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Assessment of mitochondrial dynamics in Parkinson's disease patients by Drp1 quantitative gene expression analysis: For the development of a non-invasive approach

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ABSTRACT

Neurons rely substantially on the activity of mitochondria to establish membrane excitability to conduct the complex processes of neurotransmission and plasticity. Evidence from Parkinson's disease (PD) brain samples suggested that mitochondrial dysfunction is a key contributor to dopaminergic neuronal loos in PD patients. Further, imbalance in the mitochondrial dynamics leads to elevated levels of reactive oxygen species (ROS), reduction in mitochondrial membrane potential and increased accumulation of defective mitochondria leading to neuronal death in PD patients. Hence, identifying this intricate molecular network and discovering the elements that regulate mitochondrial dynamics remains a precedence and a major challenge for further research. One of major element of mitochondrial dynamics is the dynamin-related protein 1 (Drp1) considered as master regulator of mitochondrial fission. Drp1 was discovered as a crucial player of mitophagy contributing to dopaminergic neurodegeneration in PD models. Hence, to disclose the importance of Drp1, this study was undertaken to develop a non-invasive diagnostic approach to uncover the mitochondrial dynamics that links Drp 1 to PD pathogenesis in clinical samples.

The results from this study reported that there is a significant increase in the expression of Drp1 gene in circulation of PD patients when compared to controls. The data from this study in future might help in early diagnosis of PD and further helps to design the precise therapeutic strategies to prevent neurodegeneration.

Keywords: Parkinson's disease, mitochondrial dynamics, dopaminergic neurons, Dynamin-related protein 1

INTRODUCTION

PD is a progressive degenerative neurological condition attributed to the loss of dopaminergic neurons with Synucleinopathy [1, 2]. The accumulation of α-synuclein disrupts the neural membrane and causes oxidative stress, energy depletion, inflammation, and exocytotoxicity leading to neuronal cell death [3]. Due to delayed attention to the associated symptoms, majority of the PD cases are diagnosed in advanced stages when there is significant dopaminergic neuronal loss in nigrostraiatum [4- 7]. Currently, the detection of α-synuclein in the pathological sections of the post-mortem brain is considered the most reliable method for the diagnosis of PD [8, 9]. However, the examination of the post-mortem brain fails to elucidate the exact cause of the disease. During the early onset of PD, sleep disorders and various biological alterations frequently manifest years before the onset of motor deficits and correlate with the emergence and progression of PD [10]. Thus, the identification of precise cellular and molecular signaling pathways is crucial for developing early diagnosis, prognosis, and management approaches for PD.

Available evidences suggest that mitochondria dysfunction is a major threat in the emergence of neurological disorders including PD [11]. Mitochondrial dysfunction worsens the pathology of PD and contributes towards neuronal cell death due to defects in mitophagy and loss of mitochondrial function [12]. It has been reported that altered mitochondrial fission can result in defective mitophagy leading to the degeneration of dopominergic neurons in PD [13]. As an initial response to cellular damage mitochondrial fission gets increases [14] and impaired daughter mitochondria with pathological stimuli fail to carry out the essential biological functions in neural cells and

triggers the pathways involving mitophagy, necroptosis, and neuronal apoptosis [15,16]. Thus, the structure and function of mitochondria needs a balance between the process of synthesis and division to maintain the mitochondrial integrity [17].

Among different regulators, Drp1 plays a crucial role in controlling the mitochondrial fission process along with the Fission 1 protein (Fis1) [18, 19]. It has been reported that hyper-activated Drp1 results in increased mitochondrial fission in neuronal death or mitophagy [20]. A recent preclinical study has demonstrated that altered mitochondrial dynamics due to Drp1 is a significant neuropathological factor in α-synucleinopathies [21]. Another study has reported that suppression of Drp1 helps the mitochondrial homeostasis in PD [22]. Hence, assessing the expression of Drp1, the master regulator driving mitochondrial fission PD patients may provide a newe insights for developing effective diagnosis, prognosis, and treatment modalities. The available studies provide insights into the functional properties of mitochondria through the isolated mitochondria from tissues and cells in culture [23- 25]. However, very limited knowledge exists about the mitochondria that are present in extracellular fluids, specifically in circulation. The preclinical and few clinical studies have demonstrated the secretion of mitochondria into the extracellular milieu as an important process for exchanging different molecular components with cells of the central and peripheral nervous system [26- 29; 23]. It has been demonstrated that mitochondrial dysfunction is influenced by mitochondrial DNA damage, diminished mitochondrial activity, decline in mitochondrial RNA transcripts, and decreased translation [30]. Thus, assessing the functionality of mitochondria in the circulation might reflect the intracellular metabolism and may indirectly measure the intrinsic tissue metabolic integrity [31, 32]. In this study, we quantitatively evaluated the expression of Drp1 protein in plasma samples to predict mitochondria quality control and to explore its potential usability in early non-invasive diagnosis of PD patients.

