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Prevalence and clinical effects of Lewy Body pathology in non-prion rapidly progressive dementias: a retrospective cohort study

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Abstract

Background Knowledge on the prevalence and clinical effects of Lewy body (LB) pathology in patients with rapidly progressive dementia (RPD) has been limited by the lack of a pathology-specific marker. The introduction of the alpha-synuclein (α-syn) seed amplification assay (SAA) has recently provided the first accurate in vivo biomarker of LB pathology. Based on data from limited neuropathological cohorts, we hypothesised that LB pathology is frequent in non-prion RPD and often clinically unrecognised.

Methods We studied 171 consecutively referred clinically well-characterised patients with RPD, defined as those reaching the stage of major neurocognitive disorder within one year of symptom onset. Patients diagnosed with Creutzfeldt-Jakob disease or a treatable form of RPD were excluded. Records on specific clinical features were retrospectively reviewed. We tested all patients with a validated α-syn CSF SAA to evaluate the prevalence and clinical correlates of LB pathology. Moreover, CSF biomarkers of Alzheimer's disease (AD) pathology were measured in all cases.

Results In the cohort, 39.2% (67/171) tested positive by α-syn SAA. α-syn SAA positivity was more frequently detected alone than in combination with biomarkers of AD pathology (25.1% vs. 14.0%). α-syn SAA+ status was independently associated with higher odds of fluctuating cognition (OR 2.99, 95%CI 1.46–6.25, $p=0.012$), visual hallucinations (OR 2.41, 95%CI 1.24–4.75, $p=0.027$), extrapyramidal signs (OR 4.57, 95%CI 2.35–9.11, $p<0.001$) and akinetic mutism (OR 3.77, 95%CI 1.22–12.82, $p=0.038$). The presence of at least two core features of the diagnostic criteria for Dementia with Lewy bodies yielded high specificity (83.6%, 95%CI 75.4–89.5), but low sensitivity (55.2%, 95%CI 43.4–66.5) and overall low performance (AUC 0.69, 95%CI 0.61–0.78) in discriminating α-syn+ from α-syn- participants. The presence of at least one core feature showed higher sensitivity (88.1%, 95%CI 78.2–93.8) but lower specificity (44.2%, 95%CI 35.1–53.8), also resulting in limited diagnostic accuracy (AUC 0.66, 95%CI 0.58–0.74).

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Conclusion LB pathology is prevalent among patients with non-prion RPD but not adequately predicted by clinical features. Our findings support the use of biomarkers of LB pathology in the diagnostic workup of RPD, helping clinicians provide biologically based diagnoses.

Keywords Alpha-synuclein, Rapidly progressive dementia, Prion, Seed amplification assay, Biological diagnosis, Dementia with Lewy Bodies, Alzheimer's disease, Cognitive impairment

Introduction

Rapidly progressive dementia (RPD) is typically defined as a progressive cognitive decline occurring over a significantly shorter time frame than that observed in classical neurodegenerative dementias [1]. The rapidity of progression remains variably interpreted and lacks consensus; however, most patients with RPD become dependent in the activities of daily living within one or two years from symptom onset [2–3]. Although RPD accounts for around 4% of all dementia cases, representing a relatively rare clinical entity, it is associated with a significant and growing burden of disability and mortality. Both degenerative and non-degenerative disorders, including potentially treatable neurological conditions, can cause RPD. A rapid and thorough diagnostic evaluation is therefore essential to rule out potentially treatable conditions [1, 4].

Among the degenerative causes, prion diseases, especially Creutzfeldt-Jakob disease (CJD), have classically been considered the prototypical RPD, being associated with a rapidly evolving neurological syndrome, mostly leading to death in a few months after symptom onset [5]. In recent years, the introduction of prion real-time quaking-induced conversion (RT-QuIC), a seed amplification assay (SAA), has drastically improved the diagnostic accuracy of CJD in vivo [6–7]. However, besides CJD, atypical variants of other neurodegenerative disorders, including Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB), are increasingly recognized as potential etiologies of RPD. AD represents the most common neurodegenerative diagnosis in neuropathological cohorts of patients with RPD submitted to international CJD reference centres [8–10]. Accordingly, patients with AD displaying an unexpected rapid progression of cognitive impairment or a short total disease duration have been extensively reported [11–17]. The widespread availability of accurate biomarkers reflecting AD pathophysiology has drastically improved the ante-mortem identification of AD pathology in these patients [18].

DLB has also been recognized as a potential cause of RPD, but the lack of a specific biomarker has limited the recognition of these patients in vivo. Consequently, DLB has been mainly reported as the primary neuropathological diagnosis in cohorts of patients initially suspected of CJD or with an unexpected short disease duration [19–24]. In such cases, Lewy body (LB) pathology was associated with a higher frequency of classical clinical features, such as parkinsonism and visual hallucinations, as well as with atypical signs like myoclonus [21, 23–24].

In recent years, the development of alpha-synuclein (α-syn) SAA, such as α-syn RT-QuIC, has provided the first accurate in vivo biomarker of LB pathology [25], which represents the biological substrate of DLB. In neuropathological cohorts, the assay performed on cerebrospinal fluid (CSF) samples demonstrated near-complete specificity for LB pathology and very high sensitivity in detecting subjects with advanced stages (i.e., limbic and neocortical), which are classically associated with DLB [25–28]. Furthermore, CSF α-syn SAA has demonstrated high diagnostic performance in patients with DLB across independent clinical cohorts [25, 29].

In the present study, we used the α-syn SAA to identify LB pathology in a large cohort of consecutive well-characterized patients with non-prion RPD of a suspected neurodegenerative etiology submitted to a national Reference Centre for prion disease. We retrospectively examined the clinical correlates of LB pathology and the performance of the core features of the DLB international diagnostic criteria for identifying patients with RPD and underlying LB pathology.

Methods

Inclusion and exclusion criteria

We studied subjects with suspected RPD whose CSF samples were submitted for diagnostic evaluation to the Neuropathology Laboratory (LabNP) at the Institute of Neurological Sciences in Bologna from January 2014 to December 2024 (N = 1167). Inclusion criteria were as follows: (1) no evidence of prion disease; (2) a rapidly progressive neurological syndrome leading to the stage of major neurocognitive disorder, as defined by the DSM-5 criteria [30], within one year from the onset of motor or cognitive symptoms and/or to complete functional incapacitation within two years from the onset of motor or cognitive symptoms; (3) sufficient CSF volume to perform the α-syn SAA; (4) adequate documentation of selected clinical features (see below). To fulfill point 1), we tested all submitted samples with a broad clinical suspicion for prion disease after preliminary screening (CSF t-tau ≥ 600 pg/ml) using the second-generation prion RT-QuIC [7]. Moreover, all subjects with a final diagnosis of probable/definite CJD according to international criteria were excluded [6]. Subjects receiving a final diagnosis of a treatable form of RPD (such as inflammatory, infectious

