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Survival in progressive supranuclear palsy and frontotemporal dementia

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Abstract

Objective: To compare survival and to identify prognostic predictors for progressive supranuclear palsy and frontotemporal dementia.

Background: PSP and FTD are related disorders. Homozygosity for H1 haplotype is associated with PSP, whereas several *MAPT* mutations have been identified in FTLD-tau. Survival duration probably reflects underlying pathophysiology or disease.

Methods: Patients with PSP and FTD were recruited by nation-wide referral. Survival of 354 FTD patients was compared to that of 197 PSP patients. Cox regression analysis was performed to identify prognostic predictors. FTLD-tau was defined as Pick's disease and FTDP-17 with *MAPT* mutations. Semiquantitative evaluation of tau-positive pathology was performed on all pathologically proven cases.

Results: Median survival of PSP patients (8.0 years; 95% CI 7.3 to 8.7) was significantly shorter than of FTD patients (9.9 years; 95% CI 9.2 to 10.6). Corrected for demographic differences, PSP patients were still significantly more at risk of dying than FTD patients. In PSP, male gender, older onset-age, and higher PSP Rating Scale score were identified as independent predictors for shorter survival, whereas in FTD a positive family history and an older onset-age were associated with a poor prognosis. The difference in hazard rate was even more pronounced when comparing pathologically proven cases of PSP with FTLD-tau.

Conclusion: Survival of PSP patients is shorter than of FTD patients, and probably reflects a more aggressive disease process in PSP. Independent predictors of shorter survival in PSP were male gender, older onset-age and higher PSP rating scale score, whereas in FTD a positive family history and higher onset-age were predictors for worse prognosis.

Introduction

Progressive supranuclear palsy (PSP) is clinically characterized by parkinsonism, supranuclear gaze palsy and cognitive decline,[1, 2] and shows clinical, pathological and genetic overlap with frontotemporal dementia (FTD).[3-5] A frontal presentation has been identified in 20 percent of PSP cases,[6] whereas FTDP-17 associated with microtubule associated protein tau (*MAPT*) mutations may present with the clinical picture of PSP.[7, 8] Neuronal and glial tau-positive inclusions are found in PSP and consist mainly of hyperphosphorylated four-repeat tau isoforms. In contrast to this, a subset of FTLD with Pick bodies (so-called Pick's disease) is characterized by the accumulation of three-repeat tau isoforms,[9] whereas inclusions in FTDP-17 with *MAPT* mutations variably consist of three- and four-repeat tau isoforms, depending on the location of the mutation.[10] The relevance of clinical and pathological overlap is further emphasized by the strong association between *MAPT* H1/H1 genotype and PSP.[11] Determining survival within this FTLD-PSP spectrum is of important clinical relevance and may give insight into the underlying disease process. However, only a few small studies compared survival between PSP and FTD and did not find any differences.[12, 13] Small pathological series of PSP and tau-positive and tau-negative FTLD patients have shown conflicting results regarding the effect of tau pathology on survival.[14-16] In a recent study, specific neuropsychological profiles in FTLD have been correlated to disease duration, whereas onset-age or positive family history were not.[12] Early falls and gaze palsy have been found as prognostic features in retrospective studies on PSP,[17-20] whereas the PSP Rating Scale (PSPRS) has also proven to be of predictive value in survival in a prospective longitudinal study.[21] However, this still has to be replicated. Severity of tau pathology has shown an inverse correlation with prognosis in PSP,[22, 23] whereas conflicting results have been reported in FTLD.[14-16, 24]

The aim of this study is to prospectively investigate the survival in two large cohorts of PSP and FTD patients in relationship to demographic and clinical features, and to the presence and severity of tau pathology in a subset of patients who underwent brain autopsy.

