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ORIGINAL ARTICLE

Patterns of neuropsychiatric symptoms in primary and secondary tauopathies: caregiver and patient perspectives

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Summary

Introduction/Aims: Understanding the differences in neuropsychiatric symptoms (NPSs) across tauopathies, particularly in the early stages of the disease, may aid in differential diagnosis. The aims of the research are as follows**:** a) to examine the patterns of NPSs in primary (frontotemporal dementia – FTD and progressive supranuclear palsy – PSP) and secondary (Alzheimer's disease – AD) tauopathies; b) to examine the differences in NPSs reported by patients and caregivers.

Methods: The study included 312 patients, 176 of whom had a disease duration of ≤3 years. The presence of NPSs based on caregiver's report was assessed by neuropsychiatric questionnaire (NPI). Patient's assessment of NPSs was examined by Hamilton's Depression and Anxiety Scales and the Apathy Scale.

Results: In AD, the most common and severe neuropsychiatric symptoms are mood disorders and apathy. In contrast, agitation-related symptoms are also prominent in FTD and PSP. The profile of NPSs in FTD and PSP is similar, but irritability and aberrant motor behavior are more pronounced in FTD, while sleep disturbances are dominant in PSP. The prevalence of NPSs reported by caregivers on NPI was higher than that reported by patients.

Conclusions: FTD and PSP are characterized by more frequent and more severe NPSs and have distinct psychiatric patterns compared to AD, even in the early disease course. Caregiver's observations of the patient's behavior could be of key importance in distinguishing these tauopathies, particularly in the absence of hard motor and cognitive symptoms in early disease course. Assessments of depression, anxiety, and apathy by patients themselves and their caregivers differ significantly, and data from these two sources cannot be considered interchangeable and comparable.

Keywords: tauopathies, Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, neuropsychiatric symptoms

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INTRODUCTION

Tauopathies are neurodegenerative diseases defined histopathologically by the presence of intracellular inclusions, composed of aggregates of pathologically altered tau protein (1). The most common diseases from the group of primary tauopathies include frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), and corticobasal syndrome. On the other hand, Alzheimer's disease (AD) is generally the most common tauopathy, although this disease is now classified as a secondary tauopathy, where in addition to a significant accumulation of pathological tau protein there is also an accumulation of beta-amyloid (2). Despite clearly defined clinical criteria, behind which there are unique pathohistological substrates, these diseases are often difficult to distinguish from each other during life. This especially applies to the early phases of the disease, when a significant overlap of cognitive, motor, and neuropsychiatric symptoms (NPSs) is observed, which diverge toward separate clinical presentations only in the later stages when the clinical diagnosis is easier to establish. There is increasing evidence in the literature that NPSs can even precede the first symptoms and signs of the disease, but these manifestations rarely capture the attention of doctors to the extent that cognitive and motor symptoms do (3–5). Furthermore, NPSs are increasingly integrated into research diagnostic criteria for neurodegenerative disorders (6) and are recognized as an important determinant of impaired quality of life (7, 8), which makes their evaluation even more important. A better understanding of the differences in NPS profiles manifested in the early stages of these diseases could potentially contribute to an easier differential diagnosis.

Equally important is the fact that current assessments of NPSs rely on methodologically diverse scales. Some are based on caregiver evaluations, while others rely on patient self-assessments, making it difficult to accurately understand the true severity and frequency of these symptoms.

Bearing in mind the above-mentioned data, we set the main aims of our study: 1) examination of NPSs patterns in patients with AD, FTD, and PSP, with an emphasis on the early stages of the disease, and 2) examination of differences in the profile of neuropsychiatric symptoms based on caregivers' and patients' reports.

METHODS

Our study included 312 patients with the most common forms of primary and secondary tauopathies: AD (160 patients), FTD (93 patients), and PSP (59 patients), who met the valid criteria for the diagnosis of these diseases (9-11). Patients with a history of neurological, psychiatric, or systemic diseases, as well as those with previous or current substance abuse, were excluded from the study.

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade. The informed consent was signed by patients and/or caregivers.

