



بسم الله الرحمن الرحيم

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**BASELINE PREDICTORS OF PROGRESSION OF
PARKINSON'S DISEASE IN A SAMPLE OF
EGYPTIAN PATIENTS; CLINICAL AND
BIOCHEMICAL**

Thesis

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LIST OF ABBREVIATIONS

| Abbr. | Full-term |
|-------------------|--|
| A β 42..... | β -amyloid 1–42 |
| ACE | Addenbrooke's cognitive Examination |
| AD..... | Alzheimer's disease |
| AIA..... | Autoimmune antibodies |
| ART | Akinetic rigid type |
| BBS..... | Berg Balance Scale |
| BDI | Beck depression inventory |
| BDNF..... | Brain-derived neurotrophic factor |
| CI..... | Cognitive impairment |
| CMA | Chaperone-mediated autophagy |
| CNS..... | Central nervous system |
| CSF | Cerebrospinal fluid |
| DA..... | Dopamine |
| DAT | Dopamine transporter |
| DATATOP | Deprenyl and tocopherol antioxidative therapy of parkinsonism |
| DDS..... | Dopamine dysregulated syndrome |
| DLB | Dementia of Lewy body |
| DT | Dopamine therapy |
| EMG | Electromyography |
| ENS..... | Enteric nervous system |
| FMRI..... | Functional magnetic resonance imaging |
| FOG | Freezing of gait |
| H & Y | Hoehn and Yahr |
| HDL..... | High density lipoprotein |
| HLA..... | Human leucocyte antigen |
| HSP..... | Heat-shock protein |
| ICSD | International Classification of Sleep Disorders |
| IGF-1 | Insulin growth factor -1 |

List of Abbreviations

| Abbr. | Full-term |
|------------------------|--|
| ILB | Incidental Lewy Body |
| IPAQ | International physical activity questionnaire |
| LAMP | Lysosomal- associated membrane protein |
| LC3-II | Light chain 3- II |
| LDH | Low density lipoproteins |
| LEDD | Levodopa equivalent daily dose |
| LRRK2 | Leucine-rich repeat kinase 2 |
| MAP | Microtubule-associated protein |
| MCI | Mild cognitive impairment |
| MDS | Movement Disorder Society |
| MDS-UPDRS | Movement Disorders Society-Unified Parkinson's Disease Rating Scale |
| M-EDL | Motor Aspects of Experiences of Daily Living |
| MJFF | Michael J. Fox Foundation |
| MMSE | Mini mental state examination |
| MoCA | Montreal Cognitive Assessment |
| MPP+ | 1-methyl-4- phenylpyridinium) |
| MPTP | 1-methyl-4-phenyl-1,2,5,6- tetrahydropyridine |
| MRI | Magnetic resonance imaging |
| MSA | Multiple system atrophy |
| NFOG-Q | New freezing of gait questionnaire |
| NM-EDL | Non-MotorAspectsofExperiencesofDailyLiving |
| NMS | Non-motor symptoms |
| NMSS | Non-motor symptoms scale |
| NSAID | Non- steroidal anti-inflammatory drugs |
| PD | Parkinson's disease |
| PDD | PD with dementia |
| PDQ-39 | Parkinson's disease questionnaire |
| PET | Positron emission tomography |

✍ List of Abbreviations

| Abbr. | Full-term |
|----------------------|---|
| PIGD | Postural instability and gait disturbance |
| PINK1 | PTEN-induced kinase 1 |
| PLMS | Periodic limb movement during sleep |
| PNS | Peripheral nervous system |
| PPMI | Parkinson's Progression Markers Initiative |
| PRECEPT | Parkinson Research Examination of CEP-1347 Trial |
| PSG | Parkinson Study Group |
| PSP | Progressive supranuclear palsy |
| P-tau | Phosphorylated tau protein |
| PVHs | Periventricular hyperintensities |
| QoL | Quality of life |
| RBD | REM sleep behavior disorder |
| REM | Rapid eye movement |
| SNCA | Alpha synuclein gene |
| SNpc | Substantianigra pars compacta |
| SPECT | Single-photon emission CT |
| STN | Sub-thalamic nucleus |
| TD | Tremor dominant |
| TDS | Transcranial sonography |
| t-tau | Tau protein |
| TUG | Time up and go |
| UCH-L1 | Ubiquitin C-terminal hydrolase |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| UPS | Ubiquitin-proteasome system |
| VPS32 | Vacuolar protein sorting-associated protein 32 |
| WCST | Wisconsin card sorting test |
| WMHL | White matter hyperintensity lesions |
| WMS | Wechsler Memory Scale |