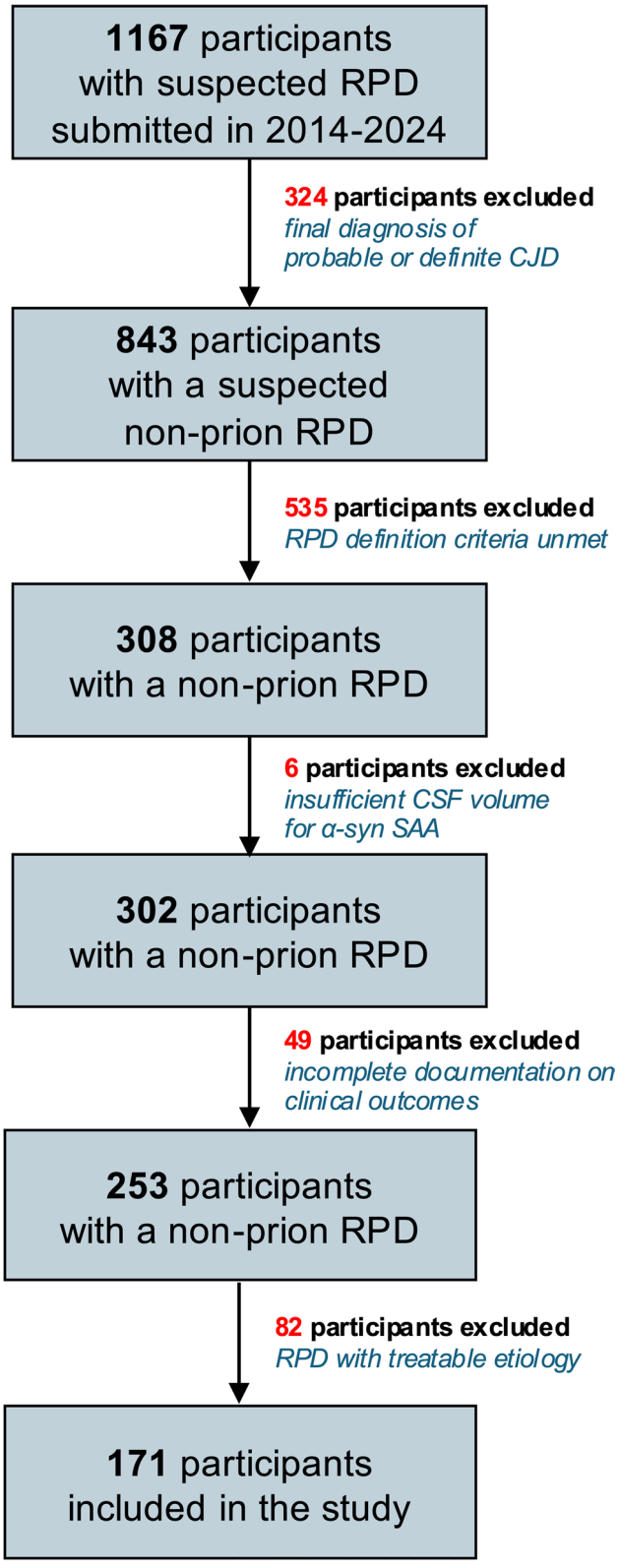

Fig. 1 Study flow chart. Abbreviations: α-syn, alpha-synuclein; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; RPD, rapidly progressive dementia; SAA, seed amplification assay

or toxic/metabolic disorders) were also excluded. The study flow-chart is summarised in Fig. 1.

Clinical assessment

Participants included in the study were evaluated by neurologists specialised in cognitive disorders at multiple Italian neurological inpatient clinics. All subjects underwent a comprehensive baseline assessment, including neurological examination, routine blood tests and brain imaging. Moreover, all participants underwent diagnostic lumbar puncture, and CSF cell count and standard biochemical analyses were available for all subjects. A minority of participants ($n = 57$, 33.3%) also underwent a comprehensive neuropsychological evaluation. Follow-up information was available for most participants ($n = 147$, 86.0%), including the date of death for deceased subjects. The remaining 24 (14.0%) had no additional clinical data beyond the baseline assessment.

In all participants, a treatable form of RPD was deemed clinically unlikely by the treating neurologist.

Medical records were reviewed to obtain a detailed past medical history, confirming the absence of neurological impairment before symptom onset. The presence/absence of selected clinical features was retrospectively evaluated for each participant by two neurologists (A.Mas. and P.P.), blinded to CSF biomarker results. These included psychiatric disturbances, fluctuating cognition, visual hallucinations, extrapyramidal signs, REM-sleep behavior disorder (RBD), pyramidal signs, myoclonus, cerebellar signs, seizures, and akinetic mutism. In a subset of participants (155/171, 90.6%), delirium episodes were also assessed. The presence of RBD was evaluated by clinical interview without the use of dedicated questionnaires. Clinical features were recorded cumulatively at baseline and, when available, at follow-up visits. Cognitive status was assessed across six domains: memory, attention, executive functions, visuospatial functions, language and praxis. A deficit in any domain was recorded when either (1) formal neuropsychological testing yielded pathological scores or (2) the treating neurologist documented clear impairment on clinical examination. When available, baseline age- and education-corrected Mini-Mental State Examination (MMSE) scores [31] were also collected.

CSF biomarkers assessment

CSF samples were obtained by lumbar puncture at the L3/L4 or L4/L5 level using a standard procedure, centrifuged, aliquoted and stored in polypropylene tubes at -80 °C until analysis. All biomarker analyses were performed at LabNP.

CSF total tau (t-tau), phospho-tau$_{181}$ (p-tau$_{181}$), Aβ_{42} and Aβ_{40} levels were determined by commercially available chemiluminescent enzyme immunoassays on the

automated Lumipulse G600II platform (Fujirebio), as previously described [32]. The inter-assay CVs were < 8% for all biomarkers. The Aβ42/Aβ40 was calculated as $A\beta_{42}/A\beta_{40}$. We used in-house validated cutoffs to determine pathological values for the AD core markers. Specifically, a CSF $A\beta_{42}/A\beta_{40}$ ratio < 0.068 was considered supportive of amyloid deposition (A+), while a CSF p-tau_{181} > 62 pg/mL was considered indicative of p-tau deposition (T+). A combined A + and T+ status was considered supportive of AD pathology (AD+) [32].

α-syn SAA was performed on CSF samples of all included participants following an established RT-QuIC protocol [25, 33]. Samples were run in quadruplicates and considered positive (α-syn SAA+) if at least three out of four positive replicates reached a threshold arbitrarily set at 30% of the median of the maximum fluorescence signal values of the positive replicates of the positive controls included in each plate. As previously described [33], CSF samples showing one or two positive replicates were tested twice more, and a final positive result was also attributed to samples with at least 4 out of 12 positive replicates.