Detailed demographic and clinical data were collected through a structured questionnaire, based on an interview with the patient and/or caregiver. Age at disease onset was defined as the age at which cognitive and/or motor symptoms attributable to these diseases first appeared. Disease duration of up to 3 years is classified as the early phase, while duration exceeding 3 years is considered the late phase. The Mini-Mental Test (MMSE) (12), the Frontal Assessment Battery (FAB) (13), and the Mattis Dementia Rating Scale (DRS) (14) were used to examine patients' cognitive status.

The presence of NPSs was assessed by the neuropsychiatric inventory (NPI), which is based on an interview with the patient's caregivers (15). It includes the frequency (from 0 to 4) and severity (from 0 to 3) of 12 neuropsychiatric domains: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disorder, appetite/eating habits. A score of 0-12 was obtained for each domain by multiplying the frequency with the severity of complaints. Composite scores for each domain were used further in the analysis. Bearing in mind that low composite scores may be trivial in the clinical context, we also analyzed patients who had a composite score ≥4 in the respective NPI domains. The total NPI score is the sum of all domain scores, ranging from 0 to 144, with higher values indicating more severe neuropsychiatric symptoms. In addition to the NPI, symptoms of depression, anxiety, and apathy were also examined with additional scales based on the patient's assessment of symptoms: the Hamilton Depression Rating Scale (HAMD) (16), the Hamilton Anxiety Rating Scale (HAMA) (17), and the Apathy Scale (AS) (18). To define the presence/absence of depression, anxiety, and apathy, previously defined *cut-off* values for these scales were used (HAMD≥8, HAMA≥13, AS≥14) (19, 20, 21).

Statistical analysis

The following software package was used for all statistical analyses: SPSS, version 23.0; SPSS Inc.; Chicago, USA.

To identify differences in the mean values of the respective variables between the three groups of patients, the ANOVA test was used (corrected for multiple testing using the Games-Hovell post-hoc test). The chi-square test and Fischer's exact probability test were used to compare categorical variables, where appropriate. Statistical significance was defined as the value of $p < 0.05$.

RESULTS

Demographic and clinical characteristics of investigated cohorts

The study included 312 patients (176 with disease duration ≤ 3 years (early phase) and 136 with disease duration >3 years (late phase)) diagnosed with AD, FTD, and PSP, whose demographic and clinical characteristics, as well as the basic differences in cognitive profiles, are shown in **Table 1**.

Patients with PSP had a later disease onset and were older at the time of evaluation. In terms of global cognitive status, measured by the DRS scale, as well as in terms of frontal cognitive dysfunction, measured by the FAB scale, patients with AD showed the lowest achievements consistently during the disease course, while PSP and FTD did not differ from each other, both in early and late phases of the disease **(Table 1)**.

The neuropsychiatric profile in early and late phases across different tauopathies

At the time of evaluation, all PSP patients had at least one neuropsychiatric symptom present (NPI>0) even in the early phase of the disease, followed by 85% of FTD and 77% of AD patients. A similar percentage of NPSs was reported by caregivers in late phases in all patient groups **(Table 2)**.

In the early stage of the disease in the group of AD patients, the highest NPI composite scores, reflecting the severity of NPSs, were recorded in the domains of apathy, depression, and anxiety **(Table 2, Figure 1)**. In primary tauopathies, both PSP and FTD, the highest scores were also recorded in the domain of apathy, even significantly more pronounced than in AD. However, the symptoms that showed a statistically significant difference in severity between Alzheimer's disease (AD) and frontotemporal dementia (FTD) or progressive supranuclear palsy (PSP) mainly fall within the agitation subsyndrome (irritability, agitation, disinhibition, euphoria, and aberrant motor behavior), as well as changes in eating habits and sleep patterns. The neuropsychiatric symptom profile in the early stages of FTD is largely similar to that of progressive supranuclear palsy PSP. However, patients with FTD exhibit more pronounced irritability and aberrant motor behavior compared to those with PSP, while sleep disturbances are more characteristic of PSP **(Table 2, Figure 1)**.

The differences in the severity of apathy, disinhibition, irritability, and sleep domains were maintained even in **the late stages** of the disease between primary and secondary tauopathies. Differences in symptoms from the domain of agitation, euphoria, aberrant motor behavior, and changes in eating habits that were observed in the early stages are lost in the late disease course. No differences were observed in the neuropsychiatric profiles between PSP and FTD in the late stages of the disease **(Table 2, Figure 1)**.

