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Survival analysis in primary progressive apraxia of speech and agrammatic aphasia

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ABSTRACT

Objective: To compare survival among patients with different combinations of apraxia of speech (AOS) and agrammatic aphasia, including those with isolated AOS (primary progressive apraxia of speech, PPAOS), both AOS and agrammatic aphasia (AOS+PAA) and isolated agrammatic aphasia (progressive agrammatic aphasia, PAA).

Methods: One-hundred-and-nine patients were recruited who had any combination of AOS and agrammatic aphasia (42 PPAOS, 56 AOS+PAA and 11 PAA) and were followed longitudinally, with 57 patients having since died. Cox proportional hazards models were used to quantify the relative risk of death across diagnoses. Adjusted survival curves are presented based on this model. We also assessed the influence of AOS and aphasia severity on survival.

Results: PPAOS had the longest survival (median survival of 5.97 years from baseline visit), followed by PAA (5.26 years) and then AOS+PAA (4.33 years). AOS+PAA had a greater risk of death than PPAOS, with a hazard ratio of 3.01 (Lower/upper CI= 1.66/5.46, $p<0.001$). Risk of death did not differ between PAA and the other groups. All results accounted for age and time from onset to baseline visit. AOS severity, independent of syndromic diagnosis, was associated with greater risk of death, with a hazard ratio of 1.35 for a one-point increase in severity. Aphasia severity was not associated with risk of death.

Conclusions: Individuals with PPAOS have better survival and reduced risk of death compared to AOS+PAA individuals. This finding will help improve prognostic estimates for these patients and supports the value of distinguishing PPAOS from AOS+PAA.

INTRODUCTION

Primary progressive apraxia of speech (PPAOS) is a neurodegenerative syndrome that is defined by the presence of apraxia of speech (AOS), in the absence of other neurological features, including aphasia, cognitive impairment or Parkinsonism[1]. Apraxia of speech (sometimes called aphemia or cortical dysarthria) is a disorder of motor planning and/or programming and affects the physical production of speech[2, 3]. The characteristic features of AOS include slow rate, articulatory distortions and distorted sound substitutions, and segmentation of syllables within or across words[4]. It is distinguishable from dysarthria, which reflects problems with the neuromuscular control or execution of speech resulting from central or peripheral nervous system damage[5, 6], and from aphasia which reflects language processing deficits that typically cross language domains (e.g. semantics, syntax, phonology) and modalities (e.g. spoken and written language comprehension and expression) (**Table 1**). Patients with PPAOS can develop dysarthria (usually spastic and/or hypokinetic) and aphasia over the course of the disease, as well as parkinsonism, limb apraxia and eventually cognitive impairment[7, 8], although in some cases the AOS remains the isolated neurological feature for many years[7, 9].

However, AOS can also commonly co-exist with agrammatic aphasia, with some patients presenting with both AOS and agrammatic aphasia (referred to here as AOS+PAA). Agrammatic aphasia is defined as a language disorder that affects language production, resulting in telegraphic speech, grammatical simplification, the omission of function words, and difficulty with syntax and verbs, among other deficits; comprehension of syntactically or grammatically complex sentences can also be impaired[10, 11]. Furthermore, although rare, patients can present with agrammatic aphasia in the absence of AOS (progressive agrammatic aphasia, PAA[12]). Patients with AOS+PAA also often develop parkinsonism, limb apraxia and cognitive dysfunction over time[12, 13]. However, patients with PAA do not tend to develop parkinsonism and limb apraxia, but instead show more rapid declines in aphasia[12].

All three of these groups of patients could be subsumed under the diagnosis of nonfluent/agrammatic primary progressive aphasia (agPPA)[14], since the current, widely used diagnostic criteria for agPPA require the presence of either agrammatic aphasia or AOS[14]. Hence, many investigators include PPAOS, AOS+PAA and PAA patients within studies of agPPA. However, we have found different neuroimaging signatures across PPAOS, AOS+PAA and PAA, and patterns of disease progression can differ across groups[1, 7, 12, 15]; hence, we have proposed that these should be separate diagnostic entities. It will be important to determine whether this diagnostic classification has implications for patients in terms of survival and ultimate prognosis. Therefore, in this study we aimed to compare survival across patients with PPAOS, AOS+PAA and PAA utilizing a large cohort of patients that has been followed for many years.

