BRIEF REPORT

Brain Atrophy Does Not Predict Clinical Progression in Progressive Supranuclear Palsy

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ABSTRACT: Background: Clinical progression rate is the typical primary endpoint measure in progressive supranuclear palsy (PSP) clinical trials.
Objectives: This longitudinal multicohort study investigated whether baseline clinical severity and regional brain atrophy could predict clinical progression in PSP–Richardson's syndrome (PSP-RS).
Methods: PSP-RS patients (n = 309) from the placebo arms of clinical trials (NCT03068468, NCT01110720, NCT02985879, NCT01049399) and DescribePSP cohort were included. We investigated associations of baseline clinical and volumetric magnetic resonance imaging (MRI) data with 1-year longitudinal PSP rating scale (PSPRS) change. Machine learning (ML) models were tested to predict individual clinical trajectories.
Results: PSP-RS patients showed a mean PSPRS score increase of 10.3 points/yr. The frontal lobe volume showed the strongest association with subsequent clinical progression (β: −0.34, $P < 0.001$). However, ML models did not accurately predict individual progression rates (R^2 <0.15).
Conclusions: Baseline clinical severity and brain atrophy could not predict individual clinical progression, suggesting no need for MRI-based stratification of patients in future PSP trials. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: progressive supranuclear palsy; atlas-based volumetry; outcome; progression; clinical trials

Progressive supranuclear palsy–Richardson's syndrome (PSP-RS) is a neurodegenerative disease characterized by brain 4R-tau accumulation and atrophy.[1,2] Several clinical trials have been carried out in PSP, measuring clinical disease progression as a primary end point to evaluate treatment efficacy.[3-6] A major

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challenge in advancing research on disease-modifying therapies, however, is the heterogeneity of clinical progression rates across patients. PSP includes several clinical phenotypes,[1] which typically show divergent clinical trajectories, with more rapid progression and shorter survival in PSP-RS than in other variants.[7-11] Moreover, although PSP-RS patients typically show a mean change of 9–11 points/yr in the PSP rating scale (PSPRS),[3-7,12-16] variability exists, and individuals may differ considerably from this group-derived average rate. This heterogeneity may affect clinical trial results, as hypothetical random differences in natural history decline among the two trial arms might exacerbate or mask drug efficacy. Baseline information on the future clinical trajectory of each patient would enable a precise baseline stratification and easy detection of deviations from the individual natural disease course. By leveraging longitudinal large-scale data from the placebo arms of several clinical trials[3-7] and a German observational study,[17] the current multicohort study aimed to investigate if baseline clinical severity and regional brain atrophy were associated at the group level with longitudinal clinical progression, and whether machine learning (ML) models may predict individual 1-year clinical progression in PSP-RS patients.

Materials and Methods

PSP-RS patients from the placebo arms of randomized controlled trials (NCT03068468,[3] NCT01110720,[4] NCT02985879,[5] NCT01049399)[6] and the DescribePSP network cohort[17] were included. A multicohort group of 258 age-matched healthy controls (HC) described in a previous study[18] was used for calculating percentage change and z scores of imaging data in PSP patients. The study population was based on these inclusion criteria: (1) probable PSP-RS diagnosis according to the MDS criteria,[1] (2) available demographic data (sex, age), (3) available PSPRS[20] scores at baseline and 1-year follow-up, (4) available baseline T_1-weighted brain magnetic resonance imaging (MRI). MR images were processed through automated atlas-based volumetry, as previously described.[18,19] Volumes were summed for bilateral regions and normalized to intracranial volume. Detailed procedures on patient cohorts and MRI processing are provided in Supporting Information.