Some of these NPSs, in addition to being characterized as the most severe, were also found to be **the most frequent**, such as apathy and depression (Table 2, Figure 1). However, the symptoms found to be mostly characteristics of primary tauopathies (FTD/PSP) (those belonging to agitation subsyndrome), occurred in less than 50% of patients **(Table 2, Figure 1)**.

Table 1. Demographic and clinical characteristics of early and late phases of primary and secondary tauopathies

	Early phase (≤3 years) N=176				**Late phase (>3 years) N=136**			
Characteristics	**AD** N=95	**FTD** N=54	**PSP** N=27	**p-value**	**AD** N=65	**FTD** N=39	**PSP** N=32	**p-value**
female: male ratio	56:39	24:30	8:19	**AD vs. PSP***	42:23	19:20	15:17	ns*
Age (years)	58.81±5.66 (38-67)	58.78±5.93	65.77±7.08	**AD vs. PSP FTD vs. PSP**	61.80±4.01	61.87±6.51	67.97±6.60	**AD vs. PSP FTD vs. PSP**
Education (years)	11.90±2.50 (4-18)	12.74±2.83	12.37±2.51	ns	11.23±3.156	11.69±3.28	11.44±3.78	ns
Disease duration (years)	2.29±0.61 (1-3)	2.14±0.68	2.32±0.66	ns	4.92±1.02	5.36±2.08	5.22±1.42	ns
Age at onset (years)	56.52±5.52 (37-65)	56.64±5.89	63.44±7.17	**AD vs. FTD AD vs. PSP PSP vs. FTD**	56.98±3.93	56.56±7.69	62.73±6.52	**AD vs. PSP PSP vs. FTD**
MMSE	17.61±5.42 (5-28)	21.87±6.45	25.07±4.44	**AD vs. FTD AD vs. PSP**	12.56±5.59	18.03±8.19	23.90±3.42	**AD vs. PSP AD vs. FTD FTD vs. PSP**
FAB total	7.59±4.07 (2-15)	9.84±5.05	10.04±3.81	ns	4.96±3.57	6.52±5.87	9.19±3.66	**AD vs. PSP**
DRS total	95.50±25.88 (22-134)	106.34±27.99	112.52±15.53	**AD vs. PSP**	73.94±33.84	92.23±35.24	103.63±23.01	**AD. vs PSP**

The figures in the table present mean values ± standard deviations with a range in the brackets. The groups of patients with a statistically significant difference were indicated in bold (ANOVA test with post hoc Games Howell, except for * where chi-square test was applied; $p<0.05$); ns: non-significant.
AD: Alzheimer's disease; FTD: frontotemporal dementia; PSP: progressive supranuclear palsy; MMSE: Mini-Mental State Examination test; FAB: Frontal Assessment Battery; DRS: Dementia Rating Scale (Mattis).

Table 2. Differences in severity and frequency of neuropsychiatric symptoms in primary and secondary tauopathies, both in early and late phases

