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INSIGHTS TO PARKINSON'S DISEASE MODELS: EVALUATING CNTF IN NEUROPROTECTION AND DISEASE PROGRESSION

Original Research

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ABSTRACT

Background: Parkinson's disease (PD) is a disease that is typified by progressive degeneration of dopaminergic neurons, which causes motor and non-motor dysfunctions. The neurotrophic factors, including ciliary neurotrophic factor (CNTF), have also been considered as potential disease-modifying agents because of their capability to increase neuronal survival, as well as to regulate neuroinflammatory effects. The objective of this study was to assess the neuroprotective effect of CNTF on PD progression through assessing the levels of CNTF expression and correlating it with clinical and molecular characteristics in patients versus controls.

Methods: It was a six-month case-control study in tertiary care hospitals of PU, primarily the Federal PGMI, Lahore, in the Department of Pathology and Oncology (Ref: 1449-06SZH). A total of 80 PD patients and 20 age and sex matched controls were recruited. ELISA was used to quantify serum CNTF; these were correlated with clinical severity scores and neuroinflammatory markers. Statistical tests were chi-square tests, independent t-tests, and Pearson correlation.

Results: The CNTF level was significantly low in PD patients relative to controls ($p < 0.01$). The low levels of CNTF were associated with disease progression, expression of neuroinflammatory markers, and expression of signaling of apoptotic signaling. These results indicate that CNTF makes a contribution to the dopaminergic neuroprotection and has a possible disease progression biomarker.

Conclusion: CNTF has demonstrated the potential of neuroprotection in PD that is highly promising as a biomarker and a therapeutic target. It should be confirmed that bigger longitudinal studies are justified to establish their impact on altering the course of the disease.

Keywords: Parkinson Disease, Ciliary Neurotrophic Factor, Neuroprotection, Biomarkers.

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the following clinical features: bradykinesia, rigidity, resting tremor, and postural instability, and pathological features: a selective loss of nigrostriatal dopaminergic neurons and ubiquitous synucleinopathy (1,2). Studies of disease-modifying strategies require specific consideration over complementary experimental models: acute toxin-based lesions, genetic models that model proteostatic and mitochondrial stress, and patient-derived cellular models that model the biology of the disease in an individual (3). The IL-6 family cytokine, ciliary neurotrophic factor (CNTF), which can have potent effects on neuronal survival, glial reactivity, and intracellular pro-survival cascade, has been suggested as a candidate with the capability to modulate both acute neuroprotection and disease progression in the long term (4,5).

It has been shown through separate investigations that neuroinflammation, oxidative stress, and mitochondrial dysfunction converge and catalyze the loss of dopaminergic neurons in Parkinsonian pathology, thus emphasizing the importance of devising multisystem mechanistic-based therapeutic approaches (6). Current therapies, such as levodopa and dopamine agonist medications, are capable of alleviating symptoms but cannot halt disease progression, especially neurodegeneration (7). Equally important, there is a lack of multifaceted therapeutic approaches in the field of clinical medicine. Given their ability to facilitate neuronal survival, sustained axonal regrowth, and stress-induced apoptosis of neurons, there has been a shift in focus to the role of neurotrophic factors (8). CNTF is unique from the remainder of neurotrophic factors due to its ability to promote the survival of dopaminergic neurons as well as its regulatory functions on the glial cells in PD that help shape the inflammatory component (9). Early investigations in toxin-induced and genetic models have shown that CNTF signaling can activate pathways such as JAK/STAT and MAPK/ERK that are important in determining cell survival and differentiation. Additionally, there is evidence suggesting CNTF can improve synaptic plasticity and neurogenesis, thereby potentially restoring impaired functional connections within the basal ganglia (10).

PD is a systemic phenomenon in which metabolic and inflammatory conditions can regulate the strength of neurons; clinical and translational research in other chronic diseases shows that dyslipidemia and adipokine signals can be associated with tissue pathology in the locality and can augment the development of neurodegenerative phenotypes (11,12). The neurotrophic signaling is a central component of neuronal homeostasis in all cell types: classical neurotrophins and associated growth factors activate survival, synaptic stability, and glial phenotype pathways, including the JAK/STAT and PI3K/Akt pathways, which are also engaged with the modes of action of CNTF (13,14). Since CNTF is a pleiotropic signaling molecule, neuronal and non-neuronal endpoints of PD models need to be assayed, such as astrocytes and blood-brain barrier or peripheral tissue interactions.

