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PARKINSON'S' BICENTENNIAL: PAST, PRESENT & FUTURE

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It has been exactly 200 years since James Parkinson first described the *shaking palsy* or *paralysis agitans*. Since then, a tremendous amount of research has taken place and our knowledge of this disease has grown exponentially. Unfortunately, there is still no curative treatment. However, our diagnostic methods have greatly improved and we are now capable of conclusively diagnosing Parkinson Disease in its pre-motor stage. Within these pre-motor stages, specific clinical phenotypes have been described, enhancing our differential diagnosis. Furthermore, with the advent of new and exciting neuronal stem cell culture and use, we are entering a new phase, one in which, perhaps, a treatment beyond symptomatic management can be obtained.

Keywords: Parkinson Disease, pre-motor stage, clinical phenotypes, diagnostic, treatment, stem cells.

Резюме

ДВОХСОТРІЧЧЯ ХВОРОБИ ПАРКІНСОНА: МИНУЛЕ, СЬОГОДЕННЯ І МАЙБУТНЄ

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Минуло рівно 200 років з того часу, як Джеймс Паркінсон вперше описав *тремтячий параліч*. З тих пір проводилася величезна кількість досліджень, і наші знання про це захворювання зросли в геометричній прогресії. На жаль, все ще недоступно лікування, яке рятує від хвороби Паркінсона. Однак, наші діагностичні методи значно покращилися, і тепер ми можемо діагностувати хворобу Паркінсона на премоторних стадіях, на яких були описані специфічні клінічні фенотипи, які поліпшили диференціальну діагностику. Крім того, з появою нових нейрональних стовбурових клітин ми вступаємо в нову фазу, в якій можливо отримати лікування, що виходить за межі симптоматичного.

Ключові слова: хвороба Паркінсона, премоторна стадія, клінічні фенотипи, діагностика, лікування, стовбурові клітини.

Резюме

ДВУХСОТЛЕТИЕ БОЛЕЗНИ ПАРКИНСОНА: ПРОШЛОЕ, НАСТОЯЩЕЕ И БУДУЩЕЕ

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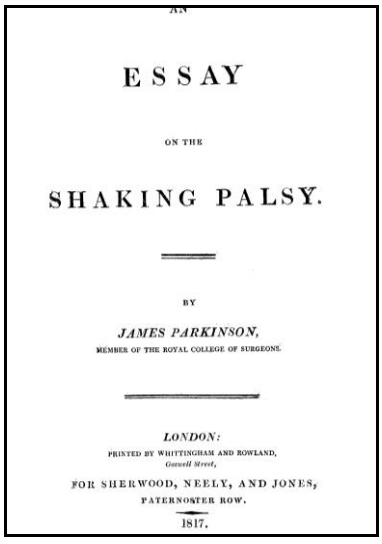
Прошло ровно 200 лет с того времени, как Джеймс Паркинсон впервые описал *дрожательный паралич*. С тех пор проводилось огромное количество исследований, и наши знания об этом заболевании выросли в геометрической прогрессии. К сожалению, все еще недоступно лечение, избавляющее от болезни Паркинсона. Однако, наши диагностические методы значительно улучшились, и теперь мы можем диагностировать болезнь Паркинсона на премоторных стадиях, на которых были описаны специфические клинические фенотипы, улучшающие дифференциальную диагностику. Кроме того, с появлением новых нейрональных стволовых клеток мы вступаем в новую фазу, в которой возможно получить лечение, выходящее за пределы симптоматического.

Ключевые слова: болезнь Паркинсона, премоторная стадия, клинические фенотипы, диагностика, лечение, стволовые клетки.

Leaping through the last two centuries

200 years ago, James Parkinson published *"An Essay on the Shaking Palsy"* (1817) (figure 1), in which, he described for the first time the so-called *shaking palsy or paralysis agitans: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured"* [1].


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Figure 1. An Essay on the Shaking Palsy

Although Parkinson was a very astute clinician and although his *Essay* remains even to this day as a preeminent work of exquisite clinical observation and description, he failed to describe *non-motor* symptoms, an essential group of symptoms, which as we will see, can precede the motor deficiencies in up to 15 to 20 years.