METHODS

Participants

One hundred and nine patients who presented with any combination of progressive AOS and/or agrammatic aphasia were recruited by the Neurodegenerative Research Group (NRG) at Mayo Clinic, Rochester, MN, between January 1st 2010 and January 16th 2019. All patients were recruited from the Department of Neurology. Patients with concurrent illnesses that could account for the speech and/or language deficits, such as traumatic brain injury, stroke or developmental syndromes, and patients meeting criteria for another neurodegenerative disease, including the logopenic and semantic variants of PPA[14] were excluded. We applied the 2017 Movement Disorder Society clinical criteria for PSP[16] using operational definitions we previously described[17] to determine whether patients met criteria for PSP, and none met possible or probable PSP criteria at presentation. Similarly, we applied the CBS clinical criteria[18] and none met criteria for probable CBS at presentation. At the first research visit each patient underwent a thorough speech-language evaluation by a speech-language pathologist (JRD, HMC, EAS, RLU) as well as a neurological evaluation, as previously described in detail[1].

All patients were enrolled into one of three NIH-funded longitudinal studies and were followed with approximately yearly research visits. A total of 57 patients have since died. Patients who dropped out of the longitudinal study were contacted in October of 2019 to determine current status. Hence, all patients, except 2 that could not be contacted, were censored (i.e. the last known date a patient was known to be alive) within the last year. Figure 1 shows the available follow-up and death/censor dates for each patient.

Speech and language evaluation

Motor speech was assessed using the apraxia of speech rating scale (ASRS) which rates the presence and prominence of a number of clinical features associated with AOS[19], and a Motor Speech Disorders[20] scale which rates the effect of any motor speech disorder (AOS or dysarthria) on communication function and speech intelligibility, independent of its specific features. Aphasia was assessed using the Northwestern Anagram Test[21] which assesses syntactic performance, and the Western Aphasia Battery[22]. The Western Aphasia Battery tests lexical content, fluency, repetition, naming, and language comprehension, and sub-scores are summed to create the Aphasia Quotient, an index of overall aphasia severity. Speech and language test scores and video recordings from each patient were reviewed by at least two speech-language pathologists and the presence/absence and severity (0-4 scale) of agrammatism and of AOS were recorded separately, each by consensus, for each patient. In order for a patient to meet criteria for having agrammatism, there had to be performance outside of the normal range on the Northwestern Anagram test or function word omissions or syntactic errors had to be present during the WAB picture description task, in general conversation, in the narrative writing subtest of the WAB. AOS was identified by consensus, based on all spoken language tasks of the WAB plus additional speech tasks that included vowel prolongation, speech alternating motion rates, speech sequential motion rates, word and sentence repetition tasks and a conversational speech sample. The

designation of agrammatism was made independent of the motor speech characteristics of speech and vice versa. Patients were diagnosed at first research visit as follows: PPAOS = AOS was present and aphasia was absent or equivocal (n=42), PAA = agrammatic aphasia was present and AOS was absent or equivocal (n=11), AOS+PAA = both AOS and agrammatic aphasia were unequivocally present (n=56) (**see Table 2 for demographic and clinical features**). A total of 20 [48%] PPAOS; 4 [36%] PAA; and 33 [59%] AOS+PAA have since died.

Neurological and neuropsychological assessments

The neurological battery included the Montreal Cognitive Assessment Battery (MoCA)[23] to assess general cognitive function and the Movement Disorders Society sponsored revision of the Unified Parkinson's Disease Rating Scale part III[24] to assess parkinsonism. The neuropsychological battery included tests for processing speed (Trail Making Test A[25]), executive function (Trail Making Test B[25]), episodic memory (Auditory Verbal Learning test[26]), visuoperceptual ability (Visual Object and Space Perception battery[27] fragmented letters) and visuospatial ability (Visual Object and Space Perception battery cube analysis).