Statistics and Machine Learning

Comparisons between groups were performed using Fisher's, Wilcoxon, analysis of variance (ANOVA), or Kruskal-Wallis test, with Bonferroni correction. Clinical progression was measured as annualized PSPRS absolute or percentage change over time, as described in Supporting Information. Associations between baseline variables and clinical progression were investigated using linear regression models (covariates: age, sex), evaluating regression coefficients (R^2) and false discovery rate (FDR)-adjusted P-values. Subsequently, we employed ML technology to predict individual clinical progression using baseline clinical and/or radiological data. We employed support vector machine (SVM) with RBF kernel,[19] and a tree-based classifier (Random Forest [RF]).[21] We used two alternative approaches: a regression task to predict the individual annualized PSPRS total score change and a classification task to distinguish "fast progressors" from "slow progressors" (stratified by the median annualized PSPRS absolute or percentage change values). Performance metrics included the R^2 (regression tasks) and area under the receiver operating characteristic curve (AUC-ROC) (classification tasks), calculated on unseen data through fivefold stratified nested cross-validation procedure. Further details are provided in Supporting Information.

Results

The cohort included 309 PSP-RS patients (Fig. S1). All subcohorts from different trials were comparable for age, sex, and clinical severity at baseline and follow-up visits (Table 1). PSP-RS patients showed ventricular enlargement and widespread brain atrophy at baseline, most prominent in the midbrain, red nucleus, subthalamic nucleus, substantia nigra, superior cerebellar peduncles (SCPs), and globus pallidus (Table S1). At baseline, volumes of several brain structures showed weak but significant associations with baseline clinical severity (PSPRS total score). The strongest associations were found for SCPs (regression-derived β: −0.36), brainstem and third ventricle (β: −0.34), midbrain, pons and medulla (β: −0.32), and inferior cerebellar peduncle (β: −0.31), all with FDR-corrected $P < 0.001$ (Table S2).

Associations between Baseline Data and Longitudinal Clinical Progression

PSP-RS patients showed significant progression in clinical scores over 1-year time (baseline vs. follow-up visit, $P < 0.001$), including SEADL, PSPRS total score, and all its categories. The PSPRS total score showed a mean annualized increase of 29.8% (10.3 points), and the progression rate was nearly identical across all subcohorts from different trials (Figs. S2 and S3). At the group level, several baseline regional volumes were associated with longitudinal clinical progression measured as annualized PSPRS score absolute change, with higher baseline atrophy corresponding to faster subsequent clinical decline (Fig. 1; Table S3). The strongest association was found for the frontal lobe (β: −0.34,

TABLE 1 *Demographic and clinical data of the study participants*

Data	All PSP patients (n = 309)	Gosuranemab cohort (n = 133)	Davunetide cohort (n = 98)	Tilavonemab cohort (n = 52)	DescribePSP cohort (n = 22)	*P*-value across PSP cohorts
Sex (M/F)	161/148	72/61	46/52	29/23	12/10	0.658[a]
Age (yr)	68.8 ± 6.5	69.6 ± 6.4	67.3 ± 7.0	68.6 ± 5.5	71.0 ± 6.9	0.032[b,★]
PSPRS total score	37.6 ± 10.3	37.3 ± 9.5	38.7 ± 10.9	36.2 ± 9.7	38.1 ± 13.3	0.721[b]
PSPRS history score	7.9 ± 3.2	7.7 ± 2.8	8.3 ± 3.4	7.4 ± 3.6	8.1 ± 3.3	0.356[b]
PSPRS mentation score	3.7 ± 2.5	3.6 ± 2.2	3.9 ± 2.8	3.5 ± 2.4	4.0 ± 2.9	0.777[b]
PSPRS bulbar score	2.8 ± 1.5	2.8 ± 1.4	2.7 ± 1.5	2.5 ± 1.3	3.1 ± 1.9	0.422[b]
PSPRS ocular score	8.9 ± 3.1	8.6 ± 3.1	9.4 ± 2.9	9.0 ± 3.0	7.7 ± 3.2	0.091[b]
PSPRS limb score	4.6 ± 2.0	4.8 ± 2.0	4.6 ± 1.9	4.3 ± 1.7	4.6 ± 2.6	0.540[b]
PSPRS gait and midline score	9.8 ± 3.7	9.8 ± 3.5	9.8 ± 3.9	9.5 ± 3.7	10.5 ± 4.2	0.927[b]
SEADL	56.8 ± 20.7	57.4 ± 20.0	56.5 ± 22.5	57.1 ± 20.3	53.2 ± 19.6	0.813[b]
Longitudinal data						
Inter-visit interval (mo)	12.0 ± 0.5	12.0 ± 0.2	12.0 ± 0.0	11.8 ± 0.5	13.0 ± 1.5	**<0.001**[b,#]
PSPRS total score at follow-up	47.9 ± 13.2	47.6 ± 13.6	48.5 ± 13.1	46.8 ± 11.9	49.8 ± 15.2	0.785[b]
Annualized PSPRS total score absolute change	10.3 ± 8.9	10.3 ± 8.6	9.86 ± 9.7	10.8 ± 8.6	10.8 ± 9.0	0.813[b]
Annualized PSPRS total score percentage change	29.8 ± 28.0	28.6 ± 26.4	28.9 ± 29.0	33.9 ± 30.8	32.2 ± 29.6	0.813[b]