MATERIALS AND METHODS

The study was conducted at Department of Neurology, Owaisi hospital and Research center, Deccan College of Medical Sciences. Necessary approvals for the protocols were obtained from Institutional Review board. Samples were collected from eligible participants attending the Out-

Patient Department of Neurology at Owaisi hospital and research. Signed informed consent forms were taken from each study participant prior to the collection of their samples.

Study population and sample collection

The study population consisted of 50 individuals (age 40-70), 25 were clinically proved PD patients and 25 Healthy controls. Clinical assessment was done by Neurologist. Clinical and demographic details were obtained in the proforma and peripheral blood sample of 3ml was collected.

The collected sample was incubated for 15 min at room temperature, following which it was centrifuged at 3000rpm to obtain serum. Separated serum was processed within 4 hours for mitochondrial extraction.

RNA extraction from Plasma and *c*DNA synthesis

Total RNA was extracted from plasma using the TRIzol reagent method (TRIzol™ Reagent, Catalog #: 15596026, Thermo Fisher) as described earlier [33]. *c*DNA synthesis was performed using 1 µg of total RNA and oligo (dT) primers. Briefly, 2 µL of oligo-dT was added to 16 µL of RNA sample, and the mixture was incubated at 65°C for 10 min in a thermal cycler. Following incubation, the reaction was subjected to 2 min of snap cooling to prevent RNA strand renaturation and hairpin loop formation. To this mixture, 8 µL of 5X RTase buffer, 2 µL of 10 mM dNTPs, 0.5 µL of RTase enzyme (5 U/µL, Fermentas), and 11.5 µL of water were added to achieve a final reaction volume of 40 µL. Finally, the *c*DNA amplification was achieved by sequential incubation at 42°C for 45 min, followed by 70°C for 15 min, and then cooled to 4°C. To verify the amplification, 5 µL of the final product was mixed with 5 µL of 1X DNA loading dye and loaded onto a 0.8% agarose gel. The amplified products were observed under UV light using a BIORAD Gel Documentation System.

Quantitative analysis of Drp1 in circulating mitochondria

*c*DNA from all samples was quantified using a NanoDrop spectrophotometer, and 5 ng of *c*DNA from each sample was utilized for quantitative RT-qPCR (CFX96, ABI 7500, Applied Biosystems) based on SYBR Green assay for selected gene Drp1 (FP: 5'- CAAAGCAGTTTGCCTGTGGA-3'; RP: 5'-TCTTGGAGGACTATGGCAGC-3'). The reaction mixture for all the primers was

prepared by adding 10 μL of 1X SYBR Green mix, 0.5 μL of 10 pmol/μL forward primer, 0.5 μL of 10 pmol/μL reverse primer, 2 μL of cDNA template, and 7 μL of deionized water (dH2O). The reaction conditions were optimized according to the melting temperature (Tm) of each primer, with the following steps: an initial denaturation at 94°C for 5 min, followed by 40 cycles of denaturation at 94°C for 30 sec, annealing at 50°C–60°C for 40 sec, and extension at 72°C for 40 sec. A final denaturation step was performed at 72°C for 5 min, followed by melt curve analysis for 15 min. To normalize the test samples, 12s primer (FP: 5'-GCTCGCCAGAACACTACGAG-3'; RP: 5'-CAGGTTTGCTGAAGATGGCG-3') was used as an endogenous control. Ct values of each sample were noted and utilized in statistical analysis to determine the fold difference. Each reaction was conducted in duplicate triplicates to reduce technical errors.

Statistical analysis

The data in this study are presented as mean ± standard deviation (SD). All statistical analyses and figures were generated using GraphPad Prism 8.4.2 (GraphPad Software Inc.). A Student's t-test was used to evaluate statistical significance between two variables.

RESULTS

Imbalance in the mitochondrial dynamics was found to be associated with the PD pathogenesis. Studies have reported the association of mitochondrial fragmentation in various PD cellular models [34]. So far, no study has demonstrated the significance of mitochondrial fragmentation in PD clinical samples. Hence, in this study for the first time we tried to tackle the importance of mitochondrial fission at molecular level for PD prognosis through the assessment of Drp1 gene expression.

Quantitative distribution of Drp1 relative expression levels

Our analysis (quantitative) showed a significant up regulation of circulating Drp1 in PD patients in comparison to the healthy controls with mean difference -3.944 ± 1.216; $p < 0.005$; Fig. 1). The relative (mean ± SD) expression of Drp1 was found 5.454 ± 3.281 in patients and 1.510 ± 1.359 in controls.

