Original Article

Association of Insulin-like Growth Factor-1 and Neurofilament Light Chain in Patients with Progressive Supranuclear Palsy

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Abstract

Background: Progressive supranuclear palsy (PSP) is the most common primary tauopathy. The definite diagnosis of PSP is established by histopathologic changes in the brain. There are no reliable blood-based biomarkers to aid the diagnosis of this fatal disease at an early stage. Also, the precise etiopathology of PSP and its variants is inadequately understood. **Objective:** Blood-based molecules such as neurofilament light chain (NfL) and insulin-like growth factor-1 (IGF-1) are shown as important markers of neurodegenerative and aging processes, respectively. These two biomarkers have not been analyzed simultaneously in PSP patients. **Methods:** To address this knowledge gap, 40 PSP patients and equal number of healthy individuals were recruited and serum levels of NfL and IGF-1 were assayed in all the study participants by enzyme-linked immunosorbent assay (ELISA). Motor and nonmotor symptoms were evaluated in PSP patients using various scales/questionnaires. Cardiac autonomic function tests were performed in a subset of patients ($n = 27$). **Results:** A significantly high serum level of NfL ($P < 0.01$) and a reduced level of IGF-1 ($P = 0.02$) were observed in PSP patients compared to healthy controls. Besides, a negative correlation ($r = –0.54$, $P < 0.01$) between NfL and IGF-1 levels was observed in PSP patients. **Conclusion:** The finding of this study reinforces the important role of blood NfL level as a potential biomarker of PSP. Further, the current study provides novel insights into the reciprocal correlation between NfL and IGF-1 in PSP patients. Combined analysis of blood levels of these two functionally relevant markers might be useful in the prediction and diagnosis of PSP.

Keywords: Biomarker, insulin-like growth factor-1, neurofilament light chain, progressive supranuclear palsy, PSP variants

Introduction

Progressive supranuclear palsy (PSP) is the third most common neurodegenerative disorder, with a prevalence rate of 7.1/100,000, and it generally occurs in the age group of sixth and seventh decades, regardless of ethnicity or race.[1] The major clinical manifestations involve vertical supranuclear gaze palsy, progressive gait disturbances, and recurrent falls, which make it distinguishable from similar parkinsonian disorders.[2] Other less-frequent symptoms such as cognitive decline, bradykinesia, rigidity, dysphagia, dysarthria, etc., may develop during the disease course.[3] Autopsy studies demonstrated aggregation of hyperphosphorylated 4R tau protein in the form of neurofibrillary tangles, leading to neuronal loss and gliosis, predominantly in the basal ganglia, brainstem, cerebellum, and, to a lesser extent, in the cerebral cortex.[3] The heterogeneous nature of the disease and presence of several overlapping symptoms led to the description of several clinical variants of PSP (PSP Richardson's Syndrome [PSP-RS], parkinsonism [PSP-P], progressive gait freezing [PSP-PGF], predominant frontal presentation [PSP-F], initial predominance of ocular motor dysfunction [PSP-OM], predominant speech or language disorder [PSP-SL], Corticobasal syndrome [PSP-CBS], and primary lateral sclerosis [PSP-PLS]).[4] The phenotypic manifestations of the variants depend on the distribution of tau pathology in the nervous system. This also determines the initial clinical presentation, the rate of progression, and severity. PSP-RS, the most common form of PSP, followed by PSP-P together account for more than 80% of the total cases.[1] Notably, the neuropathologic features remain consistent among patients with variable clinical presentation. Importantly, there is no diagnostic laboratory/genetic or radiologic test to definitely diagnose PSP. The diagnosis is established based on thorough clinical evaluation and physical findings.

Identification of potential biomarker of PSP is essential for an early diagnosis and for subtyping. Over the last decade, several attempts were made to identify biomarkers of PSP based on biological, physiologic, and radiologic studies.[5,6] A few studies suggested the altered regulation of miRNAs in

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the brain (miR-147a, miR-518e, and miR-132) as well as in the peripheral blood (miR-19b-3p, miR-33a-5p, miR-130b-3p, miR-136-3p, and miR-210-3p) and indicated their relevance in differentiating PSP from similar disorders.[7,8] Moreover, altered regulation of ubiquitin–proteasome system (UPS) and autophagy pathway associated miRNA (miR-204-3p, miR-873-3p, and miR-6840-5p) were detected in early-onset PSP group.[9] Besides miRNA, radiologic studies suggested the usefulness of magnetic resonance parkinsonism index (MRPI and MRPI 2.0) and the ratio of the pons to midbrain area (P/M) to distinguish variants of PSP.[10] Furthermore, positron emission tomography (PET) imaging revealed PSP-specific neuroinflammation and tau colocalization in the brainstem and cerebellum, which could be a potential diagnostic tool.[6] However, the high cost, invasive nature of the investigation, and non-replicability of the findings among PSP variants restrict them from clinical translations.