Methods

Patients with PSP and FTD were recruited by nation-wide referral from neurologists and by visiting patients in nursing homes.[6, 25] Detailed clinical history, including the first presentation of symptoms, was obtained from patients and their family members, and by reviewing medical records. The onset-age was defined as the age at which the first symptom attributable to PSP and FTD appeared according to the patient's caregiver and from medical records. In case of discrepancies, data from medical records were used. Data on family history were obtained using a structured questionnaire provided by spouse or first-degree relative. Family history was defined positive if at least one first-degree relative suffered from dementia, parkinsonism or motor neuron disease. All available hard copies of neuroimaging of both PSP and FTD patients were reviewed by the investigators in order to exclude other structural causes of both conditions and to semiquantitatively measure the severity of lobar atrophy.

PSP patients were neurologically examined, videotaped and the severity of their cognitive and motor functioning was scored by means of Mini-mental State Examination (MMSE), Frontal Assessment Battery (FAB), Unified Parkinson's Rating Scale-III (UPDRS-III) and PSPRS.

FTD patients underwent neurological examination, neuropsychological evaluation and neuroimaging (CT, MRI or SPECT with ^{99m}Tc -hexamethyl propyleneamine oxime (HMPAO)).

The clinical diagnosis of all patients was established in a consensus meeting according to the National Institute for Neurological Diseases and Stroke-Society for PSP (NINDS-SPSP)

criteria[2] and the Lund and Manchester criteria for FTD.[26] PSP patients were subdivided

according to phenotype as described by Williams *et al.*[27] 119 patients were classified as

Richardson's syndrome (RS) and seven cases of PSP-parkinsonism (PSP-P) were identified in our

cohort. Of 18 patients there was insufficient data available of the first two years after onset. The

remainder of the patients (n=51) could not be subdivided into a phenotype. Both studies on PSP

and FTD patients were approved by the Medical Ethics Committee of the Erasmus Medical

Centre of Rotterdam. Informed consent for participation (including blood collection) was

obtained from the spouse or a first-degree relative of each patient. *MAPT*, *CHMP2B* and *GRN* genes were sequenced in all familial FTD patients, as has been previously described.[28-30] In PSP patients with a positive family history, screening of *MAPT*, *GRN*, and *LRRK2* was performed according to previously described methods.[29, 31, 32]

The possibility of post-mortem examination was discussed with patients and their relatives during follow-up. Brain autopsy of patients who gave consent and who died during follow up was conducted by the Netherlands Brainbank according to their Legal and Ethical Code of Conduct. All brains that became available for autopsy were processed for routine staining and immunohistochemistry with AT8 (1:40, Innogenetics, Ghent, Belgium), ubiquitin (1:500, Dako, Glostrup, Denmark), three-repeat tau isoform (RD3) and four-repeat tau isoform (RD4), p62 (BD Biosciences Pharmingen, San Diego, CA, USA; 1 : 200, following 80° C antigen retrieval), TDP-43 (Proteintech, Chicago, IL, USA; 1 : 100, following pressure-cooking), β -amyloid (anti- β -amyloid, DAKO, Glostrup, Denmark, 1: 100, following formic acid pre-treatment), α -synuclein (anti- α -synuclein, Zymed Laboratories, San Francisco, California, USA; undiluted, following formic acid pretreatment). These were incubated overnight at 4 °C. Endogenous peroxidase activity was inhibited by 30 min incubation in PBS–hydrogen peroxide–sodium azide solution (100 ml 0.1M PBS, 2ml 30% H₂O₂, 1ml natriumazide). The Histostain-Plus broad-spectrum kit DAB (Zymed, San Francisco, CA, USA) was used as a detection system. Slides were counterstained with Mayer's haematoxylin and mounted in Entellan.

The neuropathological diagnosis FTLD was classified into FTLD-tau and FTLD-U (with or without TDP-43-positive inclusions).[33] FTLD-tau was defined as Pick's disease and FTDP-17 with *MAPT* mutations. Cases with FTD-MND were excluded from this study. In FTLD-tau cases, neuronal loss and tau-staining reactive neurons and glial cells were visually quantified (none, mild, moderate and severe) in the following regions: frontal lobe, temporal lobe, hippocampus, parietal lobe, caudate nucleus and substantia nigra.