DISCUSSION

Currently, neuropathology and clinical criteria are employed for the PD diagnosis. These available diagnostics can only be employed at later stages of the disease onset [35, 36]. Hence, there is a need to identify an efficient non-invasive prognostic method for early detection of PD onset to design better pharmacological treatments. Researchers have demonstrated that molecular diagnostic signatures in the blood can help in early diagnosis of PD overcoming the existing limitations [36]. Several studies reported the association of mitochondrial dysfunction in PD [37-40]. Hence, the current study aimed to find out the mitochondrial dysfunction in circulation of PD patients based on Drp1 gene expression.

Mitochondria, being dynamic structures, maintain their cellular homeostasis by coordinated process of fission and fusion. Any imbalance in the mitochondrial dynamics affects cellular bioenergetics resulting in the severe pathological conditions [41, 42]. Studies which demonstrated that Neurotoxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) causes bradykinesia, rigidity and tremors in drug addicts, shows that there is a clear association between mitochondrial dysfunction and PD [43]. Prior to the neuronal loss mitochondrial dysfunction was found to be as an early indicator of PD onset [44]. The mitochondrial complex I blockers and Parkinson's phenotype-inducing drugs promotes mitochondrial fission leading to impaired neuronal signaling in PD [45, 46].

As an initial response to cellular damage mitochondrial fission gets increases [14]. Impaired daughter mitochondria with pathological stimuli fails to carry out the essential biological functions in neural cells and triggers the pathways involving mitophagy, necroptosis, and neuronal apoptosis [15, 16]. In PD, inadequate clearance of these defective mitochondria results in the increased ROS levels and subsequent dopaminergic neuronal loss [13]. Further, deregulation of mitochondrial fission results in hampered metabolic homeostasis [47], abnormal brain formation [48], cardio vascular diseases (CVD) [49] and in the development of carcinoma [50].

Dynamin-related proteins belonging to guanosine triphosphatase (GTPase) strictly regulates the process of mitochondrial fission [51]. Additionally, neurodegenerative diseases like Alzheimer's Dementia, amyotrophic lateral sclerosis (ALS), Huntington's Disease and PD were found associated with Drp 1 dysfunction [52- 54]. Earlier study has reported that hyper activated Drp1

resulted in the increased mitochondrial fission, promoting either mitophagy or neuronal demise [20]. Research findings demonstrated that inhibition of Drp1-mediated fission improved the mitochondrial functioning in sporadic PD [34]. Another study reported that blocking of Drp1 expression in PTEN-induced putative kinase-1 deletion (PINK1$^{-/-}$) and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse models can be a potential treatment approach for PD to restore dopamine release [55].

However, less is known about the dysfunctional mitochondria that are present in extra cellular fluids in circulation. Recently, a growing body of data suggests that active mitochondria are released into extracellular fluid and functions as non-cell-autonomous signals in CNS pathology [23]. Hence, assessing the functionality of mitochondria in extracellular fluids might reflect the intracellular metabolism and serves as an indirect measure of intrinsic tissue metabolic activity [31, 32].

Hence, the current study assessed the expression of Drp1 in plasma of PD patients. The results obtained from the quantitative expression analysis of Drp1 demonstrated a significant increased expression of circulating Drp1 in PD patients when compared with the healthy control subjects (**p=0.001). These results demonstrate that the non-invasive method of monitoring Drp1 expression can help in the early diagnosis of PD and the development of therapies necessary to avert the PD'S further progression. Further, the data obtained from this study can provide insights to develop a non-invasive Drp1 based biomarker in PD patients when studied in a larger population.

CONCLUSION

Currently, there are no available treatments that can prevent the PD progression or alleviate existing deficits. Since, mitochondrial dysfunction is playing an important role in PD progression, understanding the mitochondrial dynamics might reveal the machinery involved in PD pathogenesis. This preliminary investigation showed that analyzing the quantitative expression of Drp1 in the PD patients plasma might have a substantial prognostic significance for PD diagnosis. Additionally, it could make it easier to identify PD individuals who are presymptomatic and could benefit from treatment with neuroprotective agents.

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FIGURE

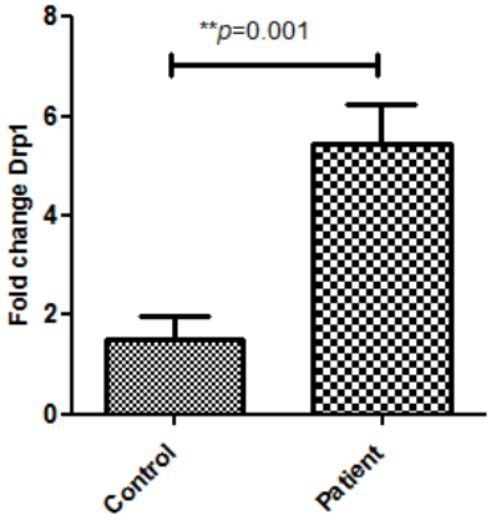

Figure 1: Relative gene expression analysis of Drp1: The relative gene expression of Drp1 was found significantly higher in PD patients when compared to healthy controls (**$p < 0.005$)