A number of recent studies have suggested functional relevance of fluid-based biomarkers, especially neurofilament light chain (NfL) in neurodegenerative diseases.[11] It is an essential protein that provides structural stability to myelinated axons. Under pathologic conditions, a high level of NfL is released directly into the cerebrospinal fluid (CSF) and subsequently to the blood in response to axonal damage.[12] NfL has been reported as a promising biomarker in several neurodegenerative diseases such as multiple sclerosis (MS), Alzheimer's disease (AD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and traumatic brain injury (TBI).[11] There are a few studies on the altered NfL levels in the blood and CSF of PSP patients. Serum NfL levels in PSP were shown to be twice as high as those in controls, and the NfL levels correlated with functional, motor, and cognitive functioning. Notably, elevated NfL levels were reported to be associated with a shorter survival when the cohort was followed up.[13] Higher levels of NfL were also reported in CSF of PSP patients, and the NfL levels correlated with the rate of disease progression and disease severity.[14] In an interesting study, blood NfL level was suggested to be useful in distinguishing parkinsonian disorder.[15]

There exists another potential factor, insulin-like growth factor-1 (IGF-1), which has diverse homeostatic roles, including early neurodevelopment, myelination, neurogenesis, and neuroplasticity.[16] IGF-1 is also being considered as a major regulator of aging processes. Under physiologic conditions, the level of IGF-1 remains high at an early age and starts declining over time, toward a reduced neuroprotective condition. Altered IGF-1 levels have been reported in various neurodegenerative diseases.[16,17] An inverse correlation of IGF-1 levels with the risk of AD development in patients with mild cognitive impairment and poor cognitive outcome after 2 years was reported.[18] However, a meta-analysis of nine studies on IGF-1 levels in AD patients showed no correlation of the levels with AD.[19] Studies on IGF-1 are very limited, and there was no significant difference of IGF-1 levels between PSP patients and healthy controls.[17,20] Currently, there is a lack of understanding on the potential functional interaction between NfL and IGF-1 in neurodegenerative diseases including PSP. It would be interesting to know whether an imbalance of these molecules with opposing effects drives the pathogenesis of neurodegenerative diseases. To address this knowledge gap, the current study explored the blood levels of NfL and IGF-1 in patients with PSP.

Methodology

Study participants

This was a prospective cross-sectional study carried out in the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), from November 2019 to November 2022. The diagnosis of PSP and subtyping were done according to the Movement Disorder Society (MDS)-diagnostic criteria for PSP, 2017.[2] The characterization of patients into various subtypes was done by the methodology provided by Hoglinger *et al*. using O, P, A, C severity gradients.[2] Only probable and possible cases were recruited into the study. A total of 40 patients diagnosed with PSP were recruited from the outpatient department, inpatient department, and Parkinson's and Movement Disorders (PDMD) clinic of NIMHANS. In addition, 40 age- and gender-matched healthy individuals with no neurologic and psychologic disorders were considered as the control group for this study. All the patients were evaluated clinically, and a detailed clinical history was recorded. The motor symptoms were assessed with disease-specific scales such as part 3 of unified Parkinson's disease rating scale (UPDRS-III) and the PSP rating scale (PSPRS). The nonmotor symptoms were evaluated using Montreal cognitive assessment (MOCA), Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale, REM sleep behaviour disorder (RBD) screening questionnaire, International Restless Leg Syndrome (IRLS rating scale), Berlin questionnaire, Hamilton depression rating scale (HAM-D), and Hamilton anxiety rating scale (HAM-A). Ethical approval was taken from the Institutional Ethics Committee NIMHANS (NIMH/DO/IEC [BS & NS DIV]/2018-19 date: 28-11- 2019), and a written consent form was obtained from each participant.