J.M. Charcot (figure 2), the eminent French neurologist, in the 1860s, based on Parkinson's' initial description, would put forth a more substantial definition including the cardinal features of resting tremor, bradykinesia and rigidity. More so, for the first time he classified the disease into two forms:

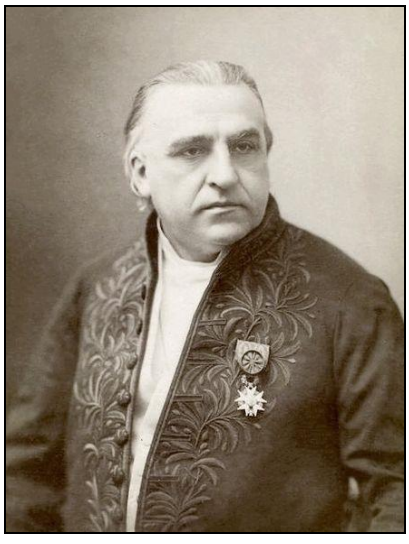


Figure 2. J.M. Charcot

(1) tremulous and (2) akinetic/rigid. In fact, it was Charcot himself who suggested changing the name from *paralysis agitans* to "Par-

kinson's Disease", noting that patients are not markedly weak and do not necessarily have tremor. Charcot also failed to include non-motor symptoms.

Leaping ahead to 1912, a prominent Jewish German-born American Neurologist by the name of Frederic Heinrich Lewy (1885-1950) discovered for the first time abnormal protein aggregates found in the brainstem neurons (and other sites) in patients with Parkinson Disease [2]. Such aggregates, i.e., Lewy Bodies, appear as spherical masses that displace other cellular / neuronal components (figure 3) and are the pathological basis for Parkinson Disease.

Figure 3**.** Lewy Bodies

In 1957, the Nobel Laureate Arvid Carlsson showed that dopamine was a neurotransmitter in the brain and not just a precursor for norepinephrine [3]. Furthermore, he also developed an assay to measure dopamine in the brain and found the highest region concentration in the basal ganglia [4]. This finding led to experiments with Reserpine, which depleted dopamine and produced a loss of movement control similar to the clinical symptoms of Parkinson Disease [5].

In the 1960s, Oleh Hornykiewicz (1960) and George C. Cotzias (1967) showed a marked depletion of dopamine in the striatum of Parkinson Disease brains [6] and demonstrated that the use of levodopa proved to be dramatically successful in reversing symptoms of Parkinson Disease [7], respectively.

As we can see, in a time span of 150 years, the humble (yet innovative) concept of James Parkinson's' "Shaking palsy" was enriched into a specialized blend of pathophysiologic discoveries. Parkinson Disease was understood to be: (1) a progressive, chronic neurodegenerative disease, (2) with slow and selective loss of dopaminergic neurons, with accumulation of Lewy Bodies in the substancia nigra and (3) it responded to levodopa or dopaminergic treatment.

Eventually, after further clinical inquest, the UK-PD-SBB (UK-PD Society Brain Bank) Criteria were developed. It summarizes the main clinical criteria for the diagnosis of Parkinson Disease [8].

Diagnosis of a Parkinsonian Syndrome

Bradykinesia and at least one of the following:

1. Muscular rigidity;
2. Resting tremor (4-6 Hz);
3. Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive disturbances.

Once 2 of these 4 cardinal criteria are met, a number of supportive criteria can confirm the diagnosis.

Supportive criteria for Parkinson Disease

At least 3 required for the definitive diagnosis of Parkinson Disease:

1. Progressive disorder;
2. Unilateral onset;
3. Persistent asymmetry affecting the onset side;
4. Levodopa response for 5 years or more;
5. Severe Levodopa induced chorea;
6. Clinical course of 10 years or more.

Furthermore, there are exclusion criteria that must be considered also before conclusively diagnosing Parkinson Disease. They are summarized below.

Exclusion Criteria

1. History of either:
   a) Repeated strokes with stepwise progression;
   b) Repeated head injury;
   c) Antipsychotic or dopamine-depleting drugs.
2. More than one affected relative.
3. Sustained remission.
4. Negative response to large doses of Levodopa.

5. Strictly unilateral features after 3 years.
6. Other neurological features:
   a) Supranuclear gaze palsy;
   b) Cerebellar signs;
   c) Early severe autonomic involvement;
   d) Babinski sign;
   e) Early severe dementia with disturbances of language, memory or praxis.
7. Exposure to known neuro-toxin.
8. Presence of cerebral tumor or communicating hydrocephalus.

