nervous system . *Neuroimaging clinics of north America* .vol 5,number 1,pp 135-153 ,1995

-Drayer BP: Imaging of the aging brain. Part 11: Pathological conditions. *Radiology* 1988; 166:797-806, 1988

-Drayer B, Burger P, Darwin R, et al: Magnetic resonance imaging of brain iron. *AJNR* 7:373-380, 1986

-Duguid JR, Delapaz R, DeGroot J: Magnetic resonance imaging of the midbrain in Parkinson's disease. *Ann Neurol* 20:744-747, 1986

-Earle KM: Studies on Parkinson's disease including x-ray, flourscent spectroscopy of formal and fixed brain tissue. *J Neuropath Exp Neurol* 27:1-14, 1968

- Eidelberg D : Positron emission tomography studies in parkinson disease. Neurologic clinics,volume 10,number 2, pp 421-421-433,1992**
- Forno LS :Concentric hyaline of intraneural inclusion of lewy type in the brain of elderly persons (50 incidental cases) . j. Am .Geriatr. soc. 1969**
- Gib WRG, Lees AJ : The relevance of the lewy body to the pathogenesis of idiopathic parkinson disease .J. Neurol Neurosurg Psychiatry ,51:745-752,1988**
- Goetz CG, Diedwerich NJ :Dopaminergic agonists in the treatment of parkinson disease. Neurologic clinics,volume 10,number 2, pp 487-527-540,1992**
- Halliwell B, Gutteridge JMC: Iron as a biological pro-oxidant. ISI Atlas Sci Biochem 1:48-52, 1988**
- Hirsch EC, Brandel JP, Galle P, et al: Iron and aluminum increase in the substantia nigra of patients with Parkinson's disease: An x-ray microanalysis. J Neurochem 56:446-451, 1991**
- Huber S, Chakeres DW, Paulson GW Kahanna R: Magnetic resonance imaging in Parkinson's disease. Arch Neurol 47:73,-737, 1990**
- Hyman C, Hofer M, Barde YA, et al: BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350:230-232, 1991**
- Jellinger K, Paulus W, Grundke L, et al: Brain iron and ferritin in Parkinson's and Alzheimer's disease. j Neural Transm 2:227-240, 1990**
- Juncos JL : Levodopa :pharmacology,pharmacokinetics and pharmacodynamics. Neurologic clinics, volume 10, number 2, pp 487-450,1992**
- Ketonen LM:Neuroimaging of the aging brain. Neurologic clinics, Vol 16, number 3,pp581-598 ,1998**
- Lees AJ : The on and off phenomenon. J Neurol, Neurosurg, Psych.(suppl.) 29-37,1989**
- LeWitt PA : Treatment strategy for extension of levodopa effect. Neurologic clinics,volume 10, number 2, pp 487-511-526, 1992**
- Obeso JA,Grandas F, Vaamondi a, Luquin MR, Artieda J, at al : motor complications associated with chronic levodopa therapy in parkinson disease. Neurology ,39 (suppl 2) :11-19,1989**
- Olanow CW : Magnetic resonance imaging in parkinsonism. Neurologic clinics,volume 10,number 2, pp 450-420,1992**
- Olanow CW: Oxidation reactions in Parkinson's disease. Neurology 40(3):32-37, 1990**
- Olanow CW, Alberts M, Djang W, Staich,H : MR imaging of putaminal iron predicts response to dopaminergic therapy in parkinsonian patients. In Dostert P, Riederer P, Strolin, Bendetti M, Roncucci R (eds): Early Markers in Parkinson's and Alzheimer's Diseases. Austria, Springer-Verlag, pp 99-109 ,1990**
- Olanow CW, Holgai RC, Murtagh R, Martinez C: MR imaging in Parkinson's disease and aging. In Calne DB ,et al (eds): Parkinsonism and Aging. New York, Raven Press, pp 155-164 ,1989**
- Olanow CW, Drayer B: Brain iron: MRI studies in Parkinson's syndrome. In Fahn S, Marsden D, Calne D, et al: Recent Developments in Parkinson's Disease. MacMillan Health Care, pp 135-143, 1987**

- Quinn N : Multiple system atrophy-The nature of the beast. J. Neurol, Neurosurg., Psych.(suppl.) 78-89,1989**
- Rojis G, Asenjo A, Chiorino R, et al: Cellular and subcellular structure of the ventral lateral nucleus of the thalamus in Parkinson's disease: Deposits of iron. Confin Neurol 26:362-376, 1965**
- Rutledge JN, Hilal SK, Silver Aj, et al: Study of movement disorders and brain iron by MR. AJNR 8:397-411, 1987**
- Sengstock Gj, Olanow CW, Dunn Aj, et al: Iron induces degeneration of substantia nigra neurons. Movement Dis 6(3):272, 1991**
- Sofic E, Paulus W, Jellinger K, et al: Selective increase of iron in the substantia nigra zona compacta of parkinsonian brains. j Neurochem 56:978-982, 1991**
- Sofic E, Mederer P, Heinsen H, et al: Increased iron (111) and total iron content in post mortem substantia nigra of parkinsonian brain. J Neural Transm 74:199-205,1988**
- The Parkinson's Study Group: Effect of Deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 321:1364-1371, 1989**
- Metwally, MYM: Textbook of neurimaging, A CD-ROM publication, (Metwally, MYM editor) WEB-CD agency for electronic publishing, version 9.1a January 2008**
-

- **Addendum**

- I am professor Yasser Metwally, professor of neurology, Ain Shams university, Cairo, Egypt
- A new version of this publication is uploaded in my site from time to time.
- You can download the current version of this publication by following the link:
<http://pdf.yassermetwally.com/paper.pdf>, or you can go to my web sites at: <http://yassermetwally.com>. or <http://pdf.yassermetwally.com> to download it
- At the end of each year, all the publications are compiled on a single CD-ROM, please contact the author to know more details.
- Screen resolution is better set at 1024*768 pixel screen area for optimum display