	Early phase (≤3 years) N=176				**Late phase (>3 years) N=136**			
	AD N=95	**FTD** N=54	**PSP** N=27	**p-value**	**AD** N=65	**FTD** N=39	**PSP** N=32	**p-value**
NPI-Delusions								
Mean value ±SD	0.24±1.16	0.37±1.74	0.93±2.56	ns	0.58±1.64	0.56±1.65	0.50±1.74	ns
Patients with symptoms present (No (%))	6 (6)	4 (7)	5 (19)	ns	10 (15)	5 (13)	4 (13)	ns
Patients with score ≥4 (No (%))	4 (4)	2 (4)	4 (15)	ns	6 (9)	3 (8)	2 (6)	ns
NPI-Hallucinations								
Mean value ±SD	0.36±1.64	0.13±0.67	0.41±1.12	ns	0.42±1.51	0.36±1.94	0.09±0.30	ns
Patients with symptoms present (No (%))	8 (8)	2 (4)	4 (15)	ns	6 (9)	2 (5)	3 (9)	ns
Patients with score ≥4 (No (%))	4 (4)	1 (2)	2 (7)	ns	4 (6)	1 (3)	0 (0)	ns
NPI-Agitation								
Mean value ±SD	0.33±1.53	2.17±3.48	1.48±3.04	**AD vs. FTD**	1.22±2.49	1.46±3.36	2.34±2.97	ns
Patients with symptoms present (No (%))	6 (6)	18 (33)	9 (33)	**AD vs. FTD AD vs. PSP**	15 (23)	7 (18)	21 (66)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	5 (5)	17 (32)	5 (19)	**AD vs. FTD**	13 (20)	7 (18)	9 (28)	ns
NPI-Depression								
Mean value ±SD	3.19±3.44	3.02±3.91	2.22±2.68	ns	2.85±3.35	2.85±3.93	3.22±2.90	ns
Patients with symptoms present (No (%))	52 (55)	25 (46)	18 (67)	ns	32 (49)	15 (39)	27 (84)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	47 (50)	23 (43)	8 (30)	ns	31 (48)	15 (39)	15 (47)	ns
NPI-Anxiety								
Mean value ±SD	1.27±2.49	1.58±2.58	1.56±2.28	ns	1.15±2.51	1.49±2.41	1.97±2.60	ns
Patients with symptoms present (No (%))	25 (26)	18 (33)	12 (44)	ns	14 (22)	14 (36)	23 (72)	**AD vs. PSP FTD vs. PSP**
Patients with score ≥4 (No (%))	21 (22)	14 (26)	7 (26)	ns	13 (20)	10 (26)	6 (19)	ns
NPI-Euphoria								
Mean value ±SD	0.24±1.54	1.42±3.47	1.44±2.79	ns	0.00±0.00	1.36±3.41	0.50±1.02	ns
Patients with symptoms present (No (%))	3 (3)	9 (17)	8 (30)	**AD vs. FTD AD vs. PSP**	0 (0)	7 (18)	8 (25)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	2 (2)	8 (15)	5 (19)	**AD vs. FTD AD vs. PSP**	0 (0)	6 (15)	1 (3)	**AD vs. FTD**
NPI-Apathy								
Mean value ±SD	3.31±4.06	6.80±4.35	6.41±4.25	**AD vs. FTD AD vs. PSP**	3.12±3.53	7.54±4.30	7.53±4.27	**AD vs. FTD AD vs. PSP**
Patients with symptoms present (No (%))	46 (48)	42 (78)	24 (89)	**AD vs. FTD AD vs. PSP**	38 (59)	32 (82)	30 (94)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	41 (43)	41 (76)	21 (78)	**AD vs. FTD AD vs. PSP**	30 (46)	32 (82)	25 (78)	**AD vs. FTD AD vs. PSP**
NPI-Disinhibition								
Mean value ±SD	0.21±1.32	3.35±4.02	2.48±3.97	**AD vs. FTD AD vs. PSP**	0.12±0.70	2.26±4.16	3.31±3.35	**AD vs. FTD AD vs. PSP**
Patients with symptoms present (No (%))	3 (3)	26 (48)	15 (56)	**AD vs. FTD AD vs. PSP**	2 (3)	10 (26)	23 (72)	**AD vs. FTD AD vs. PSP FTD vs. PSP**
Patients with score ≥4 (No (%))	2 (2)	24 (44)	7 (26)	**AD vs. FTD AD vs. PSP**	2 (3)	9 (23)	14 (44)	**AD vs. FTD AD vs. PSP**
NPI-Irritability								
Mean value ±SD	0.59±2.10	3.24±4.10	1.59±3.21	**AD vs. FTD**	0.85±2.22	1.69±3.18	2.25±2.87	ns
Patients with symptoms present (No (%))	11 (12)	26 (48)	10 (37)	**AD vs. FTD AD vs. PSP**	13 (20)	12 (31)	21 (66)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	7 (7)	23 (43)	4 (15)	**AD vs. FTD FTD vs. PSP**	7 (11)	9 (23)	10 (31)	**AD vs. PSP**
NPI-Aberrant motor behavior								
Mean value ±SD	0.56±2.13	2.81±4.36	1.30±2.79	**AD vs. FTD**	1.06±2.62	3.13±3.90	1.75±2.53	ns
Patients with symptoms present (No (%))	8 (8)	19 (35)	12 (44)	**AD vs. FTD AD vs. PSP**	12 (19)	18 (46)	18 (56)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	7 (7)	18 (33)	2 (7)	**AD vs. FTD FTD vs. PSP**	10 (15)	17 (44)	8 (25)	**AD vs. FTD**
NPI-Sleep								
Mean value ±SD	1.04±2.63	1.31±3.24	2.07±2.80	ns	0.62±1.40	1.56±3.56	3.22±3.62	**AD vs. PSP**