Standard Protocol Approvals/Patient Consents

The study was approved by the Mayo IRB. All participants consented for enrollment into the study.

Statistical methods

Cox proportional hazards models were used to quantify the relative risk across diagnoses (PPAOS, PAA and AOS+PAA) while controlling for the effects of age at first research visit and time from patient-reported onset to first research visit. The Cox model evaluates how multiple factors simultaneously affect survival time (years from first research visit to death), reporting effects as hazard ratios. Hazard ratios are a ratio of the rates of death at a given time-point and can be thought of in terms of cross-

sectional relative risk. We include time from patient-reported illness onset to first research visit as a covariate rather than back-dating our follow-up time to onset to avoid the problem of immortal time bias[28]. From the results of the Cox model we visualize expected survival to assist in contextualizing the hazard ratios. In separate Cox models, we also assessed the influence of aphasia and AOS severities (using the 0-4 qualitative scale) on survival in patients with AOS (PPAOS and AOS+PAA) and aphasia severity in patients with aphasia (PAA and AOS+PAA) while accounting for diagnosis, age at baseline, and time from onset to first research visit. To manage 1) collinearity between baseline AOS severity and time from onset to first research visit (Spearman correlation of 0.58), 2) any potential relationships between diagnostic groups and AOS or aphasia severity, and 3) to prevent overfitting (i.e. more predictors than generally would be used with the number of events in our data), an elastic-net regularization[29] was used in these second and third models. Elastic-net regularization acts as a shrinkage estimator, helping to address the issue of multiple comparisons by introducing helpful bias (toward no effect). We report only these shrunken effect estimates in these secondary models, without p-values or confidence intervals, as there is no widely accepted method of estimating whether uncertainty in the estimate arises from this helpful bias or within the independent variable itself.

Data Availability

Anonymized data will be shared by request from any qualified investigator

RESULTS

The expected survival curves visualizing the model results show that participants with PPAOS had longer survival than AOS+PAA (**Figure 2**). PAA survival was not different than either PPAOS or AOS+PAA, possibly due to the small sample size, but the effect estimates suggest that PAA survival may be somewhere between PPAOS and AOS+PAA survival. Median survival estimates from first research visit were 5.97 years (Lower CI = 5.72, Upper CI not reached) in PPAOS, 5.26 years (Lower CI = 4.07, Upper CI

not reached) in PAA and 4.33 years (Lower CI = 4.19, Upper CI = 5.40) in AOS+PAA. The Cox proportional hazard models showed that AOS+PAA had a greater risk of death than PPAOS, with a hazard ratio of 3.01 (Lower CI=1.66, Upper CI=5.46). At five years, this hazard ratio corresponds to an absolute risk reduction of 0.20 (Lower CI = 0.04, Upper CI = 0.33). The number of PPAOS cases needed to have one more PPAOS case live to five years than AOS+PAA cases, the equivalent of the number needed to treat (NNT) in a clinical trial, was 3.07 (lower CI = 2.78, Upper CI = 3.48).

Within participants who had AOS, increasing AOS severity was associated with a greater risk of death, with a hazard ratio of 1.35 for a one-point increase in severity (on a 0-4 scale). However, even accounting for AOS severity, AOS+PAA was still associated with a greater risk of death than PPAOS with a hazard ratio of 1.66 in this second model. Within participants that had agrammatic aphasia, increasing aphasia severity was not associated with a greater risk of death (a hazard ratio of 1).

