Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder following Alzheimer's disease, is characterized by the progressive loss of dopaminergic neurons in the substantia nigra. Patients present with resting tremor, muscle rigidity, postural instability and bradykinesia ***(Pan et al., 2013).***

It has been well documented that inflammation plays an important role in the pathogenesis and severity of PD several lines of research have shown that serum oxidative stress and proinflammatory cytokines, such as interleukin (IL)-1b, IL-2, IL-6, HLA-DRB1, tumor necrosis factor (TNF, mitochondrial dysfunction and activated microglia, are elevated in the brain and cerebral spinal fluid of PD patients As an antioxidant and marker of oxidant stress. Uric acid seems to hold a dual role in its impact on cerebral ischemia that is dependent on a number of conditions ***(Seet et al., 2010).***

However, in terms of PD severity, several lines of research have demonstrated consistent results. Epidemiological studies have shown that individuals with high levels of serum UA have a markedly reduced risk of developing PD ***(Winquist et al., 2010).***

Manganese (Mn) regulates numerous enzymes and is important for normal development and body function as Mn-

Superoxide dismutase. Mn-Superoxide dismutase may exert important functional effects in cerebral circulation, because endothelium expresses high levels of Mn-Superoxide dismutase and levels of Mn-Superoxide dismutase are higher in cerebral arteries than in extracranial arteries. Recent studies indicate that Mn-Superoxide dismutase protects against vascular mitochondrial DNA damage and development of atherosclerosis ***(Lien et al., 2017).***

Excessive accumulation of Mn has also induced the phenomenon also seen in PD, such as oxidative stress, impairment of glutamate transporters and excitatory neurotoxicity ***(Du et al., 2018).***

To the best of our knowledge, few studies have been performed to investigate the effects of Uric acid and Manganese in PD and VP patients. In this study we aim to biomarkers (Uric acid & Manganese) are poised to enter routine clinical practice to aid the differentiation of Vascular Parkinsonism from idiopathic Parkinson's disease (PD).

Aim of the Work

This study aims to test (Uric acid & Manganese) as indirect biomarkers in vascular parkinsonism.

Chapter 1

PARKINSONISM

Parkinsonism is a neurological syndrome with four cardinal signs: bradykinesia, muscle rigidity, tremor at rest and impairment of postural reflexes. The diagnosis depends on the presence of *bradykinesia*, which denotes slowness of movements. Related symptoms are deterioration of handwriting (micrographia), slowing of walking (including, for instance, difficulty exiting a car ***(Skogar and Nilsson, 2018).***

Classification of Parkinsonism

Parkinsonism can be classified into a broad spectrum of primary and secondary causes (table 1). Primary parkinsonism embraces neurodegenerative disorders of unknown or genetic origin. The most common type of primary parkinsonism is Parkinson's disease (PD), an idiopathic disorder which is apparently sporadic in the majority of cases. It is estimated that about 10% of PD is familial, based on single gene mutations. It is clinically important and challenging to distinguish PD from the group of degenerative disorders as atypical parkinsonism. The designation "atypical" refers to the poor levodopa response of parkinsonism and the early manifestation of additional clinical features (Parkinson plus) such as ophthalmoparesis, dysautonomia, or dementia. Finally, secondary causes must

always be ruled out as they are potentially treatable and common; for example: secondary to certain drugs like antiemetics and vascular which secondary to multiinfarct syndrome ***(Skogar and Nilsson, 2018).***