Note: The Tideglusib cohort included 4 patients only and is not shown in the table. Significant ANOVA or Kruskal-Wallis test *P*-values surviving FDR correction are highlighted in bold. Data are shown as mean ± standard deviation.
Abbreviations: PSP, progressive supranuclear palsy; PSPRS, PSP rating scale; SEADL, Schwab and England Activities of Daily Living scale.
★No differences in post hoc analyses.
#All pairwise comparisons showed significant *P*-values in post hoc analyses (after the Bonferroni correction), except for the Davunetide cohort versus Gosuranemab cohort comparison.
[a]Fisher's exact test.
[b]ANOVA or Kruskal-Wallis rank-sum test followed by pairwise *t* test or Wilcoxon rank-sum test.

$P < 0.001$) (Figs. 1 and S4). Age, sex, and baseline clinical severity were not associated with absolute change in PSPRS score. Conversely, when the percentage, rather than absolute PSPRS change, was considered, all baseline PSPRS categories and total score were associated with progression (milder baseline severity corresponding to faster progression, Table S3; Fig. S4). Baseline volumes of whole brain, cerebrospinal fluid (CSF), frontal lobe and parietal lobe confirmed their association with clinical progression in this analysis (Table S3).

Individual Longitudinal Trajectory Prediction Modeling

All the linear models described above, including a single baseline variable, explained <15% of variance in the longitudinal PSPRS score change across patients ($R^2 < 0.15$). Suboptimal results were obtained also by linear models, including multiple clinical and/or volumetric data (adjusted $R^2 < 0.25$, Table S4). Subsequently, we employed ML algorithms (SVM and RF) aiming to predict individual clinical progression in PSP-RS patients using baseline data, using both regression and classification approaches. In the regression tasks, both algorithms showed $R^2 < 0.15$ in the validation folds in predicting annualized absolute (or percentage) change in PSPRS score. Representative plots showing real and predicted PSPRS change values are shown in Figure S5. Similarly, in the classification tasks, both algorithms provided AUC-ROC values <0.70 in distinguishing fast from slow progressors in the validation folds (Table S5). Overall, ML models yielded largely suboptimal results in predicting individual clinical progression rates in PSP-RS patients.