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ABSTRACT

Background: Clinical progression of Parkinson's disease (PD) is highly heterogeneous, and its predictors are generally lacking. Identifying predictors of early disease progression is important for patients' management and follow-up. The current study aims to identify clinical, neuroimaging and biochemical baseline predictors of motor progression in patients with PD. Forty-five PD patients were assessed at baseline, 6 months and 1 year using MDS-UPDRS total and subscores, Hoehn and Yahr (H&Y), Schwab and England (S&E), International Physical Activity Questionnaire (IPAQ). Baseline New Freezing of Gait Questionnaire (NFOG-Q), Berg Balance Scale (BBS), Ten-Meter Walking Test (10-MWT), and Time Up and Go Test (TUG), Non-Motor Symptoms Scale (NMSS), Beck Depression Inventory (BDI), PD questionnaire 39 (PDQ-39), MRI brain, uric acid, lipid profile and glycated hemoglobin were performed. **Results:** Significant worsening of MDS-UPDRS total, part III scores, H&Y, S&E and IPAQ ($p < 0.001$) was detected. One-year progression of H&Y and S&E were significantly correlated to disease duration ($p = 0.014$, $p = 0.025$, respectively). Progression of H&Y was correlated to baseline TUG ($p = 0.035$). S&E progression was correlated to baseline MDS-UPDRS total score ($\rho = 0.478$, $p = 0.001$) and part III ($\rho = 0.350$, $p = 0.020$), H&Y ($\rho = 0.401$, $p = 0.007$), PIGD ($\rho = 0.591$, $p < 0.001$), NFOG-Q ($\rho = 0.498$, $p = 0.001$), and TUG ($\rho = 0.565$, $p = 0.001$). Using linear regression, there was no predictors of clinical progression among the used baseline variables. **Conclusion:** Despite the significant motor and physical activity progression over 1 year that was correlated to baseline motor and gait severity, but without predictive value, further similar and longitudinal studies are warranted to detect predictors of early progression and confirm findings.

Keywords: Parkinson's disease, Predictors, Progression, Egyptian, COVID-19

INTRODUCTION

Parkinson's disease (PD) is the most common movement disorder besides essential tremor and the second most common neurodegenerative disease (*Tanner & Aston, 2000*). Egypt has higher prevalence of PD about 35 in 100000 as was studied previously (*Khedr et al., 2015*).

The prevalence of PD in industrialized countries is generally estimated at 0.3% of the entire population and about 1% in people over 60 years of age (*De Lau et al., 2006*). The prevalence increases with advancing age both for men and women ages (*De Rijk et al., 1997*). In Europe, the prevalence at ages 85–89 has been reported as 3.5% (*Sveinbjornsdottir, 2016*).

Braak and his colleagues had mapped PD into six neuro-pathological stages. In the pre-symptomatic stages of the disease (stages 1–2), the inclusion bodies are confined to the medulla oblongata/pontine tegmentum and olfactory bulb/ anterior olfactory nucleus. With progression of the disease, substantia nigra and other nuclei of the midbrain and forebrain become affected (stages 3–4). It has been suggested that patients develop clinical symptoms of the disease at this stage. In the end stage (stage 5–6), the process enters the neocortex with a wide variety of clinical manifestations (*Braak et al., 2003*).

Most studies on the annual rate of changes of motor symptoms in early PD show large inter-individual variation, even in the first year of observation, pointing towards different progression trajectories (*Simuni et al., 2018*). Therefore, indicators for disease progression are warranted. Currently, as reported in smaller studies with a small number of parameters, the most important predictors for worse motor progression are age and motor disability at baseline (*Vu et al., 2012*). Recent findings suggest that cardiovascular risk factors such as diabetes mellitus, cigarette smoking, arterial hypertension, high cholesterol, and obesity contribute to a more severe PD phenotype, but a multimodal approach is lacking (*Malek et al., 2016*).

In general, biomarkers are classified into different types according to their intended use. Early diagnostic biomarkers can be useful to recognize PD before motor features become evident or when motor or non-motor signs or both are still insufficient to define disease. Diagnostic markers could also help to differentiate PD from other parkinsonian syndromes, as misdiagnosis often takes place early in the disease and diagnostic confirmation needs autopsy reports. The difficulty in identifying early diagnostic criteria for PD depends on the fact that no real biomarker can yet predict illness onset (*Cova & Priori, 2018*).

CSF biomarkers in PD, such as α -synuclein and neurofilaments and advanced neuroimaging have been

suggested as potential biomarker for PD, however their invasiveness and unavailability in several countries especially developing countries limit its use (*Parnetti et al., 2019*).

Therefore, investigating the available laboratory tests and MRI brain basic findings is more feasible and require further research. Previous cross section study showed promising findings of assessing serum α -synuclein autoantibodies in patients with PD, however no studies examined its predictor value of disease progression (*Shalash et al., 2017*).