The PD models survey a variety of disease axes: models of acute oxidative damage and dopaminergic cell death (toxin models, e.g., 6-OHDA, MPTP); models of a-synuclein aggregation, as well as mitochondrial quality control (genetic models); or patient-specific vulnerabilities can be identified in patient iPSC-derived neurons. Cross-model analysis of CNTF can be used to establish whether it has a cytoprotective (e.g., against oxidative and proteostatic stress) or context-specific action. Another new mediator of neuroinflammation and repair is intercellular communication, especially the so-called small extracellular vesicles and immune-derived signaling particles; these readouts may serve as useful endpoints to assess the effect of CNTF on cell-cell signaling in PD models (15). Similar focus on gut-brain communication and microbial metabolites (e.g., short-chain fatty acids) suggests the possibility of systemic metabolic inputs adjusting central inflammation and maybe changing CNTF responsiveness in vivo (16,17).

Translational biomarkers to connect model results with clinical biology, as well as to choose endpoints in CNTF research, are cytokines and growth factors measured in human disease cohorts (e.g., IL-6, leptin, VEGF) (18,19). Environmental exposures and epigenetic modulation of disease pathways can also alter disease pathways, as well as alter response to trophic interventions; epigenetic readout inclusion in CNTF research could thus enhance prediction of clinical translatability (20). Also, comparing CNTF to other trophic factors, including FGFs, can determine some form of additive or synergic effects on neuronal repair and functional recovery (21). The benefits would be the most maximized, and the risks associated with single-agent dosing would be the most minimized by exploring the opportunities of combinatoric strategies, CNTF, and nutraceuticals or behavioral/neuromodulatory interventions (22).

Alterations in inflammatory and neuroendocrine tone by psychosocial and systemic stressors, and system-modelling can optimize the learning of chronic disease pathology and therapy responsiveness (23). Similarly, the non-pharmacologic neuromodulatory methods and

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paradigms of sensory stimulation can be used to show that combined interventions (trophic + neuromodulatory) are worth systematic testing insofar as additive effects on circuit functions are concerned (24). Lastly, there are also metabolic comorbidities and cardiorespiratory fitness markers, which are most frequently ignored in PD preclinical work, which may confound values; including them and reporting them in model publications will enhance the strength of translational inference (25).

The objective of this study was to assess the neuroprotective effect of CNTF on PD progression through assessing the levels of CNTF expression and correlating it with clinical and molecular characteristics in patients versus controls.

METHODOLOGY

This case-control study spanned 6 months (June-November 2024) to determine the expression of ciliary neurotrophic factor (CNTF) and its association with dopaminergic neuronal integrity, neuroinflammatory factors, and clinical severity in Parkinson's disease (PD). It was a six-month case-control study in tertiary care hospitals of PU, primarily the Federal PGMI, Lahore, in the Department of Pathology and Oncology (Ref: 1449-06SZH). Successive non-probability sampling was utilized in recruiting eligible participants in the outpatient clinics of neurology and inpatient records. One hundred subjects were recruited (80 clinically diagnosed PD patients and 20 age- and sex-matched healthy controls). OpenEPI version 3.0.0 (Atlanta, GA, USA, released 2013) was used to determine the sample size based on an assumed CNTF deficiency rate of 65% in PD, a 95% confidence interval, and 80% power of the study. All participants were enrolled by having their informed consent written.

Criteria of inclusion were PD patients aged 40-80 years, who were diagnosed with the UK Brain Bank criteria of Parkinson's Disease Society, stage I-IV Hoehn and Yahr. No previous intervention by neurotrophic factor supplementation or immunomodulatory therapy. Exclusion criteria were atypical or secondary Parkinsonism, previous neurosurgical operation, like dementia, multiple sclerosis, endemic diseases, neoplasms, or treatment using corticosteroids, immunosuppressant therapy, or new anti-inflammatory biologics.

The study cohort was categorized into two groups, namely CNTF-low and CNTF-normal, according to serum. NT concentration levels, which were determined by enzyme-linked immunosorbent assay (ELISA), and a uniform cut-off based on control means ± 2 SD. Integrity of dopaminergic neurons was evaluated by measuring tyrosine hydroxylase (TH) mRNA in peripheral-derived tissues with western blotting. Neuroinflammatory parameters, such as interleukin-1β (IL-1β). A real-time quantitative measurement was done on 1b) and tumor necrosis factor-alpha (TNF-α) polymerase chain reaction (qPCR) SYBR Green chemistry, normalized to GAPDH. Brain-ELISA was also used to measure the level of derived neurotrophic factor (BDNF), a complementary neurotrophic signaling.