Having said this, today we see Parkinson Disease slightly different. At present, we understand this incredible disease as having many complex layers, not only associated with dopamine but also with other neurotransmitters. And perhaps, more importantly, based on modern-day research, the non-motor symptoms have acquired a newfangled plateau of importance. In a very real way, the pathophysiology underlying the non-motor symptoms tells a revealing story, one that suggests that the origin of Parkinson lies *not* in the brain but rather in the bowels [9]. These non-motor symptoms are centerpiece to the most recent developments in the understanding of Parkinson Disease.

The main non-motor symptoms that can present in Parkinson Disease are summarized in the following table 1.

Table 1

Non-motor symptoms of Parkinson Disease

Sleep disorders	Sensory manifestations	Psychiatric	Autonomic System
Insomnia Sleep fragmentation (REM sleep disorder) Parasomnias Restless leg syndrome Excessive daytime sleeping Sleep attacks	Pain Hyposmia Paresthesias Restless leg syndrome	Dementia Hallucinations Delirium Mood disturbances (depression, agitation, anxiety and panic attack)	Orthostatic hypotension Constipation Urinary problems Sexual dysfunction Sweating and thermoregulation

Because all of these symptoms are non-specific to Parkinson Disease and are very common in the elderly, Krishnan *et al* [10] conducted a study to determine whether these non-motor symptoms differ in frequency and intensity in elderly patients with Parkinson Disease in comparison to those without Parkinson Disease. The results demonstrated that patients with Parkinson Disease had a higher incidence of the majority of non-motor symptoms, mainly sleep disturbances, mood and cognition deterioration and GI tract disturbances.

More importantly, many of these non-motor symptoms can be present up to 10-20 years *before* the onset of motor symptoms appears. Constipation, REM-sleep disorder, hyposmia, depression and excessive daytime sleeping are the most frequently associated preceding symptoms. By the time motor symptoms appear, it is possible that 10-20 years of pathologic changes have elapsed. Usually, during the 3rd and 5th year of onset, patients with Parkinson disease may present with bradykinesia, rigidity and tremor. After 5 to 10 years, it is common to find motor fluctuations, dyskinesia, urinary problems, orthostatic hypotension and possibly dementia. The UK-PD-SBB Criteria are useful for diagnosing Parkinson Disease based on motor symptoms and therefore, relevant after 3-5 years of disease onset. Unfortunately, in the vast majority of cases, by the time the diagnosis is confirmed, many years of non-motor pathophysiology has progressed "under the radar". This is a clear limitation for neurologists and clinicians.

Braak Stages of Parkinson Disease

The Braak stages represent the ascending progression of Parkinson's pathology. Each stage corresponds to a particular anatomical site within the Central Nervous System and depending on which site is affected, there are corresponding clinical manifestations. The table 2 that follows represents the anatomical sites and clinical manifestations emerging from each stage.

Table 2

Braak Stages of Parkinson Disease

Stage	Affected anatomical site	Neurotransmitter affected	Main clinical manifestations
Stage 5/6	Neocortex		Cognitive impairment
Stage 4	Mesocortex		
Stage3	Midbrain (upper brainstem)	Substancia Nigra: Dopamine	Motor dysfunction
Stage 2	Pons	Locus Coeruleus: Noradrenaline Raphe Nucleus: Serotonin	Depression Sleeping disorders (REM)
Stage 1	Medulla (lower brainstem)	Nucleus of the X nerve: AcH	Association with Enteric Nervous System

Based on this classification, the non-motor symptoms (constipation, REM-sleep disorder and depression) can be traced back to the brainstem. Berg D *et al* [11] concluded that the best clinical indicator of pre-motor Parkinson Disease is REM sleep/behavioral disorder (RBD). Iranzo *et al* [12] demonstrated that a high percentage of patients with idiopathic RBD go on to develop alpha-synucleopathy. On the other hand, anosmia/hyposmia is due to Lewy Body deposit in the olfactory bulb. Importantly, as we can see from the table, the dopaminergic system is affected *after* the acetylcholinergic, serotoninergic and noradrenergic systems. This explains why the non-motor symptoms typically *precede* the onset of motor manifestations (figure 4)