The second-generation prion RT-QuIC assay was performed on all CSF samples as previously described [7].

Neuropathological examination

A subset of participants (n = 19, 11.1%) underwent neuropathological assessment following autopsy. Neuropathological examination was performed as previously described [25]. In all cases, the presence of AD neuropathological changes and LB pathology was assessed by an experienced neuropathologist (P.P.), and staging was performed according to international criteria [34–35].

Statistical analyses

Statistical analyses were performed using GraphPad Prism V. 7 (GraphPad, La Jolla, CA, USA) and R V. 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Normality of continuous variables was assessed using Shapiro-Wilk and Kolmogorov-Smirnov tests. Since variables were not normally distributed, comparisons were made using the Mann-Whitney test (for two groups) or the Kruskal-Wallis test (followed by the Dunn-Bonferroni test, for more than two groups). Fisher's exact test assessed the difference in the distribution of clinical features between groups. For subjects with a known date of death, disease duration was calculated as the time between disease onset and death.

Multivariable penalized logistic regression models according to Firth were used to evaluate the independent associations between binarized α-syn SAA and AD status (independent variables, a value of 1 indicated a positive status) and clinical outcomes (absence/presence of clinical features, dependent variables). In each model, α-syn SAA and AD status were included as covariates. Results are expressed as odds ratio (OR) and 95% confidence interval (95%CI). Similar linear regression models were used to evaluate the association between pathologies and continuous variables (i.e., corrected MMSE scores); results are expressed as β coefficients and 95%CI. These regression models underwent multiple testing corrections using the false discovery rate method at $\alpha = 0.05$ according to Benjamini-Hochberg. Specifically, we performed four independent corrections: two for clinical outcomes (one each for independent associations of α-syn SAA and AD status, 12 outcomes each) and two for neuropsychological outcomes (seven outcomes each).

To further assess whether the association between α-syn SAA positivity and clinical or neuropsychological outcomes was affected by concomitant AD+ status, additional regression models were performed using the same dependent and independent variables, including an interaction term between α-syn SAA and AD status. The associations between the interaction term and clinical and neuropsychological outcomes underwent multiple testing corrections using the same method described above (two corrections: one for 12 clinical outcomes, one for 7 neuropsychological outcomes).

Receiver operating characteristic (ROC) curves were calculated to assess the diagnostic performance of combinations of different numbers of core features from DLB international criteria [36] in distinguishing α-syn SAA+ from α-syn SAA- participants. Results are expressed as area under the curve (AUC), sensitivity, and specificity and relative 95%CI. All analyses were considered statistically significant at $p < 0.05$.

Results

Cohort definition, demographic features and prevalence of α-syn SAA positivity

A total of 1167 participants were screened for inclusion in the study. Of these 324 (27.8%) received a final diagnosis of definite/probable CJD and were excluded. Among the remaining subjects, 308 fulfilled our RPD definition. Additionally, 6 and 49 participants were excluded due to insufficient CSF volume for α-syn SAA analysis and incomplete documentation of selected clinical outcomes, respectively. Finally, 82 subjects received a final diagnosis of a treatable form of RPD and were also excluded (Fig. 1). A complete list of participants with a treatable form of RPD being excluded is provided in Additional file 1.

The final cohort comprised 171 participants. Demographic and anamnestic clinical features are reported in Table 1.

In the cohort, 67 participants (39.2%) tested positive by α-syn SAA, indicating an underlying LB pathology. Notably, all but one sample exhibited ≥ 3 positive

Table 1 Demographic and anamnestic features of included participants

	Entire cohort (*n* = 171)
Age at onset, years	73.6 (67.7–79.6), 171
Age at CSF sampling, years	74.7 (68.5–80.4), 171
Females	90/171 (52.6)
Diagnostic delay, months	6.7 (3.3–13.3), 171
Disease duration, months	20.2 (7.4–40.9), 101
Education, years	8.0 (5.0–13.0), 117
Neuropathological examination	19/171 (11.1)
History of head trauma	7/159 (4.4)
Race/ethnicity	
White/European	169/171 (98.8)
Black/African	1/171 (0.6)
Hispanic/Latin American	1/171 (0.6)
Previous ischemic stroke	11/159 (6.9)
At least two cardiovascular risk factors	80/159 (50.3)
Arterial hypertension	104/159 (65.4)
Smoking habit	34/141 (24.1)
Corrected MMSE	16.4 (12.1–23.2), 79
S+	67/171 (39.2)
AD+	90/171 (52.6)
S+/AD-	43/171 (25.1)
S+/AD+	24/171 (14.0)
S-/AD+	66/171 (38.6)
S-/AD-	38/171 (22.2)
CSF t-tau, pg/ml	495.5 (283.5–886.5), 171
CSF p-tau$_{181}$,pg/ml	56.5 (33.2–98.7), 171
CSF Aβ ratio	0.056 (0.044–0.084), 171

Continuous variables are reported as median (interquartile range), number of participants with available data. Dichotomous variables are expressed as n/number of participants with available data (%). Diagnostic delay was defined as the time between disease onset and CSF sampling. Disease duration was defined as the time between disease onset and death, when available. S+ status was defined by positive result at the CSF α-syn SAA. AD+ status was defined by both decreased CSF Aβ ratio (A+) and elevated CSF p-tau$_{181}$ (T+). CSF Aβ ratio was defined as Aβ$_{42}$/Aβ$_{40}$. Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; p-tau$_{181}$, phosphorylated tau protein at residue 181; S, α-syn SAA; SAA, seed amplification assay; t-tau, total tau protein

replicates, consistent with high seeding activity and suggesting widespread LB pathology. In a single patient only, the test was repeated three times, yielding 4/12 positive replicates.

A higher proportion of participants (90/171, 52.6%) had the biomarker signature of AD pathology, whereas 14.0% of participants were biomarker-positive for both pathologies. α-syn SAA positivity was more frequently detected alone than in combination with biomarkers of AD pathology (25.1% vs. 14.0%) (Table 1; Fig. 2). Demographic and basic clinical features of the included participants who underwent neuropathological examination are reported in Table 2.

