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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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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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Contents

List of Abbreviations

Abbr.	Full-term
Aβ42.....:	β-amyloid 1–42
ACE .....:	Addenbrooke's cognitive Examination
AD.....:	Alzheimer's disease
AIAs.....:	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

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- etrahydropyridine
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

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).***