Autonomic function test

Twenty participants of the PSP-RS group and six participants of the PSP-P group underwent a battery of tests for assessing cardiac autonomic function. Electrocardiogram (ECG) and blood pressure (BP) were recorded with the subject resting and breathing normally for 30 min. In addition, resting heart rate (HR) variability, BP, and HR response to various procedures were recorded. The recordings were done using the ECG and breathing (ethnographic) signals; the signals were conveyed to the computer through an AD converter (16 channels, Data acquisition system, Power Lab, Bella Vista, Australia) with a sampling frequency of 1024 s^{-1}. The ECG signals were acquired digitally at 256 samples per second. The baseline variables are consecutive RR intervals, measured from ECG for 1 min, and the standard deviation (SD) of the intervals. All the tests were performed in a silent room at

22°C–26°C between 9 a.m. and 11 a.m., 2 h after the patients consumed a light breakfast. The time between any two tests was standardized to normalize the HR and BP. We did not attempt to change the patient's medication before performing autonomic function test (AFT).

Collection of blood samples

Approximately 5 ml of peripheral blood was collected by venipuncture of the median cubital vein into a serum separator tube under aseptic conditions. To achieve adequate clotting, the blood was kept at room temperature for 30 min, and the clotted blood sample was then centrifuged at 3000 rpm for 15 min. The supernatant was aliquoted and stored at −80°C till analysis.

Estimation of serum levels of NfL and IGF-1

The serum levels of IGF-1 and NfL were determined in all the study participants using commercially available enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, San Diego, USA). The sensitivity of the NfL ELISA kit (MBS-765857) was 9.375 pg/ml with a range of 15.625–1000 pg/ml, and the sensitivity of the IGF-1 ELISA kit (MBS-2502577) was 0.94 ng/ml with a range of 1.56–100 ng/ml. A standard curve was prepared for each analyte, and the serum sample was analyzed in duplicate. Optical density (OD) absorbance was measured at 450 nm in a Multiskan GO plate reader (ver. 1.00.40, Thermo Scientific). Blank value was subtracted from OD of each sample, and the actual concentration was calculated in SKANIT software (ver. 3.2).

Statistical analysis

Data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows (Version 25.0; IBM Corp., Armonk, NY, USA). The normality of the data was tested using the Shapiro–Wilk test. Independent *t*-test and Mann–Whitney U test were used for continuous variables following normal and not following normal distribution, respectively. Depending upon the distribution, either the Kruskal–Wallis test or the one-way analysis of variance (ANOVA) was used for comparison between the groups. Categorical variables were analyzed by Pearson's Chi-square test. Pearson's correlation coefficient or Spearman rank correlation was used to compare the strength of association between the variables depending on the normality and arrangement of data. A P value of <0.05 was considered significant.

Results

Clinical and demographic characteristics

The demographic data of the patients and controls are presented in Table 1. Among the 40 patients diagnosed with PSP, 27 patients were categorized as PSP-RS while 10 patients were diagnosed as PSP-P and three as other rare PSP variants. There were no significant differences in demographic features among these groups. We have identified five clinical variants in our cohort. The most common clinical variant, PSP-RS, constituted 67.5% of the cases, followed by PSP-P, constituting 25% of the patients, and 7.5% was constituted by other variants. Of the three other clinical variants, one was a patient with PSP-PGF subtype, who was a 66-year-old male with 3 years of illness and a PSPRS score of 14. The second patient was a 48-year-old male diagnosed with PSP-F with a PSPRS score of 10 and he had 3 years of illness. The third case was PSP-SL, a 45-year-old female with a PSPRS score of 39 after 2 years of illness.

Clinical score examination

Detailed comparison of clinical scores between PSP-RS and PSP-P groups is presented in Table 2. Significantly higher IRLS (P = 0.04) was observed in the PSP-P group when compared to the PSP-RS group. A trend line significance was noted in PSQI global score (P = 0.06), where the PSP-RS group had a poor sleep quality and disturbances than the PSP-P group. In addition, we identified a more severe disease condition in the PSP-RS group than the PSP-P group, evaluated through the total PSPRS score (P < 0.01). Furthermore, a similar observation was noted in four components of PSPRS, such as daily activities (P < 0.01), bulbar exam (P = 0.01), ocular motor exam (P < 0.01), and gait/midline exam (P < 0.01).