DISCUSSION

This study demonstrates that participants given a diagnosis of PPAOS have better survival and lower risk of death than participants diagnosed with AOS+PAA. In fact, an AOS+PAA participant was three times more likely to die before a PPAOS participant. This finding is consistent with previous reports that have described participants with PPAOS who have survived for many years[9, 30]. The results also support the clinical validity and utility of a diagnosis of PPAOS and show that a diagnosis of PPAOS can provide essential and more accurate prognostic information to patients and families than a diagnosis of agPPA. The PAA group was much smaller than the other two groups and hence their survival estimates are less precise and we cannot draw firm conclusions about how their survival compares to the other groups.

Worse survival in AOS+PAA concurs with the fact that these participants show a faster decline in performance on tests of cognition and functional ability, as well as, as expected, aphasia, compared to

participants with PPAOS[12, 13]. At presentation, both PPAOS and AOS+PAA show atrophy on MRI and hypometabolism on FDG-PET, with PPAOS showing very focal involvement in the medial and lateral superior premotor cortex[1], while AOS+PAA shows additional more widespread involvement of the left inferior frontal gyrus (i.e. Broca's area) likely reflecting the presence of agrammatism in this group[12, 15]. In PPAOS patients that remain PPAOS over time, atrophy remains focal in the superior premotor cortex, while those that evolve into AOS+PAA show similar characteristics to those that started with AOS+PAA[31]. It may be argued that it is the focality (or lack thereof) or location of the where the pathology is in the brain that accounts for worse prognosis. It could also be related to underlying pathology although it is unknown whether the underlying pathology differs between PPAOS and AOS+PAA. Both syndromes are associated with 4-repeat tauopathies[9, 32-34], including corticobasal degeneration, progressive supranuclear palsy and globular glial tauopathy, but whether one pathology is more strongly associated with one clinical syndrome remains unknown. While we consider PPAOS and AOS+PAA as separate entities, some may consider them part of a spectrum of disease, particularly given the fact that both arise from a 4R tauopathy. Regardless, it is important to consider these entities as separate given that communication interventions differ between the syndromes. For example, patients with PPAOS can continue to communicate with written language even when speech is severely affected or the patient is mute. On-the-other hand, aphasia will also affect writing and hence written language. The findings from this study give more credence to separating these syndromes by adding survival differences to differences in management.

The severity of AOS was also associated with survival, with the relative risk of death increasing by 1.35 for every one-point increase in AOS severity. This is possibly due to an accompanying emergence of dysphagia and immobility that has been reported[7]. Hence, taking into account AOS severity at the first visit is also important to providing survival estimates for patients. We did not observe an increased

hazard ratio for death with aphasia severity; perhaps because aphasia severity is less strongly related to dysphagia severity and immobility [12].

The strengths of our study are that we studied a large cohort of over 100 patients with these relatively rare disorders that we have prospectively followed for many years, and that all patients were well characterized and diagnosed by the same team of speech-language pathologists and neurologists. Furthermore, our analysis accounted for both age and the time from onset to first research visit, showing that our findings were robust even after accounting for these variables. Limitations are that not all of our patients have died, and that our PAA cohort is small, limiting power and generalizability of our comparisons between PAA and the other two groups. Nevertheless, the study was well powered to demonstrate a difference in survival between PPAOS and AOS+PAA.

Appendix 1: Authors

Name	Location	Contribution
Jennifer L. Whitwell, PhD	Mayo Clinic, Rochester, MN	Designed and conceptualized the study; analyzed the data; obtained funding; study supervision or coordination; drafted the manuscript for intellectual content
Peter Martin, MS	Mayo Clinic, Rochester, MN	Statistical analysis; revised the manuscript for intellectual content
Joseph R. Duffy, PhD	Mayo Clinic, Rochester, MN	Major role in the acquisition of data; revised the manuscript for intellectual content
Heather M. Clark, PhD	Mayo Clinic, Rochester, MN	Major role in the acquisition of data; revised the manuscript for intellectual content
Rene L. Utianski, PhD	Mayo Clinic, Rochester, MN	Major role in the acquisition of data; revised the manuscript for intellectual content
Hugo Botha, MD	Mayo Clinic, Rochester, MN	Major role in the acquisition of data; revised the manuscript for intellectual content
Mary M. Machulda, PhD	Mayo Clinic, Rochester, MN	Major role in the acquisition of data; revised the manuscript for intellectual content
Edythe A. Strand, PhD	Mayo Clinic, Rochester, MN	Major role in the acquisition of data; revised the manuscript for intellectual content
Keith A. Josephs, MD, MST, MSc	Mayo Clinic, Rochester, MN	Designed and conceptualized the study; analyzed the data; major role in the acquisition of data; obtained funding; study supervision or coordination; revised the manuscript for intellectual content