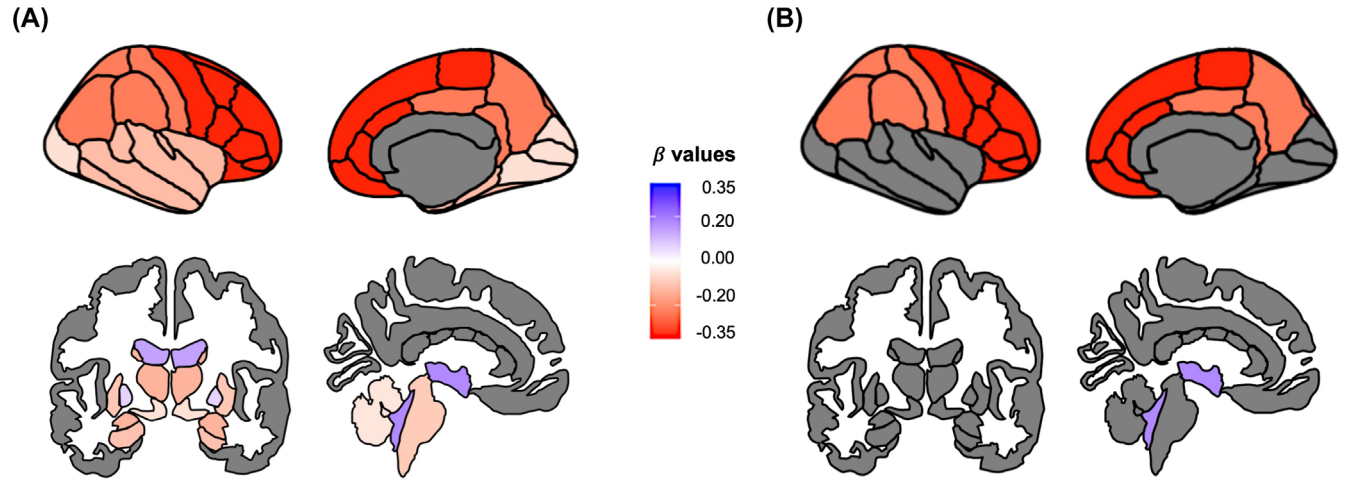

FIG. 1. The figure shows baseline regional volumes of cortical and subcortical structures associated with future 1-year clinical progression rate as measured by the annualized absolute change in the PSP rating scale total score. All associations are shown on the left (**A**), whereas only significant associations with false discovery rate (FDR)-adjusted *P*-value <0.05 are shown on the right (**B**). The color scale represents the association strength as measured by the linear regression-derived β value, with shades of red for negative associations (lower volume associated with faster progression) and shades of blue for positive associations (larger volume associated with faster progression). All models also included age and sex as follows: (annualized absolute change in the PSP rating scale ~ regional volume + age + sex). Please note that some structures (ie, cerebellar peduncles) are not shown in the figure; full data are shown in the tables. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

This study demonstrated that PSP-RS patients have variable clinical progression rates over 1 year. Patients with more atrophic frontal lobe volume at baseline visit had faster clinical progression over the following year, but neither baseline severity nor imaging regional volumetric data allowed to accurately predict individual trajectories.

In this multicohort study, we observed a mean increase of 10.3 point (29.8%) in the PSP rating scale, providing robust natural-history data in a large international population of PSP-RS patients eligible for trials. This progression rate was nearly identical across PSP-RS subcohorts from the placebo arms of previous trials, demonstrating that these groups were homogeneous for severity and progression, and can be merged for future cross-sectional or longitudinal research. A surprising insight was that around 10% of patients clinically improved over time despite PSP-RS being a progressive disease. Possible explanations include occasional misdiagnosis, day-to-day fluctuations in clinical symptoms, different physicians evaluating the patient at baseline and follow-up assessments, and placebo effects. Beyond these few atypical cases, PSP-RS patients showed great heterogeneity in individual progression rates, ranging from 0 to 40–50-point increase in the PSPRS over 1 year. Thus, we investigated the relevance of baseline clinical severity and regional brain atrophy as predictors of future clinical progression. Regarding clinical severity, we found negative associations with the annualized percentage change in the PSPRS score, but not with its absolute change. This discrepancy was possibly explained because many patients showed 10-to-20-point PSPRS score longitudinal increase, but this corresponded to variable percentage score changes depending on the baseline severity. This finding is relevant for trial design, supporting the use of PSPRS absolute rather than percentage change as clinical end point, which may require smaller sample size to detect treatment effect,[22] and is less influenced by baseline severity.