Autonomic function test

Resting HR variables, both time dependent and frequency dependent, were significantly reduced in patients compared to the laboratory control values. Total power was reduced in 96.2% (n = 26) patients. Sympathovagal imbalance was noted in 81.4% (n = 22) patients. Also, 70% (n = 19) patients had sympathetic dominance and 11% (n = 3) patients had parasympathetic dominance. The detailed scores are presented in Table S1. In addition, the Valsalva maneuver and orthostatic 30:15 ratio showed a decreased response in patients compared to the laboratory control values. The sympathetic components of the test included BP changes in the isometric handgrip and orthostatic test. Compared to the laboratory control values, there was reduced diastolic BP response during isometric handgrip. However, the median drop in systolic BP was insignificant compared to the laboratory values. We could not find any significant changes in any of the variables between the PSP-RS and PSP-P groups.

Serum levels of NfL and IGF-1

Comparison of serum levels of NfL and IGF-1 is presented in Table 1. Almost two-fold higher level of serum NfL was observed in the PSP group compared to healthy controls (P < 0.01). In addition, pair-wise comparison among PSP-RS, PSP-P, and controls groups showed a significant variation in NfL levels in the serum samples (P < 0.01) [Figure 1]. Interestingly, we observed a significant difference in NfL levels between the PSP-RS and control groups (P = 0.02) as well as between the PSP-P and control groups (P = 0.03). However, there was no significant difference in NfL levels between the PSP-RS and PSP-P groups (P = 0.77). Besides this, significantly lower level of serum IGF-1 was detected in PSP patients compared to healthy controls (P = 0.02); however, there was no significant difference in IGF-1 levels between the PSP-RS and PSP-P groups (P = 0.06) [Figure 2]. Notably, a significant negative

Table 1: Clinicodemographic data of the study participants

Variables	PSP-RS (n=27)	PSP-P (n=10)	Healthy control (n=40)	Test statistic	P
Age, Mean ± SD	61.96±5.81	64.40±4.90	59.83±7.13	40.23	0.71
Gender (female/male)	9/18	2/8	12/28	0.62	0.73
Age at onset (years), Mean ± SD	59.56±6.09	61.30±5.03	-	12.01	0.80
Duration of illness (months), Mean ± SD	27.70±15.80	38.40±23.19	-	10.63	0.39
Smoking (yes/no)	5/22	2/8	-	0.01	0.92
Alcohol (yes/no)	2/25	2/8	-	1.20	0.27
Head injury (yes/no)	1/26	1/9	-	0.57	0.45
Family history (yes/no)	0/26	1/9	-	2.78	0.10
NfL (pg/ml), Mean ± SD	84.11±51.53[a]		40.55±21.44	428.00	**<0.01**[b]
	80.27±51.57	93.99±54.99		10.97	**<0.01**[c]
IGF-1 (ng/ml), Mean ± SD	109.59±105.36[a]		127.88±56.42	505.00	**0.02**[b]
	125.48±109.89	88.03±100.19		5.51	0.06[c]

IGF-1=insulin-like growth factor 1, NfL=neurofilament light chain, PSP=progressive supranuclear palsy, PSP-P=PSP-Parkinsonism, PSP-RS=PSP-Richardson's Syndrome; P<0.05 considered significant, highlighted in bold. Median NfL level (PSP-RS/PSP-P/control): 87.7/91.9/34.0 pg/ml; median IGF-1 level (PSP-RS/PSP-P/control): 76.7/119.3/38.4 ng/ml. [a]Combined NfL/IGF-1 level of all the patients with PSP (n=40). [b]Nonparametric test using median values (Mann–Whitney U test). [c]Nonparametric test using median values (Kruskal–Wallis test)