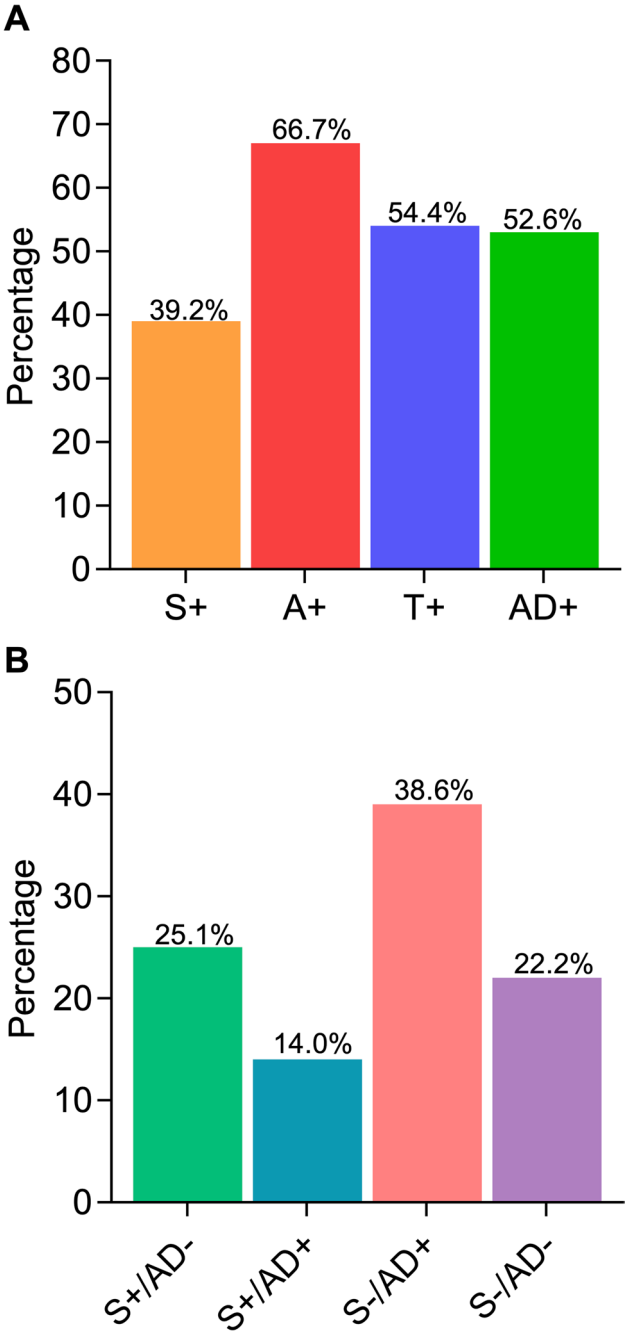

Fig. 2 Distribution of CSF profiles in the entire cohort. **A** Distribution of CSF biomarkers of LB and AD pathology in the entire cohort. **B** Distribution of the different combinations of CSF biomarkers of LB and AD pathology in the entire cohort. S+ status was defined by positive result at the CSF α-syn SAA. AD+ status was defined by both decreased CSF Aβ ratio (A+) and elevated CSF p-tau181 (T+). Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; LB, Lewy Body; S, α-syn SAA; SAA seed amplification assay

Associations of α-syn SAA status with demographic and basic clinical features

Demographic, basic clinical features and biomarker values of included participants, stratified by α-syn SAA

Table 2 Details on the included participants undergoing neuropathological assessment

	LB+ (*n* = 8)	LB- (*n* = 11)
Age at onset, years	74.7 (72.0–81.9), 8	78.2 (71.9–84.3), 11
Age at CSF sampling, years	75.6 (72.7–82.5), 8	79.2 (73.1–84.6), 11
Females	2/8 (25.0)	5/11 (45.4)
Diagnostic delay, months	3.9 (2.5–16.7), 8	6.2 (2.8–12.8), 11
Disease duration, months	8.4 (2.8–35.8), 8	7.3 (5.8–12.8), 11
S+	8/8 (100)	0/11 (0)
LB- Braak stage	4.0 (3.0–6.0), 8	0.0 (0.0–0.0), 11
A-beta Thal Phase	4.0 (3.2–5.0), 8	4.0 (3.0–5.0), 11
Tau Braak stage	3.0 (2.2–5.2), 8	4.0 (2.0–4.0), 11

Continuous variables are reported as median (interquartile range), number of participants with available data. Dichotomous variables are reported as n/number of participants with available data (%). Diagnostic delay was defined as the time between disease onset and CSF sampling. Disease duration was defined as the time between disease onset and death. S+ status was defined bv positive result at the CSF α-syn SAA. Abbreviations: A-beta, amyloid-beta; α -syn, alpha-synuclein; CSF, cerebrospinal fluid; LB, Lewy Body; S, α-syn SAA; SAA, seed amplification assay

result and combinations of α-syn SAA and AD status, are reported in Table 3.

Age at both onset and CSF sampling did not differ between α-syn SAA + and α-syn SAA- participants ($p = 0.495$ and 0.418). α-syn SAA+ participants were more frequently male than those α-syn SAA-, with a trend toward significance ($p = 0.060$) (Table 3). There were no differences in the total disease duration between α-syn SAA + and α-syn SAA- participants ($p = 0.494$) (Table 3).

We found no significant differences in demographic and basic clinical features across patients stratified by combinations of α-syn SAA and AD status (Table 3).

Demographic, basic clinical features and biomarker values stratified for AD status are reported in Additional file 2.

Associations of α-syn SAA status with clinical outcomes

Clinical outcomes for included participants, stratified by α-syn SAA status, are reported in Table 4. The distribution of clinical features stratified by combinations of

Table 3 Demographic variables and biomarker values stratified by α-syn SAA status and combinations of α-syn SAA and AD status

	S+ (*n* = 67)		S- (*n* = 104)		*p* value
Age at onset, years	74.2 (69.0–80.2), 67		73.5 (67.2–79.6), 104		0.495*
Age at CSF sampling, years	75.1 (70.4–81.5), 67		74.2 (68.0–79.9), 104		0.418*
Females	29/67 (43.3)		61/104 (58.6)		0.060†
Diagnostic delay, months	7.0 (3.2–16.3), 67		6.5 (3.3–12.5), 104		0.372*
Disease duration, months	24.3 (7.3–42.9), 47		17.1 (7.4–37.0), 54		0.494*
CSF t-tau, pg/ml	391.5 (247.0–695.8), 67		565.0 (308.3–930.5), 104		**0.034***
CSF p-tau$_{181}$, pg/ml	44.0 (31.2–75.7), 67		70.5 (35.2–113.8), 104		**0.009***
CSF Aβ ratio	0.059 (0.048–0.090), 67		0.055 (0.041–0.083), 104		0.069*
	S+/AD- (n = 43)	**S+/AD+ (n = 24)**	**S-/AD+ (n = 66)**	**S-/AD- (n = 38)**	***p* value**
Age at onset, years	75.6 (66.7–80.2), 43	72.8 (69.2–80.9), 24	75.6 (67.4–80.5), 66	71.2 (65.4–78.2), 38	0.332‡
Age at CSF sampling, years	76.0 (68.1–81.5), 43	74.3 (70.5–81.5), 24	76.2 (68.9–81.4), 66	71.6 (65.9–78.5), 38	0.208‡
Females	18/43 (41.9)	11/24 (45.8)	40/66 (60.6)	21/38 (55.3)	0.237§
Diagnostic delay, months	5.2 (3.0–14.4), 43	11.9 (4.8–18.7), 24	7.1 (3.6–13.0), 66	6.5 (2.4–8.6), 38	0.099‡
Disease duration, months	20.2 (6.6–41.9), 29	32.4 (12.9–46.0), 18	15.3 (7.4–37.0), 30	17.8 (7.0–39.4), 24	0.531‡
CSF t-tau, pg/ml	285 (234–412), 43	687 (531–1122), 24	711 (557–1078), 66	281 (203–408), 38	**< 0.001**‡
CSF p-tau$_{181}$, pg/ml	35.0 (28.0–43.5), 43	92.0 (70.2–146.3), 24	102.0 (71.0–138.0), 66	30.0 (23.0–42.5), 38	**< 0.001**‡
CSF Aβ ratio	0.074 (0.057–0.092), 43	0.045 (0.039–0.052), 24	0.044 (0.034–0.055), 66	0.089 (0.079–0.097), 38	**< 0.001**‡