Table (1): Classification of Parkinsonism**. (*Fahn, 2011*)**

A. Primary Parkinsonism
1. Parkinson's Disease (sporadic and genetic)
B. Secondary Parkinsonism (Acquired)
1. Drugs Induced: Antipsychotics drugs, antiemetics, dopamine depleting drugs like reserpine, tetrabenzine, lithium. 2. Infectious: Post encephalitic, neurosyphilis, HIV. 3. Toxins: MPTP, CO, Mn, Hg, CS2 4. Vascular: multi-infarct state of brain 5. Trauma: Pulgilistic encephalopathy 6. Hemiatrophy hemi parkinsonism 7. Brain tumors in certain locations such as basal ganglia 8. Hydrocephalus 9. Hypoxia 10. Metabolic
C. Atypical Parkinsonism
1. Progressive supranuclear palsy 2. Multiple system atrophy 3. Corticobasal ganglionic degeneration 4. ALS-Parkinsonism-Dementia – complex of Guam
D. Familial Neurodegenerative Disease causing Parkinsonism
1. Huntington's disease 2. Wilson's disease 3. Hllervorden-spatz disease 4. Olivopontocerebellar and spinocerebellar degeneration 5. Familial basal ganglia calcification 6. Familial Parkinsonism with peripheral neuropathy 7. Neuroacanthocytosis

Clinical presentation

Bradykinesia is slowness of movement involves both initiation and execution of movements. Gradually they develop difficulty washing, feeding, dressing and turning in bed. Loss of facial expression occurs early and impaired swallowing leading to sialorrhea are later features. ***(Kaegi, 2011).***

Rigidity; is constant throughout a full range of passive. If a postural tremor is superimposed it takes on a ratchet characteristic described as "cogwheel" rigidity. The rigidity initially targets limbs and later spreads axially predominantly involving limb and trunk flexors leading to characteristic stooped posturing ***(Kaegi, 2011).***

Tremor; about 40% of patients will complain of tremulousness of hand at rest, which improves with action and 80% will have an asymmetrical 3-5 Hz rest tremor evident on examination. A 4-8 Hz postural tremor is as frequent as the characteristic rest tremor. The tremor of Parkinson's disease can affect the eyelids, chin and legs in addition to arms. ***(Doyon et al., 2003).***

Gait and postural reflexes; the patient usually complains of reduced arm swing on the affected side, which is usually evident. Later a tendency to shuffle develops, followed by gait initiation difficulties, freezing and festination ***(Kaegi, 2011).***

Ocular movements; especially pursuits and reflexive saccades are preserved till late unlike progressive supranuclear palsy. However formal testing of remembered

saccades to an occluded target or anti-saccades reveals slowing ***(Zhang et al., 2015).***

Dystonia; this can be early morning or wearing off dystonia with a predilection for painful foot inversion, but can also manifest as a variety of segmental syndromes ***(Lucking et al., 2000).***

Dysautonomia; Patients frequently admit to impotence and constipation. Orthostatic hypotension may develop as the disease progresses ***(Goldstein, 2006).***

Cognition; significant subcortical dementia occurs in 25% of the patients characterized fluctuating confusion, visual hallucinations and paranoid delusions. ***(Neef and Walling, 2006).***

Table (2): Main clinical feature of the most common parkinsonian disorders **(Hughes *et al*., 2002)**.

Clinical features	Parkinson disease	Multiple system atrophy	Progressive Supranuclear palsy	Corticobasilar degeneration	Drug-induced	vascular	Wilson disease
Distribution of signs	Bilateral asymmetry	Bilateral	Symmetric axial	Very asymmetric	Bilateral symmetric	Bilateral ,more in lower body	Bilateral, symmetric
Response to dopaminergic drugs	Excellent	Moderate	0 or only initially	0	0	+, initially	0
Dystonia	Limbs	limbs	Axial/Cervical	Limbs	Limbs	0	Arms, leg and cervical
Axial rigidity	++	+++	++	+	+	0	+
Supranuclear gaze palsy	0	vertical	vertical	Vertical ,late horizontal	0	upward	Upward deficit
Postural instability	late	early	Very late	late	late	early	late
Frontal behavior	+	+	+++	++	0	++	++
Ideomotor apraxia	0	0	+	+++	0	+	0
Alien limb	0	0	+	+++	0	0	0
Cortical sensory deficit	0	0	+++	0	+	0	0
Symptomatic dysautonomia	+	+++	++	0	0	++	++
Absent:0		rare:+		common:+++		not rare:++	