The neuropathological diagnosis PSP was established according to international criteria,[34] and a semiquantitative assessment of neurofibrillary tangles (NFT), tufted astrocytes (TA), oligodendroglial coiled bodies (CB) and thread pathology (Th) in all regions was carried out by two raters (WK, JvS) using a five-point grading scale according to Williams *et al.*[23] The PSP-tau score was calculated from the combined grade of coiled bodies and thread lesions in the substantia nigra and caudate and dentate nucleus.

Follow-up of PSP and FTD patients was performed by visits to the outpatient department of the Erasmus Medical Centre or by telephone interview with relatives up to August 1, 2008.

Statistical analysis

SPSS 15.0 for Windows (SPSS, Chicago, IL) was used for analysis. Onset-age, gender and family history were analyzed by independent sample *t*-test or Chi-square test. Actuarially corrected median survival was calculated, as well as mean survival in deceased cases. Survival analysis was performed using the Cox proportional hazard model, using a backward selection procedure model. Only results of multivariate analyses are shown, with variables that were significant in the univariate analysis. As the early occurrences of clinical symptoms are incorporated into the PSPRS, these symptoms were not analyzed together with the PSPRS in one model. However, different sections of the PSPRS (history, mentation, bulbar, ocular, limb and gait sections) were analyzed separately. Entry date was set as time of first symptoms. Censoring date was either date of death or end of follow-up (August 1st, 2008). The assumption of proportionality of hazards was examined by Log-Log plots. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Onset-age and PSPRS score were categorized into quartiles. Correlation between tau pathology and disease duration and onset-age was examined using Spearman's calculation. All statistical testing took place at a 0.05 level of significance (two-tailed).

Results

The demographic data of patients with PSP and FTD are summarized in **Table 1**.

	PSP	FTD	p-value
N	197	354	
Age at symptom onset , years*	66.2 ± 8.1	57.5 ± 8.9	<0.001
Male gender, n (%)	102 (51.8)	164 (46.3)	0.220
Presence of family history, n (%)	62 (31.5)	169 (47.7)	<0.001

*Mean ± SD. PSP, progressive supranuclear palsy; FTD, frontotemporal dementia.

FTD-MND patients (n=30) were excluded, due to their known shorter disease duration. Two PSP patients died of non-natural cause and have not been included in the survival analyses. The mean onset-age and age at death of PSP patients were significantly higher than that of FTD patients. During follow-up, 133 of 197 patients with PSP died at a mean disease duration of 7.2 ± 2.6 years, whereas 242 out of 354 FTD patients had died after a mean disease duration of 9.2 ± 4.1 years.

Survival and hazard analysis of PSP and FTD

The median disease duration in PSP patients (8.0 years; 95% CI 7.3 to 8.7) was significantly shorter than in FTD patients (9.9 years; 95% CI 9.2 to 10.6) (Chi-square 17.1, p<0.001) (**Figure 1**). This worse prognosis for PSP patients than FTD patients in a univariate analysis (HR 0.634; 95% CI 0.509 to 0.788) remained significant after adjustment for gender, onset-age and family history (HR 0.766; 95% CI 0.603 to 0.975). Comparing PSP phenotypes, RS (6.8 years; 95% CI 6.3 to 7.4) was found to have shorter median survival than PSP-P (10.9 years; 95% CI 7.5 to 14.2) and the non-conclusive group (8.8 years; 95% CI 8.2 to 9.3).

Cox proportional hazards regression model of PSP patients (**Table 2**) revealed male gender, older onset-age (>72 years) and higher score on the PSPRS to be independent predictors for

shorter disease duration, after adjustment for the interval between onset and ascertainment (mean of 5.3 ± 2.6 years).