*: as derived by Mann-Whitney test. †: as derived by Fisher's exact test. ‡: as derived by Kruskal-Wallis test. §: as derived by Chi square test

Continuous variables are reported as median (interquartile range), number of participants with available data. Dichotomous variables are reported as n/number of participants with available data (%). P values are not corrected for multiple testing. P values of statistically significant comparisons are shown in bold. Diagnostic delay was defined as the time between disease onset and CSF sampling. Disease duration was defined as the time between disease onset and death, when available. S+ status was defined bv positive result at the CSF α-syn SAA. AD+ status was defined by both decreased CSF Aβ ratio (A+) and elevated CSF p-tau$_{181}$ (T+). CSF Aβ ratio was defined as (Aβ$_{42}$/Aβ$_{40}$). Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau$_{181}$, phosphorylated tau protein at residue 181; S, α-syn SAA; SAA, seed amplification assay; t-tau, total tau protein

Table 4 Clinical features stratified by α-syn SAA status

	S+ (*n* = 67)	S- (*n* = 104)	*p* value*
Psychiatric disturbances	40/67 (59.7)	54/104 (51.9)	0.347
Fluctuating cognition	27/67 (40.3)	17/104 (16.3)	**< 0.001**
Visual hallucinations	32/67 (47.8)	31/104 (29.8)	**0.023**
Extrapyramidal signs	46/67 (68.6)	31/104 (29.8)	**< 0.001**
RBD	9/67 (13.4)	0/104 (0.0)	**< 0.001**
Pyramidal signs	8/67 (11.9)	16/104 (15.4)	0.653
Myoclonus	15/67 (22.4)	13/104 (12.5)	0.095
Cerebellar signs	1/67 (1.5)	3/104 (2.9)	> 0.999
Akinetic mutism	9/67 (13.4)	5/104 (4.8)	0.082
Seizures	11/67 (16.4)	16/104 (15.4)	> 0.999
Delirium before clinical onset	14/58 (24.1)	7/97 (7.2)	**0.006**
Delirium, overall	28/58 (48.3)	33/97 (34.0)	0.091

* as derived by Fisher's exact test

Variables are reported as n/number of participants with available data (%). P values are not corrected for multiple testing. P values of statistically significant comparisons are shown in bold. Diagnostic delay was defined as the time between disease onset and CSF sampling. Disease duration was defined as the time between disease onset and death, when available. S+ status was defined bv positive result at the CSF α-syn SAA. Abbreviations: RBD: REM-sleep behavior disorder; S, α-syn SAA; SAA, seed amplification assay

α-syn SAA and AD status is shown in Fig. 3 and Additional file 3.

α-syn SAA+ participants showed fluctuating cognition, visual hallucinations, extrapyramidal signs, RBD and delirium before clinical onset more frequently than those α-syn SAA- (Table 4).

Multivariable penalized logistic regression models including α-syn SAA and AD status as predictors confirmed that α-syn SAA + status was independently associated with fluctuating cognition (OR 2.99, 95%CI 1.46–6.25, $p = 0.003$, corrected p value = 0.012), visual hallucinations (OR 2.41, 95%CI 1.24–4.75, $p = 0.009$, corrected p value = 0.027), extrapyramidal signs (OR 4.57, 95%CI 2.35–9.11, $p < 0.001$, corrected p value < 0.001), myoclonus (OR 2.71, 95%CI 1.15–6.55, $p = 0.022$, corrected p value = 0.038), akinetic mutism (OR 3.77, 95%CI 1.22–12.82, $p = 0.021$, corrected p value = 0.038) and at least one episode of delirium before clinical onset (OR 3.21, 95%CI 1.24–8.88, $p = 0.016$, corrected p value = 0.038) (Fig. 3).

In contrast, AD+ status was only associated with higher odds of myoclonus (OR 2.80, 95%CI 1.17–7.19, $p = 0.020$) and lower odds of delirium before clinical onset (OR 0.30, 95%CI 0.10–0.82, $p = 0.018$); however, both associations were not retained after correction for multiple testing (corrected p value = 0.120 for both associations) (Fig. 3). The results of multivariable models showing independent associations between α-syn SAA + and AD+ status and clinical outcomes are summarized in Additional file 4.

The interaction of α-syn SAA + and AD+ status was not associated with any clinical outcome except for psychiatric disturbances (OR 8.91, 95%CI 2.32–37.56, $p = 0.001$, corrected $p = 0.012$) (Additional file 5).

Diagnostic performance of the core features of DLB criteria in α-syn SAA + RPD participants

The proportions of α-syn SAA+ participants who show only one, at least one, or at least two core features for DLB diagnosis are reported in Fig. 4 and Additional file 6.

Compared to α-syn SAA- participants, α-syn SAA+ more often exhibited at least one ($p < 0.001$) or at least two ($p < 0.001$) core features for DLB diagnosis. The proportion of participants presenting a single core feature did not differ between the two groups ($p = 0.420$).

However, the combination of at least two core features yielded a low diagnostic performance in discriminating between α-syn SAA + and α-syn SAA- participants (AUC 0.69, 95%CI 0.61–0.78; sensitivity 55.2%, 95%CI 43.4–66.5; specificity 83.6%, 95%CI 75.4–89.5) (Table 5). The presence of at least one core feature showed higher sensitivity (88.1%, 95%CI 78.2–93.8) but lower specificity (44.2%, 95%CI 35.1–53.8), resulting in similar poor overall diagnostic performance (AUC 0.66, 95%CI 0.58–0.74) (Table 5).

Similar AUC, sensitivity, and specificity values were obtained for discrimination between α-syn SAA + and α-syn SAA- subjects stratified by AD status (Table 5).

