Movement Disorders
CLINICAL PRACTICE

LETTERS: NEW OBSERVATION

Early, Middle, and Late-Stage Progression Rates in Progressive Supranuclear palsy-Richardson Syndrome

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While most or all treatment trials in progressive supranuclear palsy-Richardson syndrome (PSP-RS) enroll early-to-mid-stage patients, many include a long-term, open-label phase, typically after one year of double-blind treatment. Little later-stage natural history data exist to assist in designing and interpreting such uncontrolled, longer-term observations.[1]

We used the 28 item scores of the PSP Rating Scale (PSPRS)[2] from a longitudinal database of 462 patients with probable PSP-RS[3,4] seen by author LIG from 1994 to 2020. We tested for differences in the rate of progression among early, middle, and late disease stages using disease periods as defined by four pathoanatomically relevant milestones (Fig. 1)***: V1: the first

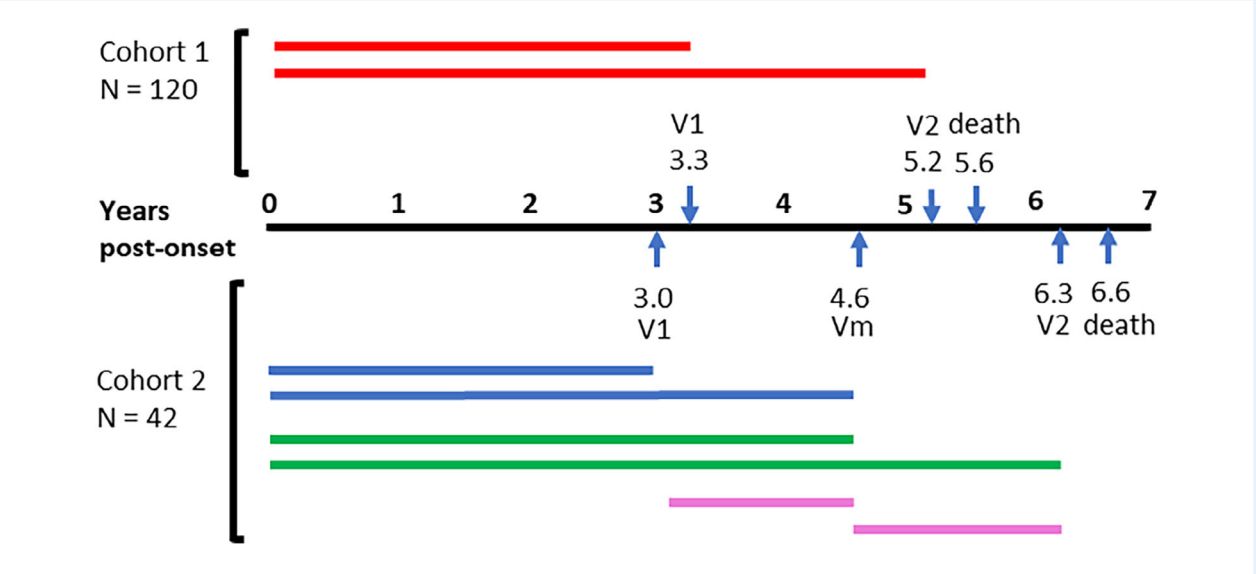

FIG. 1. Progression Rate Comparisons Performed. Each comparison was made between progression rates over the two timespans of the same color. Red: Cohort 1 ($N = 120$): Cohort with at least two visits, the last one within 1 year of death. Data comparing rates appear in Table S1. Cohort 2 ($N = 42$): Subset of the above whose maximum downgaze palsy Vm occurred between V1 & V2. Data comparing progression rates appear in Table S2.. V1, First visit with downgaze palsy; Vm, First visit with maximum downgaze palsy; V2, Last visit within 1 year of death. Figures just above/below arrows are the median years to the indicated milestone event.

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visit where PSPRS Item 15 for downgaze palsy was >0 for the first time; V2: the last visit within one year of death; Vm: the visit where PSPRS downgaze palsy reached the maximum of 4; and death. We applied the Shapiro–Wilk test, the paired *t*-test, the Wilcoxon signed-rank test, and Bonferroni correction as appropriate. We defined "clinically significant" changes in progression rate as those that were statistically significant and of magnitude >25%.

Cohort 1 comprised the 120 patients attaining scores of at least 1 on both the upgaze and downgaze PSPRS items at V1, who were deceased with known dates of death, and had their last visit V2 within 1 year of death. Cohort 2 was the 42-patient subset of Cohort 1 who reached the maximum possible downgaze score at a visit Vm occurring after V1 but before V2. Figure 1 shows the median times between milestones for both cohorts. In Cohort 1, comparison of the [onset to V1] ***vs [onset to V2] intervals showed statistically and clinically significant accelerations in progression rates in dysphagia for liquids (0.2–0.4), dysphagia for solids (0–0.3), and urinary incontinence (0–0.5) (Table S1.). In Cohort 2, the [onset-V1] vs [onset-Vm] comparison showed only dysphagia for liquids to accelerate (0–0.4) (Table S2.). For the [onset-Vm] vs [onset-V2] comparison, only dysphagia for solids (0.2–0.4) showed acceleration. The set of comparisons independent of the PSP onset date, which used our Cohort 2 to compare the [V1-Vm] interval to the [Vm-V2] interval (Fig. 1, Table S2.), showed no additional significant findings.

As in our previous work,[5] our methodology pinned measurements to benchmarks defined not by time alone, but by intervals defined by downgaze palsy, a central feature of the pathogenesis of PSP. Our unusual database allowed us to analyze patients followed to within a few months of death, on average (Fig. 1). The overall results show that three of the 28 items—dysphagia for liquids (by exam), dysphagia for solids (by history), and urinary incontinence—accelerate in their rate of progression late in the course of PSP-RS. These findings may inform clinicians' surveillance, counseling, and management and may also provide historical control data for futility trials and for controlled trials whose long-term follow-up phases include no placebo group.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

T.X.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

C.L.: 1B, 1C, 2B, 2C, 3B

L.I.G.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the Institutional Review Board of Rutgers Robert Wood Johnson Medical School and the University of Chicago Medicine. Informed consent was not necessary for this work. All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Supplemental Table S1. (Cohort 1, $N = 120$): Demographics and progression rates. V1, visit when downgaze palsy was first detected; V2, last visit within 1 year of death; IQR, interquartile range; NS, statistically non-significant; Acceleration in green; Deceleration in yellow; SD, standard deviation. ⋆: Statistically significant with more than 25% change, excluding ocular motor items, which correlate closely with downgaze palsy, our input measurement benchmark.

Supplemental Table S2. (Cohort 2, $N = 42$): Demographics and progression rates. V1, visit when downgaze palsy was first detected; Vm, visit when the maximal PSPRS item score of 4 was first detected; V2, last visit within 1 year of death; IQR, interquartile range; NS, statistically non-significant; Acceleration in green; Deceleration in yellow; SD, standard deviation. ⋆: Statistically significant with more than 25% change, excluding ocular motor items, which correlate closely with downgaze palsy, our input measurement benchmark.