Patients with symptoms present (No (%))	17 (18)	11 (20)	13 (48)	**AD vs. PSP FTD vs. PSP**	13 (20)	9 (23)	20 (62)	**AD vs. PSP FTD vs. PSP**
Patients with score ≥4 (No (%))	14 (15)	8 (15)	8 (30)	ns	7 (11)	6 (15)	14 (44)	**AD vs. PSP FTD vs. PSP**
NPI-Appetite/eating habits								
Mean value ±SD	0.75±2.39	2.76±3.86	1.48±2.78	**AD vs. FTD**	0.34±1.34	2.44±4.18	1.25±2.11	**AD vs. FTD**
Patients with symptoms present (No (%))	10 (11)	23 (43)	11 (41)	**AD vs. FTD AD vs. PSP**	6 (9)	11 (28)	13 (40)	**AD vs. FTD AD vs. PSP**
Patients with score ≥4 (No (%))	10 (11)	22 (41)	5 (19)	**AD vs. FTD**	3 (5)	10 (26)	5 (16)	**AD vs. FTD**
NPI total								
Mean value ±SD	11.56±12.77	28.81±21.70	24.46±29.33	**AD vs. FTD AD vs. PSP**	12.14±10.94	26.05±20.21	27.94±17.60	**AD vs. FTD AD vs. PSP**
Patients with symptoms present (No (%))	73 (77)	48 (85)	27 (100)	**AD vs. PSP**	56 (86)	33 (85)	32 (100)	ns
HAMA								
Mean value ±SD	3.70±3.15	4.66±3.90	5.78±4.36	ns	4.16±3.45	3.00±3.13	9.16±5.19	**AD vs. PSP FTD vs. PSP**
Patients with score ≥13 (No (%))	1 (1)	2 (6)	2 (7)	ns	40 (62)	18 (46)	6 (19)	**AD vs. PSP FTD vs. PSP**
HAMD								
Mean value ±SD	2.67±2.61	4.66±4.36	10.41±6.33	**AD vs. PSP FTD vs. PSP**	4.00±3.97	3.24±3.65	13.03±6.55	**AD vs. PSP FTD vs. PSP**
Patients with score ≥8 (No (%))	5 (9)	6 (19)	19 (70)	**AD vs. FTD FTD vs. PSP**	6 (24)	4 (19)	27 (84)	**AD vs. PSP FTD vs. PSP**
AS								
Mean value ±SD	9.96±6.47	16.44±10.22	21.07±8.29	**AD vs. FTD AD vs. PSP**	11.33±8.00	11.33±7.78	22.38±8.72	**AD vs. PSP FTD vs. PSP**
Patients with score ≥14 (No (%))	18 (32)	18 (56)	23 (85)	**AD vs. FTD FTD vs. PSP**	11 (46)	7 (35)	28 (88)	**AD vs. PSP FTD vs. PSP**

The scores on different neuropsychiatric scales are presented as mean values ± standard deviations. The distribution of patients with symptoms and those with clinically significant scores (≥4) is presented as absolute numbers, with percentages shown in the brackets. The groups of patients with a statistically significant difference were indicated in bold (ANOVA test with post hoc Games Howell and chi-square test were applied as appropriate; $p<0.05$); ns: non-significant.
AD: Alzheimer's disease; FTD: frontotemporal dementia; PSP: progressive supranuclear palsy; NPI: neuropsychiatric inventory; HAMD: Hamilton's depression scale; HAMA: Hamilton's anxiety scale; AS: apathy scale.

Differences in the prevalence of neuropsychiatric symptoms based on the caregiver's and patient's reports

The data on differences in the prevalence of depression, anxiety, and apathy obtained by caregivers and patient reports are presented in Table 3. Disconcordance between the caregiver's and patient's observations was present in all 3 mood disturbances, but it was most obvious in reporting apathy symptoms.