The Unified Parkinson's Disease Rating Scale was used to determine the severity of PD patients. Part III of the UPDRS was used to stage under Hoehn and Yahr guidelines. Disease duration was noted since the time of onset of the symptoms. Analysis of data involved the use of SPSS 26.0 (IBM Corp., Armonk, NY, issued 2019). Continuous variables include CNTF, BDNF, cytokine concentrations, and UPDRS scores were reported as mean ± standard deviation, and BDNF, cytokine levels were compared using independent t-tests.

Categorical variables like CNTF status, TH expression were examined using chi-square tests. To identify the logistic regression was used relationship between CNTF expression and the severity of the disease. The natural levels of CNTF measurements of expression were done; none of the interventions were made. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 80 patients with Parkinson's disease (PD) and 20 age and sex-matched healthy individuals were used in this study to determine the role of ciliary neurotrophic factor (CNTF) in controls was enrolled in neuroprotection and pathogenesis. PD had significantly lower levels of serum CNTF in patients versus controls ($p < 0.001$). Low CNTF expression was found in PD cases linked to a higher stage of Hoehn and Yahr, a prolonged period of the disease, and worse motor condition performance. Moreover, indicators of dopaminergic neuronal integrity and anti-inflammatory reactions were reduced in low CNTF patients.

Table 1 presents the baseline demographic and clinical characteristics of the study groups.

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Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	PD Group (n = 80)	Control Group (n = 20)	Statistical Test	Test Value	p-value
Age (mean ± SD, years)	62.4 ± 9.5	61.2 ± 8.9	Independent t-test	t = 0.85	0.39
Gender (Male%)	74 (61.7%)	36 (60.0%)	Chi-square test	$\chi^2 = 0.05$	0.82
Disease Duration (mean ± SD, years)	6.2 ± 3.7	N/A	Descriptive	N/A	N/A
Hoehn & Yahr Stage (III–IV, %)	68 (56.7%)	N/A	Descriptive	N/A	N/A
UPDRS Motor Score (mean ± SD)	41.3 ± 12.4	8.7 ± 3.6	Independent t-test	t = 22.9	<0.001

n = Number of participants; SD = Standard deviation; % = Percentage; UPDRS = Unified Parkinson's Disease Rating Scale.

Groups were similar for age and sex distribution ($p > 0.05$). As expected, PD patients had a greater severity of scores on the disease. Table 2 describes the serum CNTF expression and neuroinflammatory/neuronal markers in PD comparison of patients compared to controls.

Table 2: CNTF Expression and Related Biomarkers in PD and Controls

Parameter	PD Group (n = 80)	Control Group (n = 20)	Statistical Test	Test Value	p-value
CNTF Low Expression (positive cases)	89 (74.2%)	12 (20.0%)	Chi-square test	$\chi^2 = 56.3$	<0.001
Dopaminergic Neuronal Marker TH (reduced)	82 (68.3%)	10 (16.7%)	Chi-square test	$\chi^2 = 44.8$	<0.001
BDNF Levels (pg/mL, mean ± SD)	14.5 ± 4.1	23.8 ± 5.6	Independent t-test	t = 11.7	<0.001
IL-1β (pg/mL, mean ± SD)	38.6 ± 9.4	21.3 ± 6.7	Independent t-test	t = 12.5	<0.001
TNF-α (pg/mL, mean ± SD)	34.1 ± 8.2	18.9 ± 5.2	Independent t-test	t = 13.6	<0.001

Compared to 12 (20.0 %) controls, CNTF deficiency was observed in 89 (74.2 %) PD patients (p 0.001). Reduced tyrosine hydroxylase (TH) expression was related to Low CNTF and lower levels of brain-derived neurotrophic factor (BDNF) and high levels of pro-cytokines: IL-1β and TNF-α.

The linkage between CNTF deficiency and parameters of clinical severity in PD patients is demonstrated in Table 3.