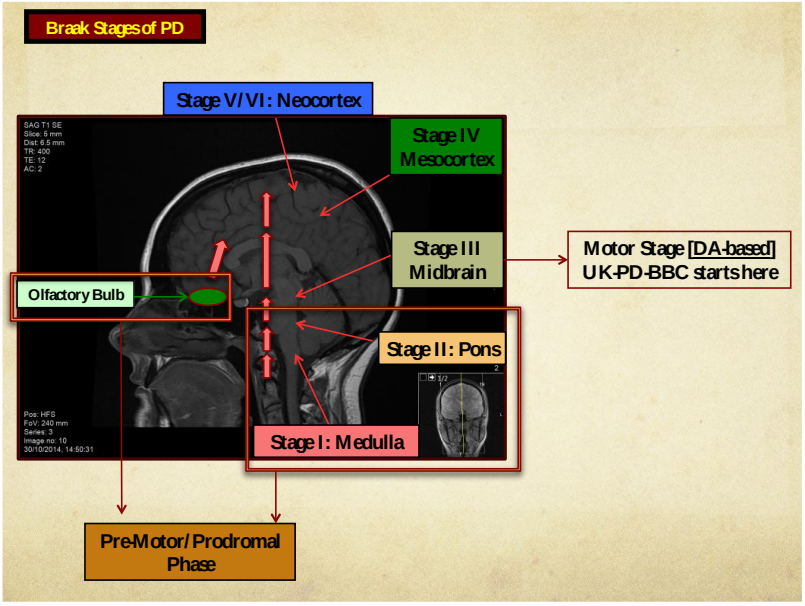


Figure 4. Braak Stages of Parkinson Disease (image done by author)

The Enteric Nervous System and Parkinson Disease

It appears that constipation can precede the onset of motor dysfunction in Parkinson Disease because Lewy Bodies are deposited in the GI tract much before they are deposited in the brainstem. Alpha-synuclein bodies (Lewy Bodies – synuclein aggregates) have been detected in Meissner and Auerbach Plexus (AEC-chromogen; Proteinase K). The PRIAMO study [13], which involved 1072 patients, found that 28% suffered from constipation; 25% had less than 3 evacuations per week and 11% had incomplete bowel

emptying. It was concluded therefore that constipation was associated with elevated risk of developing Parkinson Disease.

There appears to exist a stereotypical ascending domino-effect by retrograde axonal trans-neuronal transport; Parkinson Disease seems to be "triggered" from outside the central nervous system by an unidentified pathogen that is capable of passing the mucosal barrier of the GI and via post-ganglionic enteric neurons, entering the CNS along unmylinated pre-ganglionic fibers (figure 5). There are two types of constipation associated with Parkinson Disease: (1) Slow-transit (80%), which takes between 44-130 hours (versus non-Parkinson patients: 20-39 hours) and (2) "Outlet" constipation or ano-rectal dysfunction (20%) in which there is paroxysmal anal sphincter contraction during defecation (focal dystonia).

Non-Motor Parkinson Clinical Phenotypes

All these findings have led to the description the main non-motor clinical phenotypes in Parkinson Disease. Each one corresponds to a particular anatomical site (table 3, figure 6).

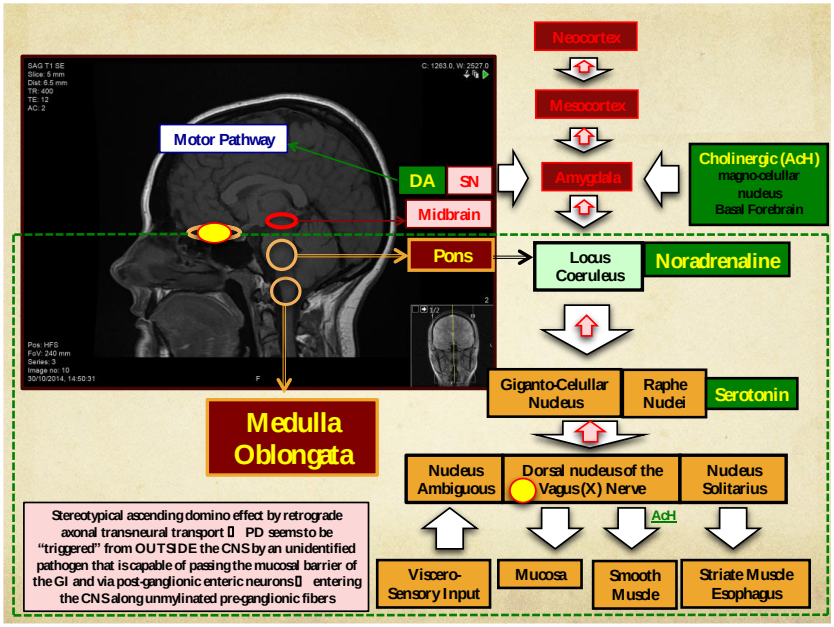


Figure 5. The Enteric Nervous System and Parkinson Disease (image done by author)