Table 2: Clinical score profiling between PSP-RS and PSP-P groups

Scale/questionnaire	PSP-RS (n=27)	PSP-P (n=10)	Test statistics	P
Epworth (normal/borderline/abnormal)	23/2/2	7/2/1	1.80	0.51
RBD (absent/present)	23/4	7/3	-	0.36
IRLS (absent/present)	23/4	5/5	-	**0.04**
Berlin (low/high risk)	17/10	6/4	-	1.00
HAM-D (normal/mild/moderate/severe)	9/15/2/1	4/5/1/0	1.01	1.00
HAM-A (normal/mild)	6/21	2/8	-	1.00
MOCA (FM-30) Mean±SD	16.96±6.46	16.80±6.34	132.00	0.92
PSQI (FM-21) Mean±SD	10.07±4.02	6.90±5.17	81.00	0.06
UPDRS-III (FM-108) Mean±SD	37.63±13.81	32.70±13.78	106.00	0.32
PSPRS (FM-100) Mean±SD	40.89±13.30	25.60±11.25	53.00	**<0.01**
PSPRS-history Mean±SD	10.15±3.85	4.90±3.99	47.00	**<0.01**
PSPRS-mental Mean±SD	2.48±2.18	1.90±1.66	116.50	0.52
PSPRS-bulbular Mean±SD	2.89±1.72	1.40±1.83	60.50	**0.01**
PSPRS-ocular Mean±SD	9.11±3.02	5.10±3.07	49.00	**<0.01**
PSPRS-limb Mean±SD	4.93±3.15	5.80±2.90	96.50	0.91
PSPRS-gait Mean±SD	11.56±5.18	6.70±2.71	59.00	**<0.01**

Berlin=Berlin questionnaire, Epworth=Epworth sleepiness scale, HAM-A=Hamilton anxiety rating scale, HAM-D=Hamilton depression rating scale, IRLS=International Restless Leg Syndrome, MOCA=Montreal cognitive assessment, PSP-P=progressive supranuclear palsy-Parkinson's, PSP-RS=progressive supranuclear palsy-Richardson's syndrome, PSPRS=PSP rating scale, PSQI=Pittsburgh sleep quality index, RBD=REM sleep behavior disorder, UPDRS-III=part 3 of unified Parkinson's disease rating scale; P<0.05 is significant, highlighted in bold

correlation between NfL and IGF-1 levels was observed in PSP patients (r = –0.54, P < 0.01) [Figure 3].

Discussion

PSP is a progressive neurodegenerative disease with a median survival rate of 4.9 years from the onset of first symptom.[21] Classical PSP has very distinct cardinal features, but clinical heterogeneity and irregular presentation often lead to an increase in misdiagnosis at the early stages. This uncertainty is even more in classifying the subtypes of PSP based on the clinical examinations. Earlier studies focused mainly on protein, miRNA, and imaging biomarkers and identified several miRNAs, altered NfL levels, and neuropathologic changes to differentiate PSP from other parkinsonian syndromes. However, the findings were heterogenous and were not reproducible upon replication. Hence, there is an urgent need to identify biomarkers having crucial roles in disease pathogenesis.

One of the salient findings of the current study was significantly upregulated serum levels of NfL in patients with PSP. A two-fold higher serum level of NfL was detected in PSP patients compared to healthy controls. Similar to the current finding, a previous study also demonstrated serum NfL level twice as high as those in controls.[13] Plasma NfL level was

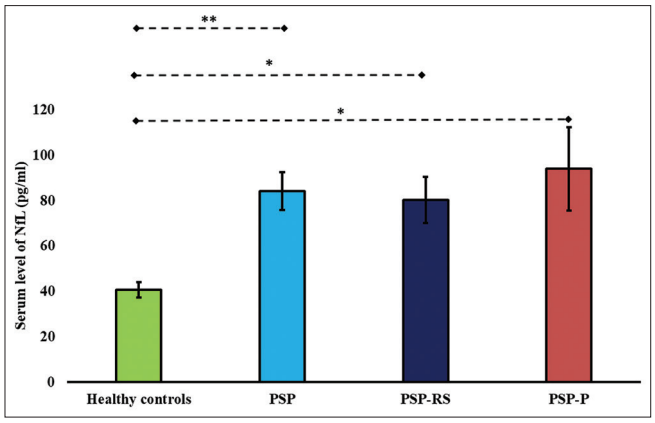

Figure 1: Differences in the serum NfL levels of healthy controls, PSP patients, and its variants. NfL = neurofilament light chain, PSP = progressive supranuclear palsy, PSP-P = PSP-Parkinsonism, PSP-RS = PSP-Richardson's Syndrome; *$P < 0.05$; **$P < 0.01$