Table 2 Multivariate Cox models in PSP patients (HR with 95% CI)

		p-value
Gender	0.627 (0.428 to 0.918)	0.016
Positive family history		ns
Estimated onset-age		
< 62	1 (reference)	
62 to 66	0.878 (0.515 to 1.498)	0.634
66 to 72	1.453 (0.846 to 2.498)	0.176
> 72	2.028 (1.211 to 3.398)	0.007
PSPRS*		
0 to 35	1 (reference)	
35 to 48	1.956 (1.068 to 3.584)	0.030
48 to 62	2.991 (1.646 to 5.435)	<0.001
> 62	8.553 (4.478 to 16.337)	<0.001

*10 patients had missing values on the PSPRS;

HR, Hazard ratio; CI, confidence interval; ns, not significant

When entering separate sections of the PSPRS in the model, only supranuclear ocular motor exam (HR 1.195; 95% CI 1.090 to 1.310) remained significant, whereas bulbar exam (HR 1.144; 95% CI 0.997 to 1.312) and gait exam (HR 1.063; 95% CI 0.999 to 1.131) were near significant.

In FTD patients, positive family history (HR 1.438; 95% CI 1.114 to 1.858) and onset-age >64 years (HR 1.656; 95% CI 1.160 to 2.363) were significantly associated with poor survival.

Looking into family history in FTD in more detail, mean disease duration of deceased FTD patients with a negative family history (9.9 years; 95% CI 9.1 to 10.6) was significantly longer than that of FTD patients with a positive family history (8.4 years; 95% CI 7.7 to 9.1; $p=0.006$). In this latter group a trend towards longer mean disease duration of patients with a *MAPT* mutation (n=36 from 10 families; 9.3 years; 95% CI 7.8 to 10.8) was found compared to patients without a *MAPT* mutation (n=83, including 17 patients with a *GRN* mutation from three families; 8.1

years; 95% CI 7.3 to 8.8; $p=0.105$). Of the *MAPT* mutations, L315R had the shortest mean disease duration ($n=5$; 5.7 ± 1.9 years), followed by P301L ($n=20$; 8.2 ± 3.0 years), whereas R406W had the longest mean disease duration ($n=4$; 17.5 ± 3.2 years). The remaining *MAPT* mutations, S320F ($n=1$), G272V ($n=5$), and $\Delta K280$ ($n=1$) all had a mean disease duration of just above 10 years. Patients with a GRN mutation had a survival of 7.7 ± 2.8 years.

Pathology

Pathological examination was available for 24 PSP patients (all RS) and 61 FTLD patients (FTLD-tau $n=32$ and FTLD-U $n=29$). Men were over-represented (70.8%) in the PSP series, and the FTLD series showed a higher percentage of a positive family history (57.6%) and younger onset-age (55.3 years) than the total group, due to significant lower onset-age for cases with *MAPT* mutations (50.9 years).

After adjustment for gender, onset-age, and family history, FTLD-tau patients remained less at risk than PSP patients (HR 0.524; 95% CI 0.282 to 0.974), and a trend towards longer survival was found compared to FTLD-U patients (HR 0.608; 95% CI 0.361 to 1.024).

The FTLD-tau group consisted of 15 sporadic cases, all of which showed pure three-repeat tau pathology, and 17 cases with *MAPT* mutation, with pure three-repeat (G272V and $\Delta K280$), pure four-repeat (P301L), or a mix of three-repeat and four-repeat (S320F, R406W and L315R) tau pathology depending on the location of the mutation. All PSP cases showed four-repeat tau pathology. The mean disease duration of sporadic Pick's disease cases was 12.1 years and was similar to that in *MAPT* cases with three-repeat tau pathology ($n=6$) of 10.2 years, whereas a trend ($p=0.098$) could be observed towards shorter survival in *MAPT* cases with 4-repeat tau pathology ($n=7$) of 8.6 years. Disease duration in *MAPT* mutations with a mix of three-repeat and four-repeat tau pathology varied considerably.