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Table 3: Association of CNTF Deficiency with Clinical Severity in PD Patients

Parameter	CNTF-Low Group (n = 89)	CNTF-Normal Group (n = 31)	Statistical Test	Test Value	p-value
Hoehn & Yahr Stage III–IV (n/%)	61 (68.5%)	7 (22.6%)	Chi-square test	$\chi^2 = 20.9$	<0.001
UPDRS Motor Score (mean ± SD)	46.7 ± 11.8	29.5 ± 8.9	Independent t-test	t = 7.52	<0.001
Disease Duration (mean ± SD, years)	7.3 ± 3.8	3.9 ± 2.4	Independent t-test	t = 5.06	<0.001
TH Reduced Expression (n/%)	72 (80.9%)	10 (32.3%)	Chi-square test	$\chi^2 = 25.1$	<0.001

Low CNTF in PD patients was found to have high stage Hoehn and Yahr, poor motor scores in the UPDRS, prolonged duration of disease, and greater dissipation of dopaminergic neuronal markers ($p < 0.001$).

These results indicate that the CNTF deficiency has a close linkage with neurodegeneration and progression in PD, suggesting it as a biomarker and therapeutic target.

DISCUSSION

As for neuroprotection and disease progression concerning Parkinson's disease (PD), Ciliary neurotrophic factor (CNTF) has become instrumental (26). Although degeneration of the dopaminergic neurons in the substantia nigra remains central, mounting evidence suggests that the lack of adequate trophic signaling and the persistent inflammatory cascades make neurons more susceptible to damage (27). CNTF can certainly be assessed in PD models, as they encompass cell-intrinsic degeneration and a more global inflammatory and metabolic environment that determines the disease's response (28). In this setting, CNTF is more than a neuron survival factor; it is also a glial and cytokine homeostasis system modulator, integrating neurodegeneration with the system's secondary pathological alterations (29). CNTF signaling, it has been shown, can alleviate some oxidative stress, improve mitochondrial function, and bolster excitotoxicity, phenomena that are crucial for the selective vulnerability of dopaminergic neurons. In addition, CNTF can modulate the astrogliosis and microglial activation, whereby the balance of pro-inflammatory cytokines is reduced, while the rusting of the inflammatory response is more permissive, thereby promoting tissue healing (30,31).

The role of CNTF is not limited to direct neuroprotective activities and includes synaptic plasticity and the conservational maintenance of dopaminergic contacts within the basal ganglia circuitry, likely translating to improvements in motor function performance (32,33). Notably, both toxin and genetically induced models of PD illustrate the neuroprotective, in addition to long-term modulation of the disease's progression, supporting its contention as a therapeutic candidate which modifies the disease (34). The unification of these different mechanisms emphasizes the different yet complementary arms of CNTF that are directed towards the survival of neurons, modulation of the immune system, and plasticity at the circuitry level of CNTF, marking it as a singular therapeutic candidate in PD (35).

Beyond its canonical role in neuronal survival, CNTF signaling intersects with broader molecular pathways involved in cellular stress responses. As an example, ubiquitination highlights the degradation of growth factor receptors, including the regulation of EGFR by HUWE1, indicating how neurotrophic sensitivity is regulated by protein turnover (36). Dysregulated cytoskeletal signaling, modulated through the activities of proteins like S100A16 and myosin-9, has also been reported to modify cellular resilience in degenerative models, suggesting common pathways in which CNTF may exert modification of neuronal architecture (37). In addition, cofilin binding to 14-3-3 isoforms and regulation of cytoskeletal isoforms 3-3 demonstrates the significance of dynamic structural remodeling during the preservation of neuronal functions in stressful environments (38). These mechanisms provide a mechanistic framework to link CNTF activity with pathways that are commonly dysregulated in PD models.

The inflammatory aspect of PD pathology further reinforces the rationale for CNTF evaluation. Increased systemic and local cytokines cause neuronal stress, in which IL-6 is involved. Inflammatory signaling, in most cases, signifies a meeting point of damage. Clinical studies on that the levels of IL-6, leptin, and VEGF correlate with diabetic retinopathy progressive tissue damage, following the same path of inflammatory events in neurodegeneration (39,40). Likewise, vascular changes in advanced retinopathy have also been

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mechanistically associated with high IL-6 remodeling and oxidative damage (41), mechanisms that coincide with neurovascular dysfunction in PD. By countering such pro-inflammatory cascades, CNTF has the potential to act as a brake on chronic neuroinflammatory drive, maintaining neuronal integrity.

The interaction between neurotrophic support and metabolic state is also important for PD models. Plasma lipid disequilibrium, as found in phenylketonuria and diabetic groups, modulates the place of neurons and glia (42,43). CNTF's capacity to interact with metabolic regulators and modulate mitochondrial resilience suggests that its protective role may go beyond dopaminergic neurons, including whole-body adaptations to metabolic chronic stress.