DISCUSSION

The study results show that NPSs occupy a significant place in the clinical presentation of various forms of tauopathies, even in the early disease course. Primary tauopathies, such as FTD and PSP, exhibit a higher frequency and intensity of neuropsychiatric symptoms even in the early stages of the disease, along with a distinct profile of neuropsychiatric characteristics. This is in contrast to AD, which represents secondary tauopathies. The most prominent and frequent symptoms of AD belong to mood disorders (depression/anxiety), together with apathy. In addition to these symptoms, NPSs from the agitation subsyndrome on NPI play an important role in FTD and PSP, especially in the early stages of the disease, making a distinction toward AD easier. The profile of NPSs within primary tauopathies is very similar, but more pronounced irritability and aberrant motor behavior is a dominant feature of FTD, while sleep disturbances are noted to be mainly characteristic of PSP. Estimates of the prevalence of depression and anxiety, and especially apathy, obtained from caregivers and the patients themselves differ significantly, and the reports from these two sources cannot be considered interchangeable and comparable.

The general patterns of NPSs in the examined tauopathies obtained using the NPI in this study are comparable to the results of previous research. The most common neuropsychiatric symptoms in AD were apathy, followed by depression and anxiety (22–25), which aligns with the symptom profile observed in our patients. In line with previous reports, our data indicate a specific pattern of neuropsychiatric disorders of primary tauopathies, in contrast to AD (24, 26, 27). Namely, we showed that apathy, together with symptoms from the subdomain of agitation, as well as appetite/eating and sleep disorders, constitute a specific behavioral construct in FTD and

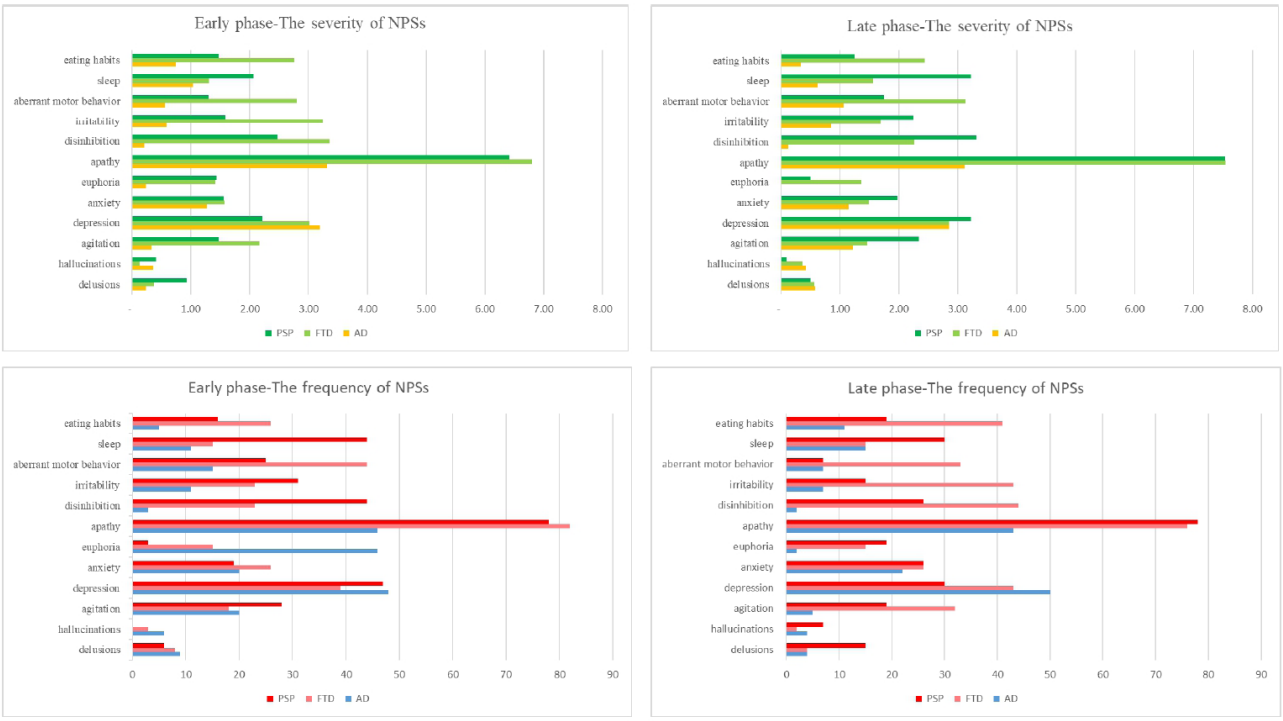

Figure 1. Neuropsychiatric inventory composite scores reflect the severity of symptoms (upper graphs) and the percentage of patients with clinically significant scores ≥4 for each symptom (lower graphs) in early and late phases across different tauopathies.
PSP: progressive supranuclear palsy; FTD: frontotemporal dementia; AD: Alzheimer's disease; NPSs-neuropsychiatric symptoms