Chapter 2

PARKINSON'S DISEASE

Two hundred years after James Parkinson's seminal essay on 'the shaking palsy'. Beyond the perception of Parkinson disease as a disorder of movement, it has since become apparent that a multitude of non-motor features, such as cognitive impairment and autonomic dysfunction are part of the disease and add considerably to overall burden ***(Poewe et al., 2017).***

Thus, modifying disease progression and further delaying disability are the key unmet needs to be addressed by current and future research efforts. ***(Pringsheim et al., 2014).***

Epidemiology

Worldwide incidence estimates of Parkinson disease range from 5 to >35 new cases per 100,000 individuals yearly, which probably reflects differences in the demographics of the populations studied or in study methods. In a population-based study in Minnesota (USA) with pathological validation of clinical diagnoses, the incidence of Parkinson disease was 21 cases per 100,000 person-years. Parkinson disease is rare before 50 years of age, but the incidence increases 5–10-fold from the sixth to the ninth decade of life. The global prevalence, conservatively

estimated at 0.3% overall, likewise increases sharply with age to >3% in those >80 years of age ***(Savica et al., 2013).***

Mortality is not increased in the first decade after disease onset, but increases thereafter, eventually doubling compared with the general population. Improvement in health care has led to longer survival, which is associated with increasing prevalence of Parkinson disease over time in one 20-year study. The number of people with Parkinson disease is expected to double between 2005 and 2030. Years lived with disability and disability-adjusted life years due to Parkinson disease increased between 1990 and 2010, and a progressive increase in the personal, societal and economic burden associated with the disease is expected in the future as the world population ages ***(Murray et al., 2012).***

Parkinson disease is twice as common in men as in women in most populations, although in a few populations, including one study from Japan, no difference or even a female excess was observed. A protective effect of female sex hormones, a sex-associated genetic mechanism might explain this male preponderance, although disparities in health care could also contribute ***(Pringsheim et al., 2014).***

The incidence of Parkinson disease is significantly greater in individuals exposed to certain environmental factors, such as pesticides and traumatic brain injury, and lower in smokers or caffeine users ***(Ascherio and Schwarzschild, 2016).***

Mechanisms/pathophysiology

Neuropathology

Characteristic features of Parkinson disease include neuronal loss in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation. Although neither the loss of pigmented dopaminergic neurons in the substantia nigra nor the deposition of α-synuclein in neurons is specific for Parkinson disease, these two major neuropathologies are specific for a definitive diagnosis of idiopathic Parkinson disease when applied together ***(Halliday et al., 2011).***

The dramatic loss of dopaminergic neurons is restricted to the ventrolateral substantia nigra with relative sparing of other midbrain dopaminergic neurons, but becomes more widespread by end-stage of the disease. Loss of these dopaminergic neurons even early in the disease suggests that the degeneration in this region starts before the onset of motor symptoms. ***(Dijkstra et al., 2014).***

The other required neuropathology is the abnormal deposition of α-synuclein in the cytoplasm of certain neurons in several different brain regions. Lewy bodies, which are largely made up of aggregated α-synuclein, were the first to be described over a century ago. The Lewy pathology initially occurs in cholinergic and monoaminergic brainstem neurons and in neurons in the olfactory system, but is also

found in limbic and neocortical brain regions with disease progression ***(Braak et al., 2003).***

Some of the proteins encoded by genes associated with Parkinson disease are involved in a set of molecular pathways that, when perturbed, can trigger a neuropathology that resembles, or is indistinguishable from, sporadic Parkinson disease. In addition, large genome-wide association studies (GWAS) confirm that some of these genes are also affected in sporadic Parkinson disease. Examples of these pathways are: α-synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, axonal transport and neuroinflammation ***(Nalls et al., 2014).***