Associations of α-syn SAA and AD status with neuropsychological outcomes

AD + but not α-syn SAA+ status, was associated with a lower corrected MMSE score (β -3.06, 95%CI -5.66 – -0.46, $p = 0.021$) and with the presence of language deficits (OR 2.38, 95%CI 1.01–5.85, $p = 0.049$). However, neither association survived correction for multiple comparisons ($p = 0.073$ and $p = 0.114$ respectively) (Additional file 7). α-syn SAA positivity was not independently

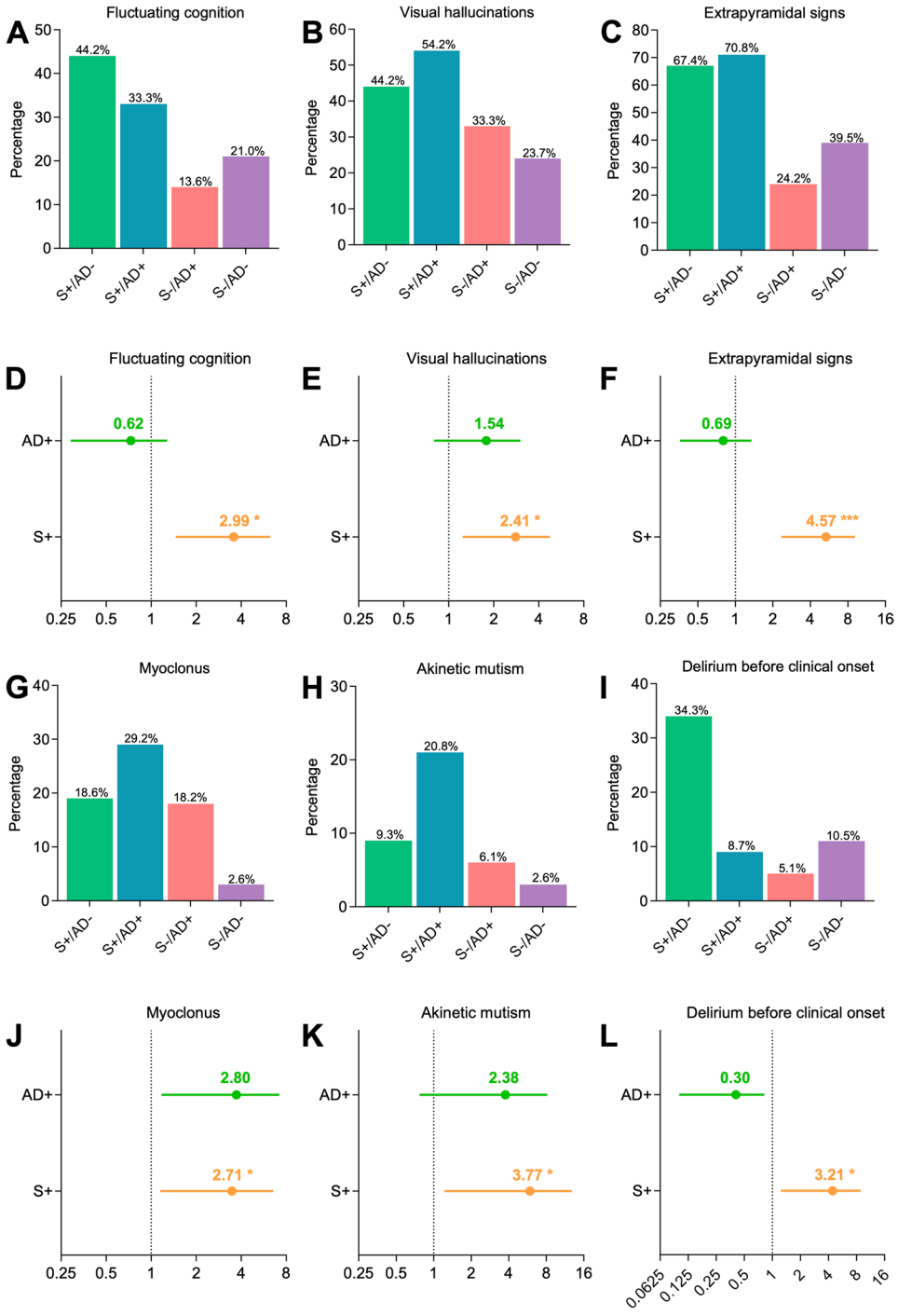

Fig. 3 Independent associations of α-syn SAA and AD status with clinical outcomes. (**A**-**C**); (**G**-**I**) Percentage of participants showing different clinical features stratified by combinations of CSF profiles; values are expressed as percentage of subjects with available data; (**D**-**F**); (**J**-**L**) Independent associations of α-syn SAA + and AD+ status with clinical outcomes; dots represent the ORs and error bars show the 95%CI; values were obtained from multivariable penalized logistic regression models. For each clinical outcome, binarized α-syn SAA and AD status were included as predictors in the same model; asterisks mark the statistically significant associations. Strenght of the statistical significance is based on p values corrected for multiple comparisons using the false discovery rate according to Benjamini-Hochberg. Two independent corrections were performed (one each for the independent effect of α-syn SAA and AD status, across 12 clinical outcomes). S+ status was defined bv positive result at the CSF α-syn SAA. AD+ status was defined by both decreased CSF Aβ ratio (A+) and elevated CSF p-tau181 (T+). Abbreviations: AD, Alzheimer's disease; ORs, odds ratios; S, α-syn SAA; SAA, seed amplification assay

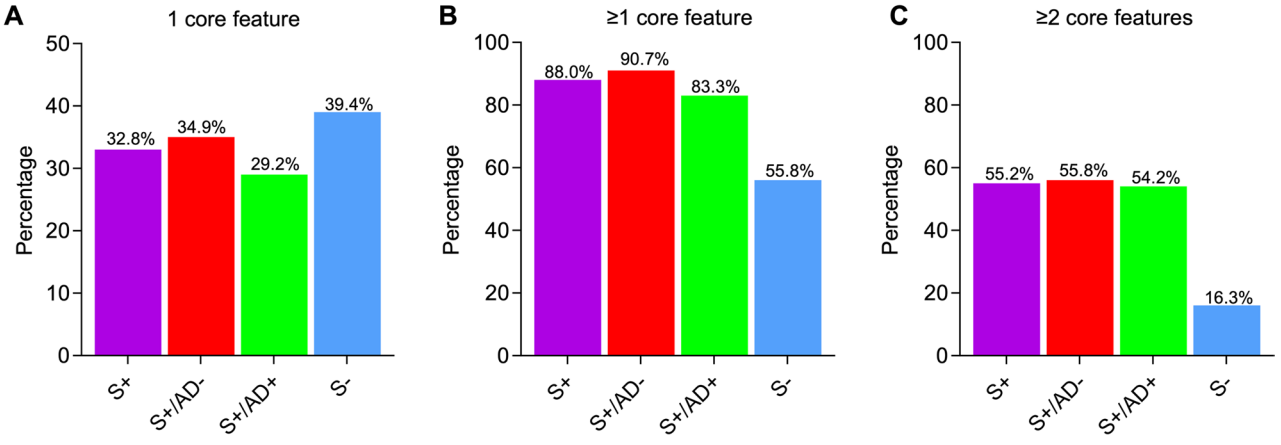

Fig. 4 Prevalence of different numbers of core features for DLB stratified by α-syn SAA and AD status. Percentage of participants showing only one (A), at least one (B) or at least two (C) core features for DLB diagnosis stratified by α-syn SAA and AD status. S+ status was defined bv positive result at the CSF α-syn SAA. AD+ status was defined by both decreased CSF Aβ ratio (A+) and elevated CSF p-tau181 (T+)