Table 3. The differences in the prevalence of depression, anxiety, and apathy between caregivers' and patients' reports in patients with AD, FTD, and PS

		Depression-HAMD			Anxiety-HAMA			Apathy-AS		
		Significant ≥8	**Trivial** <8	**p**	**Significant** ≥13	**Trivial**<13	**p**	**Significant** ≥14	**Trivial** <14	**p**
AD	**Significant NPI**	9	27	**0.009**	0	1	ns	**19**	**15**	**0.002**
	Trivial NPI	2	43		18	63		**10**	**35**	
FTD	**Significant NPI**	6	19	ns	2	0	ns	**24**	**15**	**0.001**
	Trivial NPI	4	24		11	40		**1**	**12**	
PSP	**Significant NPI**	23	0	**0.001**	6	7	**<0.001**	**45**	**1**	**0.001**
	Trivial NPI	23	13		2	44		**6**	**7**	

The figures in the table present absolute numbers of patients. P-value, Fischer exact test ($p<0.05$); ns= non-significant.
AD: Alzheimer's disease; FTD: frontotemporal dementia; PSP: progressive supranuclear palsy; NPI: neuropsychiatric inventory (significant-if composite score for certain domain is ≥4); HAMD: Hamilton's depression scale; HAMA: Hamilton's anxiety scale; AS: apathy scale.

PSP. The different NPS profiles between primary and secondary tauopathies are most noticeable in the early stages of the disease, while with the disease progression, differences are still present but to a lesser extent. This implies that paying attention to the spectrum of NPSs in the early phases of tauopathies is particularly important for the differential diagnosis when early distinction in the absence of hard motor and cognitive signs is not possible.

Although very frequent in all tauopathies, mood changes (depression, anxiety) did not prove to be significant in distinguishing these diseases, as it had been shown in previous research (28-31). Conversely, when apathy occurs with greater intensity and frequency, it is more indicative of FTD and PSP than (AD). Apathy is generally considered to be a consequence of lesions in multiple brain regions, but several imaging studies in degenerative dementias have indicated a significant association of apathy with atrophy and hypometabolism of the medial frontal cortex (predominantly the anterior cingulum) (32, 33). Interestingly, the atrophy of this brain region is also associated with disinhibition and aberrant motor behavior (32), which in our study also stood out as significant symptoms in distinguishing AD from primary tauopathies.

As already mentioned, the profile of NPSs in FTD and PSP in our cohorts turned out to be very similar, both in terms of the total NPI score and in terms of the severity/distribution of the most prevalent symptoms, similar to the study by Yataba et al. (34). However, we need to be cautious in the interpretation of such results, bearing in mind that our FTD cohort is amorphous, without making a distinction between behavioral and language variants of FTD. A recent study comparing different variants of FTD found that delusions, along with symptoms from the agitation subdomain and euphoria, were less prominent in PSP compared to the behavioral variant of FTD (35). In our study, the presence of irritability in early phases was a characteristic mainly of FTD, which is in line with recently published data where irritability was the most common NPS in prodromal FTD (36). On the

other hand, sleep disturbances were the most valuable in differentiating PSP not just from AD, but also from FTD. A very recent study has also shown that the presence of sleep disturbance at the initial visit predicted significantly greater odds of PSP pathologic diagnosis compared to non-PSP tauopathies (37).

Finally, positive psychiatric symptoms, such as hallucinations and delusions, rarely occurred in our patients with tauopathies, a result that corresponds to most previous findings (30, 31, 38). These symptoms are more often part of the clinical spectrum of synucleinopathies and arise as a consequence of the complex interplay of the neurodegenerative process itself and the application of dopaminergic therapy (38).

The prevalence of anxiety, depression, and apathy reported on the NPI by caregivers was higher than reported by patients themselves. This contrasts with the observations in other neurodegenerative diseases, such as Parkinson's disease and multiple system atrophy, where patients report more symptoms than their caregivers can register (39, 40). In the domains of anxiety and depression, the greatest discrepancy was observed in PSP patients, while the discrepancy in apathy reports was consistent in all patients. The key to explaining this inconsistency may lie in the pronounced symptoms of apathy, which include indifference and a lack of insight into the symptoms.