Regarding brain atrophy, patients with more severe brain atrophy had worse clinical symptoms and progressed faster in the subsequent year. Brainstem structures showed the highest atrophy degree and the strongest associations with clinical severity at baseline, whereas cortical structures (frontal and parietal lobes) were more associated with subsequent clinical progression. In particular, the frontal lobe volume (showing mild atrophy at baseline) was the most associated imaging variable with subsequent decline, with faster progression in patients displaying more severe baseline atrophy. A similar phenomenon was observed in a recent study,[23] where the midbrain and cerebellum correlated with disease severity at baseline, whereas other regions (nucleus accumbens and putamen) showed stronger correlations with survival. A possible explanation may be that midbrain is early affected in PSP-RS,[24] and is already atrophic when patients undergo their first MRI scan, correlating with clinical severity but not providing information on future progression. Conversely, the cortical or striatal involvement occurs later,[24] and these structures are atrophic only in a patient subset at the stage they are enrolled in trials; thus, patients who already display frontal lobe atrophy likely have more widespread neurodegenerative

processes compatible with faster symptom progression in the following months. These results expand the current knowledge on features associated with clinical progression in PSP-RS, currently including clinical scales,[14,25] MRI,[14,26-28] positron emission tomography (PET) data,[25,29] and fluid biomarkers.[30,31] In addition, we first investigated whether these group associations may translate into individual predictions using ML technology. We employed RF and SVM models to estimate the disease progression in individual patients using baseline clinicoradiological data, but the models did not explain more than 15% of variability in progression rates across subjects and failed in distinguishing "fast progressors" from "slow progressors" (AUC-ROC <0.70). Overall, these data demonstrate limited usefulness of structural MRI and baseline severity for patient stratification in terms of future progression. In this study, we used robust and well-known ML models (SVM, RF), which are commonly employed in research as they are relatively easy to implement at limited computational cost. This approach can facilitate comparisons with other data sources (diffusion imaging, PET, fluid biomarkers, etc.), which may be more informative to this aim. For the sake of completeness, an eXtreeme Gradient Boosting (XGB) and an ensemble stacking model combining SVM, RF, and XGB were also tested (data not shown), obtaining very similar results. However, artificial intelligence technology is rapidly evolving, and future studies are warranted to investigate whether advanced deep learning or data fusion strategies might overcome the limitations of current approaches.

This study has several strengths. First, the large multicohort of PSP-RS patients ensure generalizability of the results. Second, our cohort mainly included patients from PSP clinical trials, thus generating evidence useful for future trial design. Third, all MRI measures were obtained using automated operator-independent volumetry. Fourth, we employed ML algorithms based on mathematically different prediction methods, and the results were consistent, providing a solid basis for justifying the conclusions. Among limitations, we focused on patients fulfilling inclusion criteria of previous trials, typically consistent with PSP-RS phenotype[7,32]; thus PSP variants were not included. Second, baseline PET and fluid biomarker data (ie, neurofilament light chains or exosome protein levels[33]) were not available; integrating different biomarkers may lead to better prediction of progression rates, as demonstrated in the Alzheimer's field,[34] and future studies addressing this point are warranted. Third, although we measured clinical progression using the PSPRS change, we did not include outcome measures as milestones or survival.

Overall, this study demonstrated that regional brain atrophy was associated with 1-year clinical progression at the group level but had limited potential in predicting individual trajectories. These findings may be relevant for trial design, suggesting that MRI-based stratification of patients at baseline may not significantly impact the trial results in PSP-RS. ■

Author Roles: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.
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H.-J.H.: 1C, 3B
N.S.: 1B, 3B
G.C.P.: 1B, 3B
A.S.: 1B, 3B
J.L.: 1B, 3B
J.P.: 1B, 3B
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Data Availability Statement

The data that support the findings of this study are available from the owners of data, that were collected in clinical trials. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of the owners of data, that were collected in clinical trials.

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Appendix B

Alzheimer's Disease Neuroimaging Initiative (ADNI)

A complete list of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.