Table 5 Diagnostic performance of different numbers of DLB core features in the identification of α-syn SAA+ participants

	n	AUC	Sensitivity	Specificity
One core feature				
S + vs. S-	67 vs. 104	0.53 (0.44–0.62)	32.8 (22.8–44.7)	60.6 (51.0–69.4)
S + AD- vs. S-	43 vs. 104	0.52 (0.42–0.62)	34.9 (22.4–49.8)	60.6 (51.0–69.4)
S + AD+ vs. S-	24 vs. 104	0.55 (0.42–0.68)	29.2 (14.9–49.2)	60.6 (51.0–69.4)
At least one core feature				
S + vs. S-	67 vs. 104	0.66 (0.58–0.74)	88.1 (78.2–93.8)	44.2 (35.1–53.8)
S + AD- vs. S-	43 vs. 104	0.67 (0.58–0.76)	90.7 (78.4–96.3)	44.2 (35.1–53.8)
S + AD+ vs. S-	24 vs. 104	0.64 (0.52–0.75)	83.3 (64.1–93.3)	44.2 (35.1–53.8)
At least two core features				
S + vs. S-	67 vs. 104	0.69 (0.61–0.78)	55.2 (43.4–66.5)	83.6 (75.4–89.5)
S + AD- vs. S-	43 vs. 104	0.70 (0.60–0.80)	55.8 (44.1–69.6)	83.6 (75.4–89.5)
S + AD+ vs. S-	24 vs. 104	0.69 (0.56–0.82)	54.2 (35.1–72.1)	83.6 (75.4–89.5)

AUC, sensitivity and specificity values are reported as main value (95% confidence interval). S+ status was defined bv positive result at the CSF α-syn SAA. AD+ status was defined by both decreased CSF Aβ ratio (A+) and elevated CSF p-tau_{181} (T+). Abbreviations: AD, Alzheimer's disease; AUC, area under the curve; DLB, Dementia with Lewy bodies; S, α-syn SAA; SAA, seed amplification assay.

associated with deficits in any of the examined neuropsychological domains (Additional file 7).

The interaction of α-syn SAA + and AD+ status was not associated with any neuropsychological outcome (Additional file 8).

Discussion

Neuropathological studies have shown that atypical presentations of non-prion neurodegenerative diseases are a frequent cause of RPD [8–10, 19, 24]. However, the lack of a pathology-specific biomarker validated in vivo has limited the estimation of the prevalence of LB pathology in patients with suspected neurodegenerative RPD in whom prion disease was excluded. In this study, we used CSF α-syn SAA to evaluate the prevalence and clinical correlates of LB pathology in a large cohort of consecutively referred well-characterized patients with non-prion RPD of a suspected neurodegenerative etiology.

Biomarker signature of AD pathology was detected in 52.6% of participants, which is broadly consistent with the reported prevalence of AD pathology in neuropathological cohorts of patients with nontreatable forms of RPDs [8–10]. In contrast, positivity for LB pathology was higher in our study than in the neuropathological cohorts (39.2% vs. 2–26%), which can at least partially be explained by the lack of details on co-pathologies in most of the analysed studies.

In a recent study in a large cohort of patients with "classical" slowly progressive cognitive impairment (primarily of degenerative or vascular origin) [37], biomarker evidence of AD pathology was found in 54% of participants, consistent with the findings in our RPD cohort. In contrast, the prevalence of LB pathology, assessed by CSF α-syn SAA, was lower than in our RPD cohort (23% vs. 39%). At the same time, the proportion of participants showing biomarker positivity for both pathologies was similar in the two cohorts. These results may suggest that

pure LB pathology is a relatively frequent cause of neurodegenerative RPD, while the comparable distribution of S+/AD+ profiles across cohorts with different speeds of progression seems to exclude the co-occurrence of both pathologies as a primary driver of rapid progression.

Previous clinico-pathological studies showed that subjects with a degenerative RPD may present with a clinical phenotype that is atypical for the underlying pathology, when compared with the prevalent slowly progressive phenotype [21, 23–24]. When assessing the independent correlates of α-syn SAA positivity in our RPD patients, we found significant associations between α-syn SAA+ status and DLB core features, including fluctuating cognition, visual hallucinations, and extrapyramidal signs, as well as atypical features such as akinetic mutism and myoclonus. These results align with previous reports but also suggest that atypical features are related to LB pathology rather than potential co-pathologies (including AD pathology). Given the weak statistical association, albeit still significant after correction for multiple comparisons, future studies should replicate these findings.

In contrast to the non-prion RPD, we could not confirm the association between α-syn SAA+ status and clinical features in a subgroup of subjects with RPD caused by CJD (Additional file 9). This is probably due to the relatively low LB pathology burden typically detected in CJD patients as copathology [27] and the extremely variable and severe clinical phenotype of prion disease [6–7].

Interestingly, α-syn SAA positivity was also independently associated with a previous episode of delirium in our RPD cohort. The association of prodromal delirium with LB pathology is well established [38–39], and most of the previously reported patients with RPD and LB pathology had experienced at least one episode of delirium or acute encephalopathy [21, 23]. Here, we confirm that approximately 25% of our α-syn SAA+ participants had a previous episode of delirium. These findings, albeit preliminary given the weak statistical association, highlight the importance of systematically investigating the presence of prior episodes of acute encephalopathy in the diagnostic workup of patients with RPD, as they may indicate an underlying LB pathology. Notably, a previous delirium was significantly more frequent in participants with α-syn SAA + and AD- profile than in those showing biomarkers of both pathologies, further underlying its specific association with LB pathology.

Interestingly, the interaction of α-syn SAA + and AD+ status was significantly associated with higher odds of psychiatric disturbances. However, this result must be interpreted cautiously, given the wide confidence interval.