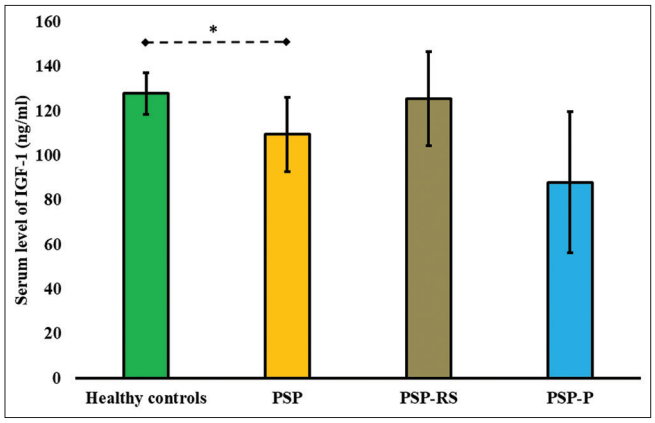

Figure 2: Differences in the serum IGF-1 levels of healthy controls, PSP patients, and its variants. IGF-1 = insulin-like growth factor 1, PSP = progressive supranuclear palsy, PSP-P = PSP-Parkinsonism, PSP-RS = PSP-Richardson's Syndrome; *$P < 0.05$

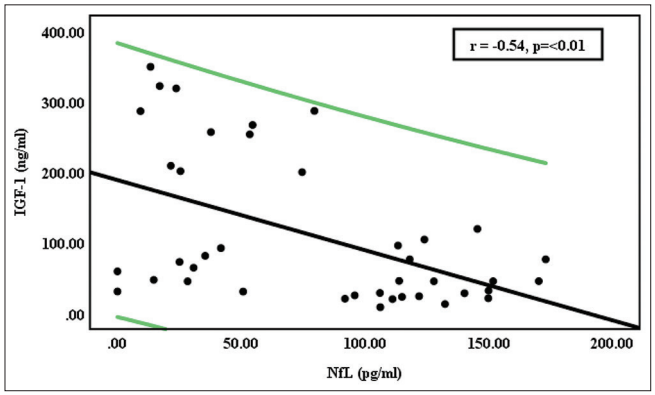

Figure 3: Correlation between serum levels of NfL and IGF-1 in PSP patients. IGF-1 = insulin-like growth factor 1, NfL = neurofilament light chain, PSP = progressive supranuclear palsy

associated with the clinical disease progression.[22] Besides in plasma, the level of NfL was also reported to be high in CSF of patients with PSP.[23] Notably, plasma NfL was suggested as a disease progression biomarker of PSP by recent studies.[14,22] Though a similar NfL profile was observed across the current and other studies, serum NfL level was not found to correlate with the disease severity in the current study.

Another important finding of the current study was significantly decreased serum levels of IGF-1 in patients with PSP. To the best of our knowledge, this is the first report showing decreased levels of IGF-1 in PSP. A few earlier studies have demonstrated altered levels of IGF-1 in neurodegenerative diseases, including Parkinson's disease, however, the findings are not consistent.[18,24] Importantly, IGF-1 level was consistently shown to be associated with cognitive dysfunction in PD patients.[24] However, in the current study, there was no correlation between serum IGF-1 levels and cognitive function of PSP patients. There is a lack of understanding on the role of IGF-1 in PSP. Both the earlier studies were conducted in a very small cohort of PSP patients, and no differences in IGF-1 levels were found between PSP patients and healthy controls.[17,20]

The role of IGF-1 in aging and cell metabolism is well established. In the central nervous system (CNS) of adult individuals, IGF-1 and insulin signaling pathways are shown to have neurotrophic effect and also regulate energy metabolism.[16] IGF-1 is also involved in memory and learning, neuronal plasticity, as well as in maintaining synaptic integrity and sustaining dendritic arborization in adult neurogenesis.[16] In addition, both the expression of tau gene and the phosphorylation of tau protein are regulated by insulin and IGF-1 stimulation.[25] In general, IGF-1, upon binding to its receptor IGF-1R, activates intrinsic tyrosine kinase and phosphorylates the serine residue of insulin receptor substrate (IRS).[26] The phosphorylated IRS then promotes activation of phosphoinositide 3-kinase (PI3-K), which further activates Akt. Akt is the master regulator of several downstream cellular survival pathways.[16] It exerts an antiapoptotic environment through direct inhibition of caspase-9 and glycogen synthase kinase 3b (GSK-3b).[27] Furthermore, it stimulates the activation of antiapoptotic protein, called B-cell lymphoma extra-large (Bcl-XL) through activated cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB).[28] Subsequently, Bcl-XL inhibits the apoptotic process by blocking caspase-9.[29] On the other hand, Akt can directly inhibit nuclear factor kappa light chain enhancer of activated B cells (NF-kB) or indirectly through mitogen-activated protein kinase/extracellular signal-regulated kinase (MAP-K/Erk) axis in association with glucagon-like peptide 1 (GLP-1).[30] Therefore, reduced release of IGF-1 in the brain can promote apoptosis of neuronal cells and thus serve as one of the contributors toward lowered neuroprotection in neurodegenerative diseases.