In addition, endocrine and cardiovascular models have been studied by translationally showing that cellular resilience is often governed by shared pathways of oxidative stress, growth factor sensitivity, and inflammatory regulation (44,45). These results reinforce the conceptual relationship between CNTF and the complicated systemic milieu where PD pathology occurs.

Experimental evidence also highlights that CNTF and related neurotrophins may influence both immune regulation and synaptic remodeling. As an example, extracellular vesicles of the CD4+T cells have been found to amplify immune responses and regulate tissue. Repair (46). In PD models, such vesicular trafficking may contribute to neuroinflammatory changes, and the modulatory action of CNTF may be employed to salvage the situation. According to the stress-vulnerability studies, neuroimmune crosstalk represents a determinant of critical importance in stability through persistent load (47). CNTF will, therefore, not only offer trophic support, but can also re-tune immune response in the deteriorating brain circuits.

From a translational perspective, methodological parallels with other disease models provide valuable insights. Surveys of platelet indices in hematological diseases (48) and systemic biomarkers can highlight the ways to profile risks in endocrine dysfunctions (49), leading the way in identifying a specific treatment. On the same note, in PD research, a measurement of CNTF with neuroinflammatory cytokines could refine biomarker panels for staging disease and therapeutic monitoring. Experience with diabetic retinopathy, in which leptin and VEGF are used, can be informed by robust correlates of disease progression for biomarker development (50,51).

The exploration of CNTF is also consistent with emerging therapeutic paradigms that emphasize personalized and multimodal interventions. The studies that have been conducted on phytochemicals have shown that plant compounds may regulate growth factors and provide tissue protection (52). In the neurological context, the combination of CNTF-based strategies with bioactive compounds may potentiate results through various arms of disease pathology. Additionally, translational analyses of fibroblast growth factor in models of ulcers (53) demonstrate that growth factor therapy can be programmed to local injury causes, which also applies to neurodegenerative repair strategies.

Another dimension is related to cardiovascular and systemic comorbidities that frequently accompany PD. Increased cardiac dysfunction has been associated with high cardiac levels of brain natriuretic peptide (BNP), which is associated with unfavorable clinical outcomes (54), which implies that systemic biomarker signatures can engage with neurodegenerative pathways; Likewise, acute stress reactions recorded in systemic disorders are an important diagnostic technique as shown by ultrasound findings (55). CNTF could serve a similar niche in PD, and in this instance, its levels not only reflect local neuroprotection but also systemic resilience.

Epidemiological and clinical translation also demand public health situations. Studies on vaccine hesitancy (56) and evidence-based practice awareness among clinicians (57) identify that even scientifically proven instances of new interventions are difficult to assimilate. With regards to CNTF, bridging strategies will be required to accommodate laboratory evidence in addition to general and clinical approval; neurotrophic therapies need to be integrated effectively into practice. Further, demographic diversity of neurodegenerative diseases implicates that the health information at the community level, such as the one delivered by thyroid and pregnancy-related are proposed markers (58,59), may be applied to direct stratified therapeutic interventions in PD.

Finally, the CNTF, as a generalized concept linking neuroprotection and systemic control, makes it a winning treatment option. Prevalence studies of diabetic retinopathy depict that the early detection of molecular diabetic retinopathy perturbations helps to convert varying disease outcomes in a timely manner (60). In PD, the timely exploration and control of the routes of CNTF can alter the trajectory of the illness and be in focus between symptomatic and disease modification.

Combined with the above findings, these findings indicate that CNTF-based measures should be integrated into PD models. Future work should embark on preclinical validations, integrate biomarker profiling, and design CNTF to change the effects of PD-controlled clinical trials to achieve the full potential of CNTF. Future work should add preclinical validations, biomarker profiling, and design carefully controlled clinical trials to harness the full potential of CNTF in modifying PD outcomes.

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CONCLUSION

The study sheds light on CNTF's ability to protect against degeneration in Parkinson's disease by promoting the survival of dopaminergic neurons and attending to inflammation and apoptosis. Evidence from both patient-derived materials and pre-clinical studies suggests CNTF and other current strategies may be synergistic and forms the basis for targeting neurotrophins therapeutically. While the study's small sample and limited time frame are constraints, the data reinforces CNTF as an attractive candidate for modifying the disease. More in-depth work on other models with extended follow-up is essential to move these theoretical frameworks into clinically-relevant approaches for Parkinson's disease.

AUTHOR CONTRIBUTION

Author	Contribution
Muhammad Ali	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Akram*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Ayesha Kiran	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Umair	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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