We then examined the diagnostic performance of the combination of at least two core features, currently required by the international diagnostic criteria for a "probable" DLB diagnosis [36], in identifying α-syn SAA+ participants in the RPD subgroup. The criteria yielded low sensitivity (around 50% of cases were correctly identified) and high specificity, resulting in low overall accuracy. Similar results were obtained when stratifying α-syn SAA+ participants by AD status. The criterion "presence of at least one core feature" (possible DLB diagnosis) yielded a similar poor diagnostic value. Two or more core features have been reported in approximately 60–80% of patients with classical, slowly progressive, neuropathologically confirmed DLB [40–41]. Moreover, at least two core features were identified in more than 90% of CSF α-syn SAA+ patients with classical DLB in a recent study [42]. On the other hand, a similar low percentage of α-syn SAA+ participants, identified using an in vivo biomarker approach, met clinical criteria for DLB in a large cohort of cognitively impaired individuals [37]. Taken together, these results suggest that reliance on clinical criteria may result in underrecognition of LB pathology, even in the context of RPD. Consistently, DLB appears underdiagnosed in clinical RPD series [16, 43–45].

Of note, only a small proportion of our patients had data on the supportive biomarkers included in the international criteria, limiting our ability to fully assess their diagnostic performance. However, we acknowledge that access to such biomarkers may be substantially restricted in severely compromised patients, as often encountered in RPD.

Lastly, we found no significant associations between α-syn SAA+ status and deficits in any single neuropsychological domain. On the other hand, an AD+ status was associated with language impairment, further supporting the well-known atypical cognitive presentations of this pathology in the context of RPD [17]. However, this association was not retained after correction for multiple testing. Furthermore, the lack of association of LB pathology with decreasing MMSE scores highlights the need for alternative cognitive scales to track the severity of cognitive impairment due to LB pathology in patients with RPD [21].

Our study has limitations. Firstly, our RPD patients were evaluated at different Neurological Centres in Italy, which may have introduced heterogeneity in the collection of clinical and neuropsychological data. Furthermore, data were retrospectively collected, which may have affected the completeness of the information. As an example, the prevalence of RBD may have been underestimated in our cohort. Moreover, the limited number of participants undergoing a complete neuropsychological examination may have prevented us from reaching more extensive conclusions on the neuropsychological profile of α-syn SAA + RPD patients. Additionally, given the current lack of biofluid biomarkers of other neuropathologic entities potentially associated with an RPD

syndrome, such as PSP or CBD, we cannot exclude that some α-syn SAA+ participants may also harbor alternative pathologies contributing to the clinical phenotype. Finally, the almost exclusive representation of participants of White/European ethnicity may limit the generalizability of results to clinical groups from different ethnic backgrounds.

On the other hand, the inclusion of a large cohort of well-characterized RPD patients submitted to an Italian CJD reference centre is a significant strength of our work. Moreover, the prediction of underlying LB and AD pathologies using accurate in vivo biomarkers represents an original contribution to the current literature on RPD.

Conclusions

In conclusion, our study demonstrates that a substantial proportion of patients with a non-prion RPD referred to a CJD reference centre show a positive α-syn SAA, suggesting an underlying LB pathology. An α-syn SAA+ status is independently associated with classical features of DLB and with atypical manifestations such as akinetic mutism and myoclonus. Overall, core features of DLB, alone or in combination, showed a poor diagnostic performance in identifying α-syn SAA + RPD participants. This supports the inclusion of α-syn CSF SAA in the diagnostic workup of RPD as a biomarker of underlying LB pathology.

Abbreviations

α-syn	Alpha-synuclein
AD	Alzheimer's disease
AUC	Area under the curve
CI	Confidence interval
CJD	Creutzfeldt-Jakob disease
CSF	Cerebrospinal fluid
CV	Coefficient of variation
DLB	Dementia with Lewy Bodies
LB	Lewy Body
MMSE	Mini-Mental State Examination
OR	Odds ratio
RBD	REM-sleep behavior disorder
p-tau$_{181}$	Phosphorylated tau protein at residue 181
ROC	Receiver operating characteristics
RPD	Rapidly progressive dementia
RT-QuIC	Real-time quaking-induced conversion
SAA	Seed amplification assay
t-tau	Total tau protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-026-02004-9.

Additional file 1: Details on final diagnoses of subjects with a treatable form of rapidly progressive dementia

Additional file 2: Demographic and clinical features stratified by AD status

Additional file 3: Clinical outcomes stratified by combinations of α-syn SAA and AD status

Additional file 4: Independent associations of α-syn SAA and AD status with clinical outcomes

Additional file 5: Independent associations of α-syn SAA and AD status and their interaction with clinical outcomes

Additional file 6: Distribution of different numbers of core features for DLB diagnosis across groups

Additional file 7: Independent associations of α-syn SAA and AD status with neuropsychological outcomes

Additional file 8: Independent associations of α-syn SAA and AD status and their interaction with neuropsychological outcomes

Additional file 9: Clinical features stratified by α-syn SAA status in a population of subjects with RPD due to Creutzfeldt-Jakob disease

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Authors' contributions

AMas: design and conceptualization of the study, major role in the acquisition of data, statistical analysis and interpretation of the data, drafting and revising the manuscript for intellectual content; SCal: major role in the acquisition of data, analysis of the data, revising the manuscript for intellectual content; SB: major role in the acquisition of data, revising the manuscript for intellectual content; FM: major role in the acquisition of data, analysis of the data, revising the manuscript for intellectual content; AMam: major role in the acquisition of data, analysis of the data, revising the manuscript for intellectual content; MT: major role in the acquisition of data, analysis of the data, revising the manuscript for intellectual content; AR: major role in the acquisition of data, analysis of the data, revising the manuscript for intellectual content; ER: major role in the acquisition of data, analysis of the data, revising the manuscript for intellectual content; GMB: major role in the acquisition of data, revising the manuscript for intellectual content; VM: major role in the acquisition of data, revising the manuscript for intellectual content; NM: major role in the acquisition of data, revising the manuscript for intellectual content; CF: major role in the acquisition of data, revising the manuscript for intellectual content; AMar: major role in the acquisition of data, revising the manuscript for intellectual content; MS: major role in the acquisition of data, revising the manuscript for intellectual content; ML: major role in the acquisition of data, revising the manuscript for intellectual content; SM: major role in the acquisition of data, revising the manuscript for intellectual content; AC: major role in the acquisition of data, revising the manuscript for intellectual content; LB: major role in the acquisition of data, revising the manuscript for intellectual content; SCap: major role in the acquisition of data, revising the manuscript for intellectual content; PP: design and conceptualization of the study, major role in the acquisition of data, interpretation of the data, drafting and revising the manuscript for intellectual content.

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Data availability

Raw data is available upon reasonable request. The requests should be addressed to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted in compliance with the revised Declaration of Helsinki for the protection of human participants and Good Clinical Practice guidelines, and was approved by the local ethics committee (approval number AVEC:18025, 113/2018/OSS/AUSLBO). Written informed consent was given by study participants or their next of kin.

Consent for publication
Not applicable.

Competing interests
C.F. has received travel grants or attended conferences upon invitation from Biogen, Sanofi, Novartis and Alexion and has received speaking honoraria from Novartis, Sanofi and AstraZeneca. The other authors have no competing interests.

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