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Table 1: Characteristics of degenerative motor speech disorders (apraxia of speech and dysarthria) and aphasia

Sign	Characteristic	Types	Anatomic correlate
Apraxia of Speech (AOS)	Motor speech disorder affecting planning or programming. Typically characterized by slow speaking rate, distorted sound production and sound substitutions, additions, repetitions, and prolongations. Groping, with trial and error articulatory movements are often observed.[2]	• Phonetic (type 1)[4] • Prosodic (type 2)[4] • Mixed (type 3)	Superior lateral and medial premotor cortex
Dysarthria	Motor speech disorder affecting the execution of speech. Dysarthria characteristics downstream of speech planning and programming and are mostly distinct from the characteristics of AOS. Examples of dysarthria characteristics that do not overlap with AOS include hoarseness, breathiness, strained-harsh voice, variability in loudness, hypernasality and accelerated rate[6].	• Spastic • Hypokinetic • Hyperkinetic • Flaccid • Ataxic • Mixed	Upper motor neuron (spastic), basal ganglia (hypo and hyperkinetic), lower motor neuron (flaccid), cerebellum (ataxic)
Aphasia	Aphasia implies impairment in the primary domain of language, vocabulary, semantics, phonology, and syntax. These characteristics can be observed in both spoken and written language comprehension and expression. Involvement of any of these characteristics may lead to a diagnosis of primary progressive aphasia[35].	• Agrammatic[14] • Semantic[14] • Logopenic[14] • Unclassified	Broca's area (agrammatic), left anteromedial temporal lobe (semantic), and left temporoparietal cortex (logopenic)

Table 2: Demographic and clinical features at time of first visit

	PPAOS (N=42)	AOS+PAA (N=56)	PAA (N=11)
Age, years	72 (62, 78)	68 (62, 73)	69 (65, 75)
Sex, % female	23 (54.8%)	29 (51.8%)	7 (63.6%)
Time from onset to first research visit, years	3 (2, 5)	3 (2, 4)	2 (1, 2)
AOS Severity (0-3 scale)*	1 (1, 2)	2 (1, 3)	0 (0, 0)
Aphasia Severity (0-3 scale)*	0 (0, 0)	1 (1, 2)	2 (1, 2)
Apraxia of Speech Rating Scale (/52, higher is worse)	15 (11, 21)	17 (12, 25)	2 (1, 4)
Motor Speech Disorder Scale (/10)	7 (6, 8)	6 (5, 7)	10 (10, 10)
Northwestern Anagram Test (/10)	10 (9, 10)	7 (5, 8)	5 (3, 8)
Western Aphasia Battery - Aphasia Quotient (/100)	98 (96, 99)	86 (81, 94)	89 (81, 92)
Western Aphasia Battery – Fluency subscore (/10)	10 (9, 10)	6 (5, 9)	6 (6, 9)
Montreal Cognitive Assessment Battery (/30)	28 (26, 29)	24 (21, 25)	23 (22, 24)
Movement Disorders Society sponsored revision of the Unified Parkinson's Disease Rating Scale part III (/100)	12 (5, 17)	11 (6, 20)	7 (2, 10)
Trail Making Test A, MOANS	9 (7, 11)	7 (5, 9)	7 (5, 10)
Trail Making Test B, MOANS	9 (7, 11)	8 (5, 9)	6 (3, 9)
Auditory Verbal Learning Test delayed recall MOANS	11 (10, 14)	9 (8, 11)	6 (5, 8)
Visual Object and Space Perception battery - fragmented letters (/20)	20 (19, 20)	20 (19, 20)	19 (19, 20)
Visual Object and Space Perception battery – cube analysis (/10)	10 (9, 10)	9 (7, 10)	9 (8, 10)