Several limitations of our study should be emphasized. First, our research is primarily based on the NPI questionnaire, which is solely based on caregivers' assessment, and it must be taken into account that the NPS may be underestimated or overestimated to a certain extent. Since the NPI refers to a period no longer than one month before examination, the problem of errors in recalling symptoms cannot be ignored. Second, depression, apathy, and anxiety were also assessed using additional questionnaires but were not diagnosed according to clinically validated criteria, which requires caution when interpreting the data. Third, FTD and PSP include a whole spectrum of clinically heterogeneous diseases, which were not taken into consideration during this research.

CONCLUSION

Neuropsychiatric symptoms are a prominent feature in the clinical presentation of both primary and secondary tauopathies, even in the early stages of the disease. FTD and PSP are characterized by distinct psychiatric constructs in contrast to AD, with more severe and more frequent NPSs. Involving family caregivers through structured interviews on changes in patients' behavioral aspects using the NPI could be crucial for differentiating tauopathies in the early stages of the disease, when clinical symptoms are emerging but motor and cognitive signs are not yet apparent. Estimates of the prevalence of depression and anxiety, and especially apathy, obtained from caregivers and the patients themselves differ significantly, and the reports from these two sources cannot be considered interchangeable and comparable.

Author Contributions:

A. the conception or design of the work;
B. the acquisition, analysis, or interpretation of data;
C. preparing the draft of the manuscript
D. interpretation of the revised version of the manuscript.

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OBRASCI NEUROPSIHIJATRIJSKIH SIMPTOMA U PRIMARNIM I SEKUNDARNIM TAUOPATIJAMA IZ UGLA NEGOVATELJA I PACIJENATA

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Sažetak

Uvod/ciljevi: Poznavanje razlika u profilima neuropsihijatrijskih simptoma (NPS) u primarnim i sekundarnim tauopatijama, naročito u ranim fazama bolesti, može biti od značaja u njihovoj diferencijalnoj dijagnozi. Ciljevi rada: a) ispitivanje obrazaca NPS kod primarnih (frontotemporalna demencija – FTD i progresivna supranuklearna paraliza – PSP) i sekundarnih tauopatija (Alchajmerova bolest – AD); b) ispitivanja razlika u NPS prijavljenih od strane samih pacijenata i njihovih negovatelja.

Metode: Ispitivanje je obuhvatilo 312 bolesnika, od kojih 176 sa trajanjem bolesti ≤3 godine. Prisustvo NPS bazirano na proceni negovatelja procenjeno je neuropsihijatrijskim upitnikom (NPI). Procena NPS od strane pacijenata ispitivana je Hamiltonovim skalama depresije i anksioznosti i skalom apatije.

Rezultati: Najizraženiji i najčešći NPS u AD su poremećaji raspoloženja/apatija, dok se u FTD i PSP beleži i značajna učestalost simptoma iz podsindroma agitacije. Profil NPS u FTD i PSP je sličan, ali su iritabilnost i poremećaj motornog ponašanja izraženiji u FTD, dok je poremećaj spavanja dominantna karakteristika PSP. Prevalencija anksioznosti, depresije i apatije prijavljena na NPI upitniku od strane negovatelja, bila je veća od one prijavljene od strane samih pacijenata.

Zaključak: FTD i PSP karakterišu različiti psihijatrijski obrasci u odnosu na AD, sa težim i češćim NPS. Procena negovatelja o promenama u ponašanju pacijenata, mogla bi biti od ključnog značaja za diferencijalnu dijagnozu ovih tauopatija u ranom toku bolesti, posebno u odsustvu jasnih motornih i kognitivnih simptoma. S druge strane, procene simptoma depresije i anksioznosti, a posebno apatije, od strane samih pacijenata i njihovih negovatelja se značajno razlikuju, te se podaci iz ova dva izvora ne mogu smatrati zamenljivim i uporedivim.

Ključne reči: tauopatije, Alchajmerova bolest, frontotemporalna demencija, progresivna supranuklearna paraliza, neuropsihijatrijski simptomi

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