Synuclein proteostasis

Intraneuronal protein aggregates that are largely made up of a-synuclein are found in all patients with Parkinson disease. Similarly, GWAS have revealed a single-nucleotide polymorphism associated with the *SNCA* locus that alters the risk for sporadic Parkinson disease and is associated with increased expression levels of a-synuclein. ***(Nalls et al., 2014).***

a-Synuclein acquires neurotoxic properties during a pathogenetic process in which soluble a-synuclein monomers initially form oligomers, then progressively combine to form small protofibrils and eventually large, insoluble a-synuclein

fibrils (that is, the aggregates that make up Lewy pathology) ***(Wales et al., 2013).***

Synuclein degradation

Several lines of evidence suggest that impairment of the degradation systems (Lysosomal autophagy system and ubiquitin–proteasome system) could contribute to a-synuclein accumulation. Increasing age the greatest risk factor for Parkinson disease is associated with reduced LAS and ubiquitin–proteasome system functions, which is consistent with observations of increased levels of α-synuclein in nigral dopaminergic neurons during normal ageing ***(Chu and Kordower, 2007).***

Prion-like propagation of α-synuclein

The prion-like hypothesis for a-synuclein posits that once a-synuclein aggregates have formed in a neuron, they can be transported intra-axonally to other brain regions, be released into the extracellular space, be taken up by neighbouring neurons and seed aggregation of endogenous a-synuclein once inside their new cellular host. Thus, initial a-synuclein misfolding in a small number of cells could progressively lead to the spread of a-synuclein aggregates to multiple brain regions over years or decades following the initial insult ***(Tyson et al., 2016).***

Mitochondrial dysfunction

Several lines of evidence have implicated mitochondrial dysfunction as a key element in the pathogenesis of Parkinson disease. An emerging picture is one of a vicious cycle in which a-synuclein aggregation and mitochondrial dysfunction exacerbate each other, which could explain why these cellular changes are observed together in degenerating neurons in Parkinson disease ***(Lamberts et al., 2015).***

Target genes are generally underexpressed in Parkinson disease. It has been proposed that low levels of a-synuclein are normally present in mitochondria, but that accumulation of the protein inside mitochondria leads to mitochondrial complex I deficits and oxidative stress. ***(Lamberts et al., 2015).***

Oxidative stress

Evidence that oxidative stress, as a consequence of mitochondrial dysfunction, is increased in the brain tissue of patients with Parkinson disease is compelling, but it is debatable whether it occurs early or late during the demise of neurons. Mutations in DJ-1 protein (also known as *PARK7*), The PARK7 gene provides instructions for making the DJ-1 protein. Studies indicate that the DJ-1 protein has several functions. One of the protein's functions may be to help protect cells, particularly brain cells, from oxidative stress, which cause early-onset autosomal recessive Parkinson

disease, are associated with increased cellular oxidative stress. Knocking out *Dj1* in mice results in increased protein oxidation in stressed nigral dopaminergic neurons ***(Di Nottia et al., 2016).***

Neuroinflammation

Neuroinflammation is probably an essential contributor to pathogenesis. Catecholaminergic neurons in the brain tissue of patients with Parkinson disease and cultured dopaminergic neurons (when exposed to activated microglia or l-DOPA) have been reported to be particularly inclined to express MHC class I proteins, which exposes them to cytotoxic T cell-mediated death if they present antigens ***(Schapansky et al., 2014).***

GWAS indicate that genes associated with the risk of developing Parkinson disease often encode proteins that are expressed in immune cells and that are involved in immune regulation, such as LRRK2 (which is involved in autophagy by immune cells). ***(Ma et al., 2016).***

Motor circuit pathophysiology

The motor circuit consists of corticostriatal projections from the primary motor cortex, supplementary motor area, cingulate motor cortex and premotor cortex, terminating on dendrites of striatal medium spiny neurons. The striatal projections to these output nuclei are divided into 'direct' and 'indirect' pathways ***(Tyson et al., 2016).***