Another important finding of the current study was a significant negative correlation between IGF-1 and NfL levels in the serum of PSP patients ($r = -0.54$, $P < 0.01$). This and the above findings on two important biomarkers with opposing functions provide new insights into the pathobiology of PSP.

Based on these findings, an imbalance of NfL and IGF-1 can be suggested to drive the pathogenetic pathway of PSP. Therefore, combined analysis of serum levels of both NfL and IGF-1 can serve as important and more reliable biomarkers of PSP.

Conclusion

The present study evaluated the clinical scores, standard autonomic function tests, and serum levels of NfL and IGF-1 in patients with PSP. The PSP-RS group showed a much more severe condition than the PSP-P group, regardless of age and gender. Elevated serum level of NfL further reinforces the importance of NfL as a biomarker of PSP. Reduced level of IGF-1 suggests that a deficient IGF signaling might play a key role in modulating PSP pathogenesis. This study, for the first time, reports a possible implication of Nfl and IGF-1 imbalance in the pathobiology of PSP, and both these serum markers might serve as important biomarkers of PSP. A relatively small sample size is the only limitation of this study. Future studies on a large cohort might be useful in validating our findings and also establishing these two elements as potential biomarkers of PSP.

Ethical standard

We confirm that we have read the journal's position on issues involved in the ethical publication and affirm that this work is consistent with those guidelines. Written informed consent was obtained from all the patients included in the study.

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Conflicts of interest

There are no conflicts of interest.

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Table S1: Comparison of cardiac autonomic functions between PSP-RS and PSP-P groups

Parameters	PSP-RS ($n=20$)	PSP-P ($n=6$)	Laboratory control value	*P*
Deep breathing difference	6 (5, 10.5)	5.2 (2.6, 6.7)	>15	0.26
Valsalva ratio	1.15 (1.1, 1.2)	1.1 (1.05, 1.16)	>1.21	0.42
Orthostatic test (max: min ratio)	1.04 (1, 1.1)	1.02 (1, 1.12)	>1.04	0.87
Isometric handgrip (Δ↑DP mmHg)	10.5 (5, 13.5)	7.5 (5.5, 20)	>15	0.82
Orthostatic test (Δ↓SP mmHg)	0 (-2.5, 10.25)	-2.5 (−8.25, 6.25)	<10	0.48
SDNN (in ms)	18.5 (10.75, 21.57)	14.8 (9.7, 21.6)	141±39	0.52
RMSSD (in ms)	8.6 (5.1, 15.6)	9.4 (3.4, 13.4)	27±12	0.48
Total power (in ms^2)	277 (120, 671)	285 (42, 507)	3466±1018	0.30
Low-frequency power (in ms^2)	63.3 (18.3, 115.5)	101.7 (13.9, 411.9)	1170±416	0.90
High-frequency power (in ms^2)	30.12 (6.6, 76.2)	37.3 (6.3, 61)	975±203	0.90
Low frequency (normalized units)	58.5 (47.5, 75)	66.1 (17.8, 79.2)	54±4	0.87
High frequency (normalized units)	25.9 (16.7, 39.4)	25.7 (10.4, 44.4)	29±3	0.69
LF/HF ratio	1.99 (1.3, 2.8)	2.3 (1.4, 4.3)	0.5–1.5	0.46

LF/HF=low frequency/high frequency, PSP-P=progressive supranuclear palsy-Parkinson's, PSP-RS=progressive supranuclear palsy-Richardson's syndrome, DP=diastolic pressure, SP=systolic pressure, RMSSD=root mean square of successive differences between normal heartbeats, SDNN=standard deviation of NN intervals; $P<0.05$ is significant. Note: Data of one patient is not shown in the table as the patient had a variant other than PSP-RS and PSP-P clinical variants