The FTLD-U cohort consisted of nine type 1, 16 type 2 and four type 3 (all four with GRN mutation) cases. Survival of pathological GRN cases did not significantly differ from the total

group of deceased GRN cases or FTLD-U type 2 cases (8.4 ± 3.1 years), but was significantly shorter than survival of FTLD-U type 1 cases (11.6 ± 5.0 years).

Tau pathology quantification

Neuronal loss in PSP cases was most prominent in subthalamic nucleus, globus pallidus, dentate nucleus and substantia nigra. Tau pathology consisting of globoid neurofibrillary tangles, tufted astrocytes and glial coiled bodies varied considerably between cases, with the subthalamic nucleus, thalamus, substantia nigra, basal pontine nuclei, locus coeruleus and dentate nucleus regions most severely involved. The severity of tau pathology, expressed in the tau-score, showed a significant negative correlation with disease duration (**Figure 2**), but was not correlated with onset-age.

For the FTLD-tau group, neuronal loss in frontal, temporal and hippocampus regions was severe in most cases, whereas parietal, caudate nucleus and substantia nigra regions showed a variable neuron loss. Tau-positive inclusions showed a similar pattern of topographic distribution with severe tau pathology in frontal and temporal cortex and hippocampal regions, whereas the severity of tau pathology was more variable in parietal cortex, caudate nucleus and substantia nigra. Astrocytic tau pathology was severe in the L315R mutation, but only mild in other *MAPT* mutations and sporadic Pick's disease. No significant correlation could be found between disease duration and either neuronal loss or tau-reactivity in any region.

Discussion

This study is the largest prospective population-based study comparing the survival between patients with PSP and FTD, and showed significantly shorter disease duration in PSP. This difference was even more pronounced when comparing pathologically proven cases of PSP with FTLD-tau. This study replicates, for the first time, the prognostic value of the PSPRS with a sharp increase of probability of death above a score >60. In PSP patients, male gender and older

onset-age were also independent predictors for shorter disease duration, whereas a positive family history and an older onset-age were associated with a poor prognosis for FTD.

Our observation of a shorter disease duration in PSP than in FTD contrasts with two other studies,[12, 13] in which the small number of PSP patients may explain the lack of correlation. Our findings are probably close to true survival rates, as the patients were population-based ascertained. Looking into the natural history of PSP separately, the mean disease duration of deceased cases of 7.2 years in the present study comes very close to 6.8 years found in the only other large prospective study by Golbe *et al.*,[21] whereas a large retrospective study[20] showed shorter survival of 5.7 years. This was also true for RS cases in the clinicopathological study by O'Sullivan *et al.* (6.2 years),[35] whereas a much longer survival was found for PSP-P patients (11.6 years). Although our PSP-P group consists of only 7 cases, due to the strict use of NINDS-SPSP criteria, the difference in survival compared to our RS cases was striking as well. The effect of higher onset-age on survival in the present study was also found in retrospective studies,[20, 21, 35] whereas our observed predictive value of gender contrasted to a weak or absent effect on survival in several other studies,[18, 20, 21] but not all.[35] The prognostic significance of older onset-age in PSP resembles observations made in Alzheimer's disease[36] and Parkinson's disease (PD), whereas there is conflicting evidence regarding effect on prognosis of male gender in PD.[37] A good explanation for lower survival in men with PSP in our study is lacking. The finding might perhaps be explained by differences for gender in co-morbidity at higher age. However, such data are not available in our study.

The predictive value of the PSPRS score for survival in PSP patients confirms the first observations made in a tertiary referred cohort of Golbe *et al.*[21] and also proves its predictive value in a population-based cohort. In line with Golbe's observations, a sharp rise in mortality risk was seen in patients with a PSPRS score above 60. Only the subsections supranuclear ocular motor exam, bulbar exam and gait exam were of prognostic value in our study. The replication of Golbe's findings on the PSPRS has implications for its potential use in clinical trials.