Table 3

Non-Motor Parkinson Clinical Phenotypes

Phenotype	Clinical manifestations
Brainstem Phenotype	1. Sleep dominant sub-type a) Excessive daytime sleeping (EDS) b) REM-behavior disorder (RBD) 2. Autonomic dominant sub-type a) GIT b) GUT c) Adrenergic (orthostatic hypotension)
Limbic Phenotype	1. Depression dominant subtype 2. Fatigue dominant subtype (serotonin) 3. Pain dominant subtype 4. Weight loss dominant subtype
Cortical Phenotype	1. Apathy 2. Amnesic: mild cognitive impairment (MCI) 3. Dementia

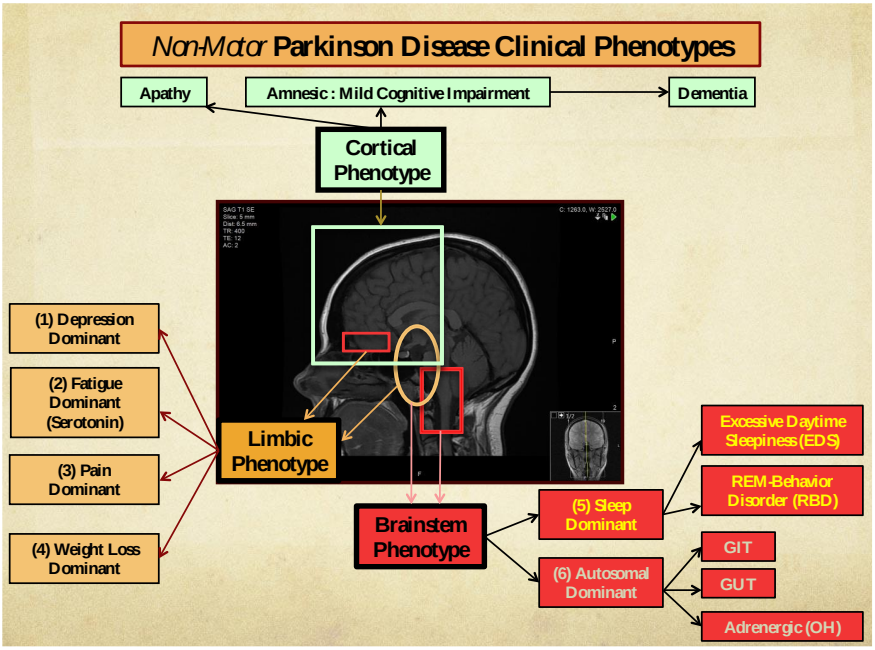


Figure 6. Non-Motor Parkinson Clinical Phenotypes
(image done by the author)

Environmental factors and early diagnosis in Parkinson Disease

Based on the insightful results from on-going research, the etiology of Parkinson has greatly diversified. Apart from genetic factors (Alpha-synuclein, Parkin gene, UCH-L1, LRRK2, etc.), we can also consider environmental factors such as pesticides, rural living and fungicides.

There is a growing interest in the environmental factors related to Parkinson Disease, especially due to the extension of the Braak stage to include the enteric nervous system. It has been proposed that well water, agricultural chemicals (and rural/farming land) can gain access to the CNS via the GI system: after entering the mouth, they are transmitted to the GI system and then ascend to the CNS. On the other hand, pesticides, herbicides and certain metals can gain access to the CNS via the nose and in turn, cause olfactory bulb dysfunction, providing another potential etiology to Parkinson Disease (figure 7).