Results are shown as median (1st and 3rd quartiles). MOANs = Mayo Older American Norms (mean of 10 in a normal population with standard deviation of 3). *Rater judgments of severity determined by consensus between two speech-language pathologists (0=absent, 1=mild, 2=moderate, 3=severe).

Figure Legends

Figure 1: Swim plot of follow-up by calendar year

Each individual is represented by a horizontal segment in this plot, colored and arranged by diagnosis group. The calendar date of the first visit is the dark square in each segment. Left of the dark point represents the time from onset to first visit, and right of the point represents follow up from first visit, thus the total length of the line is used in the time-to-event analyses. An × at the end of a segment indicates the patient has died, a • indicates a censor (i.e. the last known date a patient was alive).

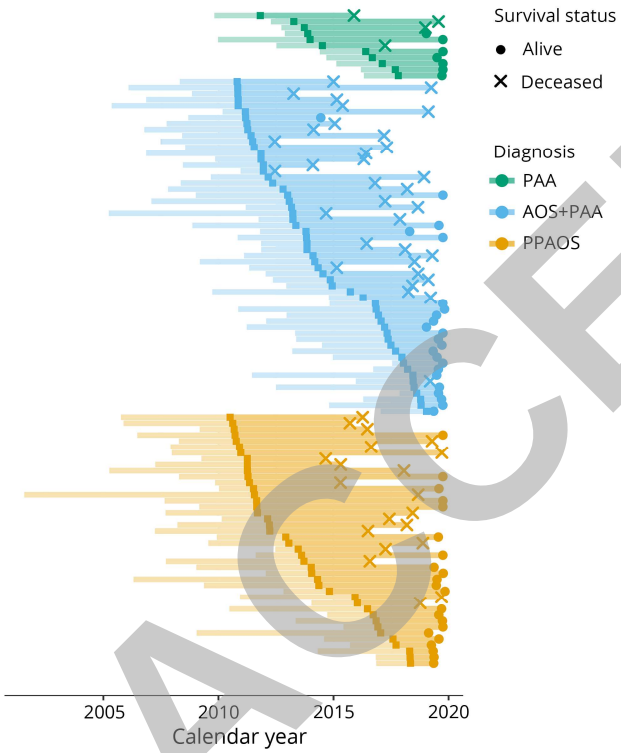
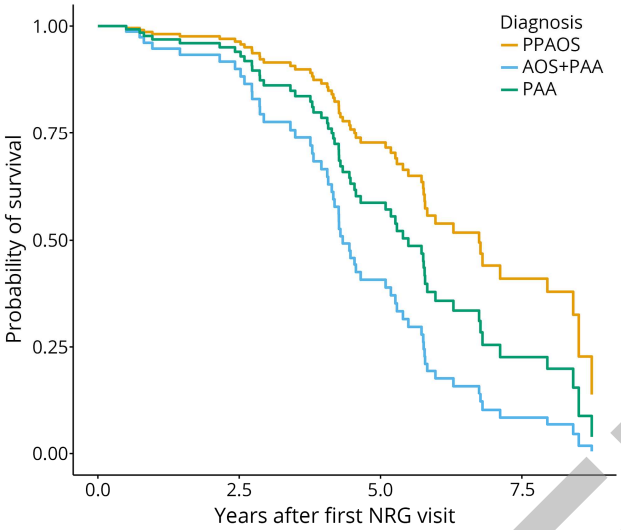


Figure 2: Visualization of the Cox model results depicting expected survival by diagnosis group, PPAOS, AOS+PAA and PAA.



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