Shorter survival in FTD patients with a positive family history in this study contrasts with other studies on the natural history of FTD,[12, 13, 24, 38, 39] and may suggest a more malignant disease process for hereditary forms. This is especially true for patients with *GRN* mutations and hereditary FTLD with an unknown genetic defect, both groups exhibiting ubiquitin pathology,[40] whereas *MAPT* mutations showed a trend towards longer disease duration.

However, as several mutation carriers were related, we cannot exclude other familial genetic factors influencing the disease duration within the families. The absence of an association between positive family history and survival in other studies may be explained by a low number of patients or an unknown family history.

The longer survival of FTLD-tau group than compared to pathologically proven PSP cases supports the hypothesis of a different disease process. The mean disease duration in the present series of 11.1 years is similar to that in the study by Hodges *et al.* (9.0 years).[24] The shorter survival of tau-positive cases (6 years) in the study by Xie *et al.*[16] can be explained by the inclusion of PSP and CBD cases. Our findings are very similar to the observations made by Hu *et al.*,[14] which showed that three-repeat FTLD-tau have longer survival than four-repeat FTLD-tau and four-repeat controls, comprising PSP and CBD patients, and supports the idea that FTLD-tau patients tend to have a more indolent disease course than PSP.

The observed negative correlation between the severity of glial tau pathology and disease duration in PSP patients is in line with the study by Josephs *et al.*[22] The severity of oligodendroglial tau pathology in the substantia nigra and caudate and dentate nucleus represented the overall tau pathology reliably in the study by Williams *et al.*, which again correlated negatively with disease duration,[23] and was shown higher in RS than in PSP-P. Due to the absence of PSP-P in our pathological cohort, we could not replicate the latter finding. The correlation between the type and severity of tau pathology indicates that pathophysiological mechanisms determine the disease progression. Small sample size, a semiquantitative method of scoring, and different *MAPT* mutations with different functional effects may have hampered our

analysis in FTLD. The association in FTLD between shorter survival and abundant tau pathology in basal ganglia in the study by Xie *et al.*[16] could not be confirmed by our study, and should probably be explained by the inclusion of PSP and CBD cases in their analysis. The best strategy would be to extend the survival analysis to a much larger series of pathologically proven FTD cases, which have been prospectively ascertained during life in order to collect reliable clinical information.

One of the drawbacks of the present study is a selection bias towards typical cases, and therefore missing cases with PSP-P, a subgroup that usually has a longer disease duration and an atypical presentation. Furthermore, as the population of the study consists of cases alive at the time of entry, there may be some degree of survival bias. A final drawback is that there was pathological confirmation in only 24 of 133 of the deceased patients. However the NINDS-SPSP criteria show a good positive predictive value for probable PSP (100%) and possible PSP (83%) in patients presenting with parkinsonism,[34] but also in patients presenting with dementia (96% for combined possible and probable PSP).[41] Also, no large differences were found between our clinical and our pathological cohort.

In conclusion, this large prospective study showed that survival in PSP is shorter than in FTD. This difference in prognosis was even more pronounced when comparing pathological PSP cases with FTLD-tau. Within the PSP group, male gender, older onset-age, and higher PSPRS score were independent predictors for shorter disease duration, whereas a positive family history and an older onset-age were associated with a poor prognosis in FTD. The significant effect of diagnosis on survival may suggest that the underlying pathophysiology in PSP is more aggressive than in FTD. This perspective should help clinicians anticipate disease progression of patients with PSP and FTD.

Disclosure

The authors report no conflict of interest

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Figure legends

Figure 1 Kaplan Meier survival curve for PSP and FTD patients

Figure 2 Disease duration of pathologically proven PSP cases according to PSP-tau score

(Spearman's rho -0.44 , $p=0.045$)