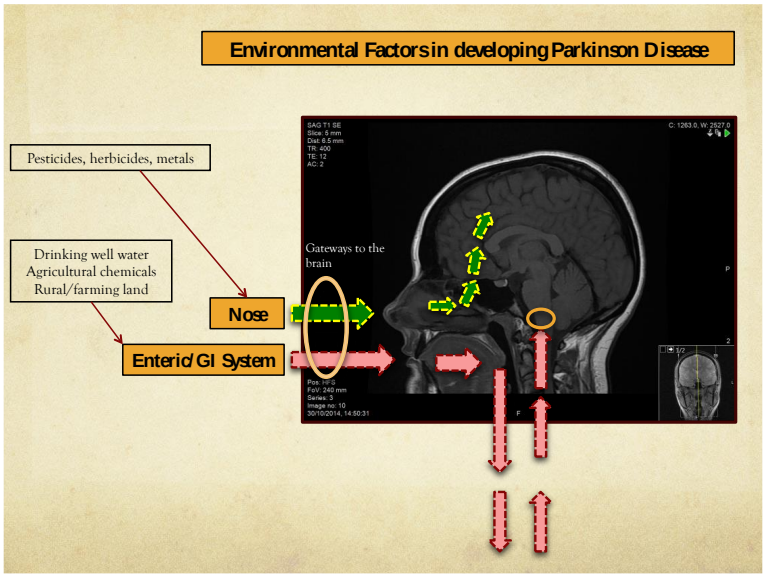


Figure 7. Environmental factors and early diagnosis in Parkinson Disease
(image done by author)

Cigarette smoking and caffeine consumption change the microbial flora of the gut (mitigating intestinal inflammation), causing less aggregation of alpha-SN in the enteric nervous system, leading to a diminished risk of developing Parkinson disease.

Interestingly, there have been several authors who have proposed a link between GI bacteria and the development of Parkinson Disease. In one study, *Prevotellaceae* was been found in 78-80% of Parkinson patients.

All these factors must be considered when diagnosing a patient with Parkinson Disease. Undoubtedly more research is required, however, there appears to be a strong link between environmental factors and the development of Parkinson Disease.

If we suspect that a patient might have a non-motor phenotype of Parkinson Disease, besides considering the environmental and genetic factors in the etiology, carrying out a DAT-scan might provide useful insight into the dopaminergic activity of the CNS. Canepa [14] published a case of "Park-sleep", one of the non-motor Parkinson phenotypes, diagnosed on the basis of REM-sleep disorder (without motor dysfunction), subtle basal ganglia changes visualized on the MRI scan and importantly, abnormal dopamine uptake seen on DAT scan. This led to an early diagnosis of Parkinson Disease and an appropriate management of the patient's co-morbidities.

Diagnosing Parkinson Disease before the motor onset phase is extremely important. By the time motor problems appear 50-70% of dopaminergic neurons in striatum are dead. Intervention in early motor phase of Parkinson Disease might be too late to protect striatal dopaminergic terminals from destruction. Furthermore, damage to the dopaminergic nigro-striatal pathway is *complete* within 4 years after diagnosis of Parkinson Disease [15].

The use of DAT-scans provides 87-98% sensitivity and 80-100% specificity for differentiating Parkinsonian syndromes (PD, MSA, PSP) from those with essential tremor and healthy controls. However, it is not useful to differentiate *amongst* parkinsonian syndromes. In vascular Parkinsonism the DAT scan is characteristically normal [16].

Future treatments of Parkinson Disease: are stem cells a viable option?

The role of innovative therapies must be considered, despite many contradictory and inconclusive results. The complete and specific role of stem cells in Parkinson Disease remains to be determined.

One of the most promising results comes from Brazzini *et al* [17] who used autologous implantation of adult stem cells (via supra-selective intra-arterial catheterization) in 36 male patients and 14 female patients with Parkinson Disease. His research group found that in a mean-follow up of 7.4 months +/- 4.5, patients showed a median improvement of 51.1% and quartile deviation of 24.8% on the Unified PD Rating Scale. They showed significant improvement in disability, activities of daily living, depression and overall quality of life. No complications were observed. Furthermore, in 8 patients, follow-up MR spectroscopy revealed mean improvements in N-acetyl-aspartate/creatine ratio from 1.805 to 2.07 (12.8%) and from 1.25 to 1.88 (43.5%) in right and left basal ganglia, respectively, versus pre-procedural values. They concluded that treatment of Parkinson Disease patients with intra-arterial autologous implantation of adult stem cells is feasible and safe and results in improved severity of disease and quality of life.

However, such results must be taken with caution. Despite this promising result, much remains to be understood. Many questions still remain to be answered. Undoubtedly, in the years to come we will continue to learn from the many ongoing research projects regarding the implementation of stem cells in such disease.

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